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Dengue in India: An Overview

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ABSTRACT

Background: Dengue fever has become a major public health concern in our country, causing significant morbidity and mortality. Because there is no definite drug or commercially available vaccine for dengue, prevention is the only option. As a result, early reporting of dengue cases is required in order to implement preventive measures before the disease spreads to epidemic proportions. Therefore, healthcare providers should notify every dengue incident to local authorities in the current format, including the District Health Officer or Chief Medical Officer of district concerned and the Municipal Health Officer of municipality concerned every week (daily during the transmission period).

Materials and Methods: The data on dengue (2015-2021 till Oct.) was available at the National Vector Borne Disease Control Programme under the Ministry of Health & Family Welfare, Government of India, and has been used in this paper.

Results and discussion: During the last two decades (2000-2009 and 2010-2019), significant geographical spread of the dengue has been experienced in India with the repeated outbreaks, and an 11 fold increase in number of cases. Despite an increase in the incidence of dengue fever, the case fatality rate in India has decreased from 3.3% in 1996 to 0.4% in 2010 to 0.1% in 2019. Early diagnosis and timely referral play a critical role in bringing down Case Fatality Rate (CFR).

Conclusion: Dengue is a manifestation arising from the process of increasing vector density and adaptation to human habitation, as well as human lifestyle transformation, unplanned developmental activities exacerbated by climate change.

Keywords: Dengue Fever, Dengue Haemorrhagic Fever, Aedes Mosquitoes, DENV

INTRODUCTION

Dengue fever has become a major public health concern around the world, particularly in tropical and subtropical regions. Dengue fever (DF) is a self-limiting disease that accounts for vast majority of dengue infections. Dengue is wide-spread throughout tropics, with the local variations in the risk caused by factors such as temperature, rainfall, relative humidity and an unplanned rapid urbanization. The dengue causes wide range of diseases. This could range from the subclinical disease (where people are unaware they are infected) to the severe flu-like symptoms in persons who are infected. Although it is less common, but a few people develop very severe dengue that can result in a variety of complications such as organ impairment, severe bleeding, or plasma leakage. The severe dengue has the higher risk of mortality if not managed appropriately. Severe dengue was identified first during the dengue epidemics in Philippines, and Thailand in the 1950s. [1] Severe dengue fever now affects the majority of Asian, and the Latin American countries and it is the leading

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cause of hospitalization, and death among the children, and adults in above mentioned regions. Dengue is caused by a virus of the flavi-viridae family and there are four distinct, but very closely related; serotypes of virus which cause dengue (DENV-1, DENV-2, DENV-3 and DENV-4). It is believed that recovering from infection provides the lifelong immunity towards that serotype. After recovery, though, cross-immunity to other serotypes is partial, and only for a short time. The risk of severe dengue is increased by subsequent infections (secondary infection) by other serotypes. The dengue virus is spread by the female mosquitoes, primarily of the species 'Aedes aegypti' and, to lesser extent, 'Aedes albopictus'. These mosquitoes also transmit the yellow fever, chikungunya, and zika viruses. [2] Dengue has an alarming impact on human health in addition to global and national economies. When the susceptible vectors are exists in these new areas, DENV is transported frequently from one to another place by infected travellers. [3]

