

Emerging Therapy of Dengue

More Pranoti Sahebrao¹, Pallavi Jadhav²

^{1,2}Dept of Pharmacology

^{1,2}Peatibhatai Pawar College of Pharmacy, Shirampur.

I. INTRODUCTION

Dengue fever is the quickest rising arboviral contamination spore. Dengue has the most essential arboviral contamination world with extra than 30 million. Dengue fever estimated to happen every year. The dengue virus is the motive of dengue fever. Dengue viruses are arthropod its born viruses (arboviruses) in the genus *Flavivirus* [1]. (Family *flaviviridae*) with the fantastic polarity. Single-stranded RNA. is utilized *Aedes* (*stegomyia*) spp primarily. *Albopictus* as vector for domestic and peridomasti transmission. And