PROBLEM STATEMENT

The worldwide burden of dengue: Dengue fever (DF) and its severe forms: Dengue haemorrhagic fever (DHF) and the Dengue shock syndrome (DSS) have emerged as major global public health concerns. Over the past three decades, there has been a dramatic global increase in the frequency of dengue fever, DHF, and DSS, and their epidemics. Dengue is found in the tropical and subtropical regions all over the world, primarily in the urban, and semi urban areas, but now, it is spreading to rural areas as well. According to a recent estimate, 390 million dengue infections happen each year, with 96 million presenting clinically with the severity of disease. According to another study on prevalence of dengue, 3.9 billion people are risk of getting infected with dengue viruses. [4] Only 9 nations had severe dengue epidemics prior to 1970. More than 100 nations in WHO regions of Americas, Africa, South-East Asia, Eastern Mediterranean, and Western Pacific are now endemic. [5] Americas, Western Pacific, and South-East Asia Regions (SEAR) are most severely affected, with Asia accounting for 70% of the global disease burden. Over the last two decades, the number of dengue cases reported to WHO has increased more than 8 fold, from 505,430 cases in 2000 to over 2.4 million in 2010, and 5.2 million in 2019. Between 2000 and 2015, the number of reported deaths increased from 960 to 4032. Every year, globally, about 500,000 people with DHF require hospitalization. Approximately 90% of those affected are children under the age of five, and about 2.5% of those affected die. Dengue fever is second most common cause of fever among the travelers returning from low-and middle-income countries, after malaria. In 2020, dengue exaggerated many countries with an increase in cases in Brazil, Bangladesh, Cook Islands, India, Ecuador, Indonesia, Mauritania, Maldives, Mayotte (Fr), Singapore, Nepal, Sri Lanka, Thailand, Sudan, Yemen and Timor-Leste. [6] The COVID-19 pandemic is putting an enormous burden on global healthcare, and management systems. The combined impact of the COVID-19 and dengue epidemics has potential to be devastating for the vulnerable populations. In 2019, the largest number of dengue cases ever reported globally. The 2016 year was also marked by the large dengue outbreaks, with region of Americas reporting more than 2.38 million cases. Brazil alone contributed approximately 1.5 million cases that year, roughly three times more than in 2014; 1,032 deaths were reported in this region. In the same year, Western Pacific Region depicted over 375,000 suspected cases, with the Philippines reporting 176,411 and Malaysia reporting 100,028 cases, representing similar burden for both countries. In 2017, the significant reduction was observed in Americas from 2,177,171 infections in 2016 to 584,263 in 2017. [7] This represents the reduction of 73.0%. During 2017, only Panama, Peru, and Aruba saw a surge in the cases. Similarly, a 53.0% reduction in the severe dengue infections was also documented during 2017. [8] The post-zika outbreak period (after year 2016) saw a decrease in dengue cases, but the exact factors causing this decrease are still unknown.

Dengue burden in India: Dengue fever has become more prevalent in India in recent years as a result of rapid urbanization, lifestyle changes, and poor water management, including improper water storage practices in urban, peri-urban, and rural areas, which has resulted in the proliferation of the mosquito breeding sites. Disease has the seasonal pattern, i.e. the cases peak after the monsoon, and they are not uniformly distributed throughout the year. However, in southern states, and Gujarat, transmission is perennial. [9] Dengue fever has spread significantly geographically in India over last 2 decades (2000-2009 and 2010-2019), with repeated outbreaks and an 11-fold increase in number of cases.[10] Not only is number of cases are increasing as disease is spreading to new regions, but the explosive outbreaks are also occurring. The 2016 year was marked by widespread dengue outbreaks around the world. In 2015, Delhi recorded its worst outbreak with 15,867 cases. [11] Dengue fever was first observed in India in 1956, in the Vellore district of Tamil Nadu. [12] The first DHF outbreak was reported in Calcutta (Kolkata), in West Bengal, in year 1963. Since then, all states, and union territories in India (except Ladakh, and Lakshadweep) have identified dengue cases, and deaths. Dengue fever outbreaks been reported in several parts of country, including newer areas. [13-15] The number of states, and the Union Territories (UTs) reporting cases increased from 8 (7 states and one UT) in 2000 to 35 (28 states and 7 UTs) at present.

Approximately 188,401 cases were identified in 2017, with 325 deaths. As seen from Table-1, highest number of infections was reported from Tamil Nadu, followed by Kerala, Karnataka, then Punjab and West Bengal. [16] All four serotypes, i.e. DENV-1, 2, 3, and 4 been isolated in India but at present the DENV-1, and DENV-2 are widespread. [17]

Table 1: Dengue/DHF situation in India - Dengue Cases and Deaths in the Country since 2015

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

[*C=Cases, D=Deaths, **NR=Not Reported; #Till Oct 2021]

Source: National Vector Borne Disease Control Programme (NVBDCP), Ministry of Health & Family Welfare, Government of India[16]

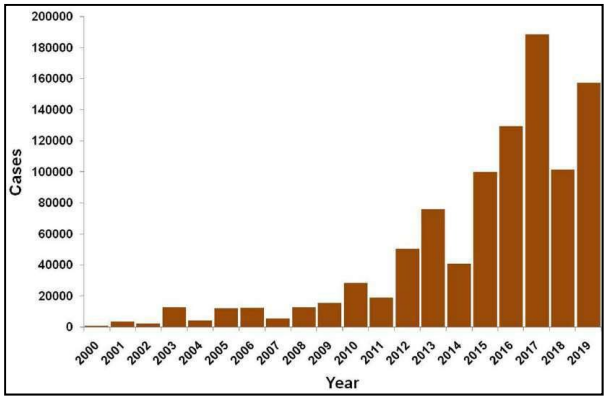

Figure 1: Dengue morbidity trends in India during 2000-2019 [19]

In the 20th century, there was the significant rise in number of infections reported in 2003, 2010, 2012, and 2013, with an exponential increase beginning in 2015 onwards. During this time, repeated dengue outbreaks were reported in states of Andhra Pradesh, Goa, Delhi, Haryana, Karnataka, Gujarat, Kerala, Rajasthan, Maharashtra, Pondicherry, Uttar Pradesh,

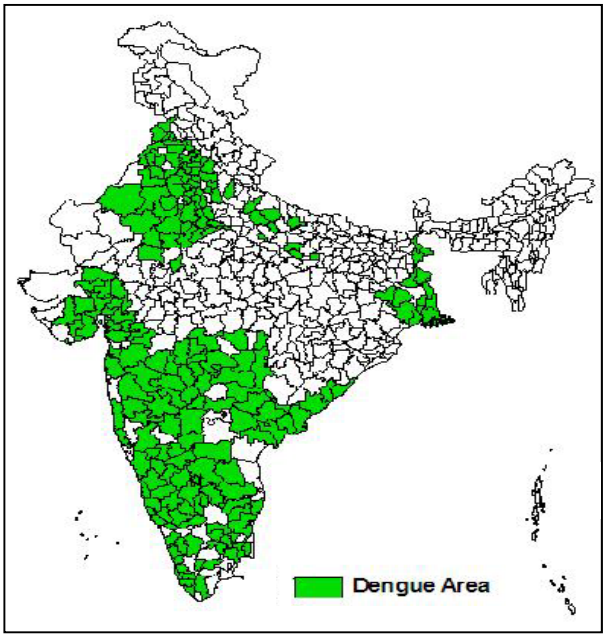

Figure 2: Distribution of dengue/DHF in India

Source: National Vector Borne Disease Control Programme (NVBDCP), Ministry of Health & Family Welfare, Govt of India

Tamil Nadu, Punjab, and West Bengal. In 2017, dengue cases were to be the highest in India. Figure-1 depicts the annual morbidity trend for dengue from 2000 to 2019.

Seasonal trend of dengue: The seasonal pattern of disease occurrence suggests that climate is a significant driving force in dengue incidence. Most of the country receives rainfall during monsoon season (July to September), and majority of the dengue cases have been observed to occur during this time. Rainfall and temperature are important climatic factors in dynamics of the vector abundance and disease transmission. [20]

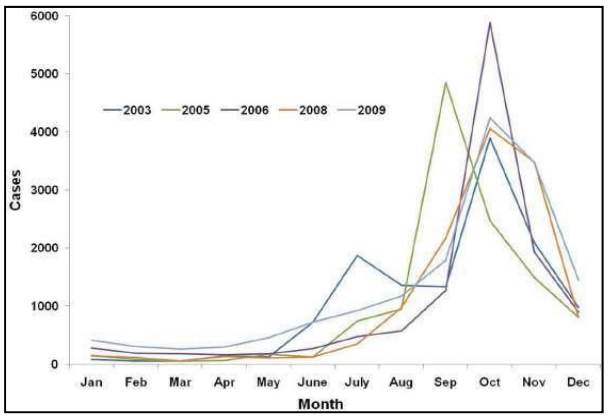

Figure 3: Dengue trend during 2003-09 in India

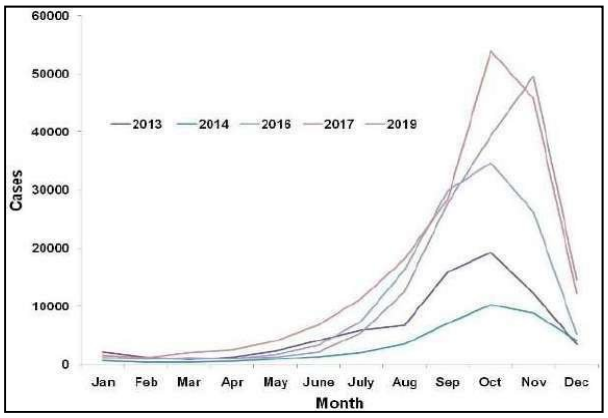

Figure 4: Dengue trend during 2013-19 in India

As illustrated in Figure-3, in 2003-2009, from month of September to November, 65.6% of the total cases were reported, followed by 19.2% from June to August, and the lowest numbers of cases (4.1%) were reported during months of March, April and May. [6] A similar trend was observed in recent decade from 2013 to 2019. A total of 68.0% cases were reported during September to November, 17.7% during June to August and the lowest number of cases, i.e., 4.1%, were reported during months of March, April and May (Figure-4). Though the disease has a seasonal pattern with the peak of transmission occurring after the monsoon, the seasonality and transmission pattern were not clear till recent years.

EPIDEMIOLOGICAL DETERMINANTS:

Agent factors:

A) Agent: Dengue virus is a member of the flaviviridae family. There are 4 virus serotypes known as the DENV-1, DENV-2, DENV-3 and the DENV-4. Infection with any of the virus serotypes results in lifelong immunity to that serotype. [21] The severe form of the dengue. i.e., DHF/DSS is caused by secondary infection with dengue serotype-2 or multiple infections with different serotypes. [22] The first infection most likely sensitizes the patient, whereas second infection with a different serotype seems to result in immunological catastrophy. The pathogenesis of the severe syndrome involves pre-existing dengue antibodies. It is postulated that virus antibodies are formed within the few days of second dengue infection and that the non-neutralizing enhancing the antibodies promote the infection of the higher numbers of the mononuclear cells, followed by release of cytokines, vasoactive mediators, and pro-coagulants, resulting in the Disseminated Intravascular Coagulation (DIC) seen in haemorrhagic fever syndrome. [23]

B) Vector: 'Aedes aegypti' and 'Aedes albopictus' are the two most important vectors of dengue. It is a small, black mosquito with white stripes and is approximately 5mm in size. It is also known as the 'tiger mosquito'. It takes about 7 to 8 days for the virus to develop in its own body and spread the disease. They both carry high vectorial competency for dengue virus, i.e., high susceptibility to infecting virus, ability to replicate the virus, and ability to transmit virus to another host. The primary vector of DENV is the Aedes aegypti mosquito. It lives in the urban habitats and breeds generally in the man-made containers. Aedes aegypti is the day-time feeder, with peak biting periods early in morning, and in evening before sunset. [24] A female Aedes aegypti frequently feeds several times between each egg-laying period. [25] Once the female has laid eggs, the eggs may remain feasible for several months and would hatch when they come into contact with water. Aedes albopictus, the secondary vector of dengue in Asia, has spread to over 32 states in the United States and above 25 countries in European region.

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: Mosquitoes can 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 (are presymptomatic), and people who display no sign/ symptoms of illness (they are asymptomatic). [27] Human to mosquito transmission could occur up to 2days before somebody shows the symptoms of illness, up to 2 days after fever has resolved. [28] The risk of 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. [26] Most individuals are viremic for around 4 to 5 days but viremia could last for about 12 days. [29]

Other modes of the transmission: Mosquito vectors are primary mode of the transmission of Dengue virus between the humans. However, there is evidence of possibility of the maternal transmission (from the pregnant mother to the baby). While vertical transmission rates seem to be low, the risk of vertical transmission appears to be related with the timing of the dengue infection during pregnancy. [30] When a mother does have a DENV infection while she is pregnant, babies may suffer from pre-term birth, low birth-weight, and foetal distress. [31]

DISEASE CHARACTERISTICS: SIGNS & SYMPTOMS

Dengue is a flu-like illness that primarily affects infants, young children, and adults, but rarely results in death. Symptoms generally last for 2 to 7 days, after the incubation period of 4 to 10 days after bite from the infected mosquito [32]. DENV infections might be asymptomatic, or may lead to (a) 'Classical' dengue fever; (b) Dengue haemorrhagic fever without shock; and (c) Dengue haemorrhagic fever with shock/ Dengue shock syndrome (DSS).

Classical dengue fever: Dengue fever can affect people of all ages, and both genders. Children generally have the milder form of the disease than adults. The illness is usually characterized by the incubation period of 3-10 days (usually 5-6 days). Onset is sudden with chills, and very high fever, muscle, and joint pains, severe frontal-headache, which prevent all the movement. Within 24 hours retro-orbital pain, predominantly with eye movements, or the eye pressure and photophobia develop. Other common symptom includes extreme weakness, constipation, anorexia, altered taste sensation, abdominal tenderness, and colicky pain, dragging pain in inguinal region, general depression and sore throat (Figure-5). Fever usually ranges between 39°C to 40°C. Fever is usually, but not always, followed by the remission lasting a few hours to about 2 days (biphasic curve). Skin eruptions seen in about 80.0% cases during remission, or during second febrile phase, that lasts for 1-2 days.

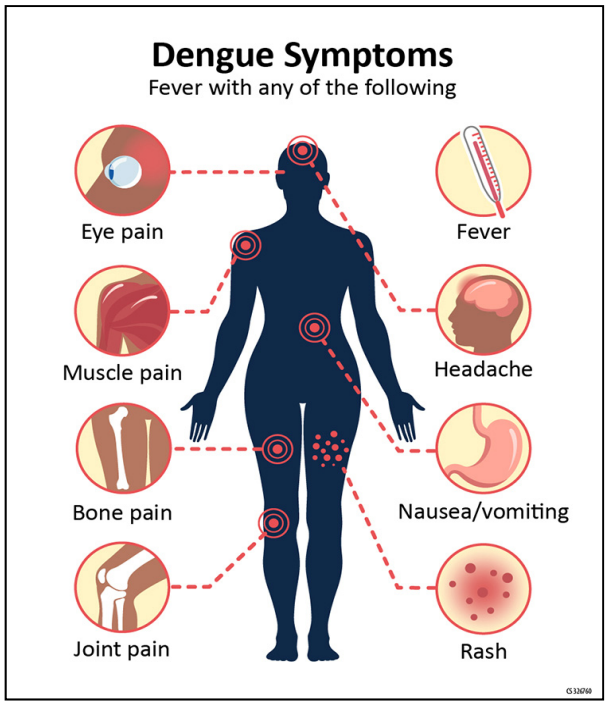

Figure 5: Dengue Symptoms

Source: Centers for Disease Control and Prevention

During first half of febrile period, rash might be diffuse mottling, flushing or fleeting pin-point eruptions on face, chest, and neck, followed by the conspicuous rash which may be macula-papular or scar-latiniform on the 3rd or 4th day. It usually begins on chest, and trunk, and then spreads to the extremities and, in rare cases, the face. It might be accompanied by hyperaesthesia and itching. The rash can last from 2 hours to many days, and is sometimes followed by desquamation.[33] Fever usually lasts about 5 days, and rarely above 7 days, after which recovery is usually complete, though convalescence may be prolonged.

Dengue haemorrhagic fever: Dengue haemorrhagic fever is particularly the severe form of the dengue fever. Course of the dengue illness could be divided in three phases-Febrile phase, Critical phase and Recovery phase. (Figure-6)

(a): Febrile phase: The illness usually begins sharply with a high grade of fever, headache, and facial flushing after a 4-6 days incubation period. Anorexia, epigastric discomfort, vomiting, right costal margin tenderness, and the abdominal pain are all common symptoms. During first few days, the illness is related to the classical dengue fever (DF), but macula-papular rash, usually of the rubelliform type, is less common. It might appear early, or late in course of the illness. Occasionally, temperature might be 40°C to 41°C and febrile convulsions might occur, predominantly in infants. [32] Plasma leakage and abnormal haemostasis, as manifested by a rising haematocrit value and moderate to severe thrombocytopenia, are the major patho-physiologic changes that determine severity of disease in DHF and distinguish it from DF. These two clinical laboratory changes stand out as

distinct and consistent findings. The commonest hemorrhagic phenomenon is the positive tournicate test. It is done by inflating the blood pressure cuff to the midpoint between systolic, and the diastolic pressure for about 5 minutes. When 10 or more petechiae per 2.5 x 2.5cm (1 inch-square) are observed, then test is considered to be positive. In DHF, test generally gives the definite positive with 20 petechiae, or more. [17]

(b): Critical phase: During defervescence, when temperature drops to about 37.5°C to 38°C, or less and remains below this, generally on days 3-7 of illness, the increase in the capillary permeability in parallel along with the increasing levels of haematocrit might occur. This marks beginning of critical phase. Period of the clinically significant plasma leakage is usually between 24 and 48 hours. Plasma leakage is typically preceded by progressive leucopenia, which is followed by the rapid decrease in the platelet count. Pleural effusion is mostly on right side and depending on degree of the plasma leakage, and volume of the fluid therapy, ascites might be clinically detectable. It has been discovered that gall bladder oedema precedes plasma leakage. As a result, chest X-rays and abdominal ultrasound could be useful diagnostic tools. When the critical volume of the plasma is lost due to leakage, shock occurs. It is frequently preceded by tenderness, or abdominal pain, clinical fluid accumulation, persistent vomiting, lethargy, mucosal bleeding, restlessness, liver enlargement greater than 2cm, and oliguria. When a person is in shock, his body temperature may drop below normal. Prolonged shock causes progressive organ weakening, metabolic acidosis and the disseminated intravascular coagulation due to the resulting organ hypo-perfusion. This leads to the severe haemorrhage, causing haematocrit to reduce in severe shock. The patients having severe bleeding may have an increase in white cell count during this stage of dengue. Organ impairment like encephalitis, severe hepatitis, myocarditis, and/or severe bleeding, might also occur in the absence of obvious plasma leakage, or shock. Dengue cases with warning signs will most likely recover with the early intra-venous rehydration. Some cases of the dengue fever will progress to severe dengue fever. [34]

(c): Recovery phase: If patient survives in critical phase within 24-48 hours, there is the gradual reabsorption of extra-vascular compartment fluid over the next 48-72 hours. The general state of well-being improves, gastrointestinal symptoms subside, appetite returns, hemodynamic status stabilizes and the diuresis occurs. Some patients may develop a rash of '**isles of white in sea of red'**. Some people may develop generalized pruritus. During this stage, bradycardia and electrocardiographic changes are common. Because of the dilutional effect of the reabsorbed fluid, haematocrit stabilizes, or might be lower. The white blood cell count usually begins to rise soon after defervescence, but the platelet count usually recovers later than the white blood cell count. If excessive intravenous fluids are administered, respiratory distress from the massive pleural effusion, and ascites can occur at any time. Excessive fluid therapy is associated with pulmonary oedema, or CHF during the critical and/or recovery phases.

Severe dengue: Severe dengue is characterized by one or more of following symptoms: Plasma leakage (which can result in shock (dengue shock) and/or fluid accumulation, with or without respiratory distress); Severe bleeding; and Severe organ impairment.

As the dengue vascular permeability increases, hypovolaemia worsens and leads to shock. It usually occurs around defervescence, on the 4th or 5th day of illness (range: 3-7 days), and is preceded by warning signs. The compensatory mechanism that maintains the normal SBP during initial stage of the shock also causes tachycardia, and the peripheral vasoconstriction along with decreased skin perfusion, leading to cold extremities, and delayed capillary refill time. As peripheral vascular resistance rises, diastolic pressure increases towards systolic pressure, and pulse pressure narrows. Dengue shock patients are frequently conscious and lucid. Finally, there is the decompensation and both the pressures abruptly disappear.

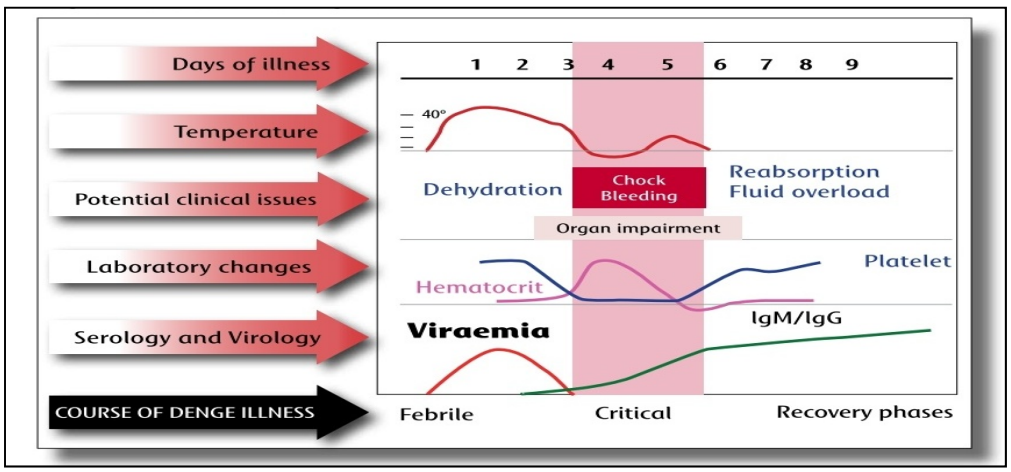

Figure 6: Course of dengue illness

Prolonged hypotensive shock, and hypoxia can result in multi-organ failure and a challenging clinical course. If a child's pulse pressure is <20mmHg or he or she exhibits signs of the poor capillary perfusion, patient considered to be in shock (cold extremities, and delayed capillary refill, or rapid pulse rate). A pulse pressure of <20mmHg in adults may indicate more severe shock. The patients having severe dengue might have the coagulation abnormalities but these are rarely severe enough to cause major bleeding.[33] When major bleeding occurs, it is always accompanied by profound shock, which, when combined with hypoxia, thrombocytopenia, and acidosis, can result in multiple organ failure, and the advanced disseminated intra-vascular coagulation. Massive bleeding might occur without the need for prolonged shock when ibuprofen, acetylsalicylic acid (aspirin), or corticosteroids are used. Even in absence of the severe plasma leakage, or shock, unusual manifestations such as acute liver failure, and encephalopathy might occur. Some dengue cases have also been linked to cardiomyopathy and encephalitis. However, the majority of dengue deaths occur in patients who are in profound shock, especially if the situation is complicated by fluid overload.

CRITERIA FOR THE CLINICAL DIAGNOSIS

The summary of the clinical diagnosis of DF, and DHF is given below: [35]

Types	Diagnosis
Dengue Fever (DF)	Probable diagnosis A case compatible with the clinical description of dengue fever is "an acute febrile illness of 2-7 days duration with 2, or more of following manifestation: "Headache, retro-orbital pain, myalgia, arthralgia/bone pain, rashes, haemorrhagic manifestations" Or "Non-ELISA based NS-1 antigen/IgM positive" (The positive test by RDT would be considered as probable because of the poor sensitivity, and specificity of the currently available RDTs.) Confirmed diagnosis A case that fits clinical description of the dengue fever and includes at least one of following: • NS1-ELISA demonstration of the Dengue virus antigen in the serum samples • Positive ELISA test results for IgM antibody titre in a single serum sample • Detection of the viral nucleic acid using a polymerase chain reaction test (PCR). • Isolation of Dengue virus (Virus culture positive) from serum, plasma and, leucocytes. • After two weeks, IgG sero-conversion in paired sera resulted in a fourfold increase in IgG titre.
Dengue Haemorrhagic Fever (DHF)	• Acute onset of the fever of 2 to 7 days duration. • Haemorrhagic manifestations shown by any of following: petechiae, positive tourniquet test, purpura, or ecchymoses or the bleeding from mucosa, gastrointestinal tract, injection sites or other locations. • Platelet count $\leq$ 100,000 cells/mm^3 • Rising haematocrit/haemo-concentration $\geq$20% from baseline, or evidence of the plasma leakage like pleural effusion, ascites or hypo-proteinaemia/albuminaemia.

LABORATORY DIAGNOSIS

DENV infection can be diagnosed using a variety of methods. These include the virological tests (which detect virus components directly) and the serological tests (that detect human derived immune components formed in response to virus).The different diagnostic approaches might be more, or less correct depending on time of the patient presentation. Serological and virological testing should be performed on collected patient samples during first week of the illness. [3] During 2007, the Government of India established the laboratories network in India in collaboration with the respective state governments, with about 110 Sentinel Surveillance Hospitals (SSHs) equipped with laboratory support in the affected states. To ensure uniformity in diagnosis, National Institute of Virology (NIV) in Pune was entrusted with the production and distribution of IgM capture ELISA (MAC-ELISA) test kits to the laboratories. In 2010, under this program, ELISA-based NS-1 was introduced for early diagnosis. These SSHs are linked to Apex Referral Laboratories (ARLs), which have advanced diagnostic facilities. In 2020, there were 695 SSHs and 16 ARLs that provide diagnostic services in our country. [6]

Virological methods: During first few days of an infection, virus might be isolated from blood. There are several reverse transcriptase polymerase chain reaction (RT–PCR) methods available. RT–PCR assays are generally sensitive but they need specialized equipment, and the technical training for those who perform the tests. So, they are not available always in all the medical facilities. RT–PCR products from the clinical samples can be used for virus genotyping, allowing comparisons with the virus samples from different geographical locations. The virus can also be identified by testing for NS-1 antigen, a virus-produced protein. i.e. non-structural protein. For this, rapid diagnostic tests (RDT) are commercially available, because it only takes about 20 minutes to determine result, and test doesn't require any specialized laboratory techniques, or equipment.

Serological methods: Serological tests, such as enzyme-linked immune sorbent assays (ELISA), can detect IgM, and IgG anti-dengue antibodies, confirming

presence of recent or the past infection. IgM antibodies are evident within 1 week after the infection and peak 2-4 weeks after illness onset. They are detectable for approximately 3 months. Presence of IgM indicates that you have recently been infected with DENV. Levels of IgG antibody take longer time to develop than the IgM antibody levels, but IgG antibodies remain in body for years. Presence of IgG indicates a previous infection.

CLINICAL MANAGEMENT

Guidelines for treatment: A Complete Blood Count (CBC) of patient must be completed at first visit. In early febrile phase, the haematocrit test determines the patient's own baseline haematocrit. A rapidly decreasing platelet count parallel to rising haematocrit compared to baseline indicates that the disease has progressed to plasma leakage or critical phase. Patient's body fluid volume must be maintained at all times during severe dengue treatment. Patients with dengue fever should seek medical attention as soon as warning signs appear. There is no definite treatment for dengue fever/DHF. Control of the Aedes aegypti mosquito is an only method of choice. Mortality can be significantly reduced with early detection, proper case management and the symptomatic treatment.

Acetaminophen or paracetamol are the most effective treatments for these symptoms. Avoid NSAIDs (nonsteroidal anti-inflammatory drugs) like ibuprofen and aspirin. These anti-inflammatory medications cause thinning of blood, and increase risk of haemorrhage.

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 reconstitution, 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 6 hours of opening/reconstitution or at end of vaccination session, whichever comes first. [33]

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 controlling 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 removing 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 exposure 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 Sensitilizing 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.

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. [36]

The 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.

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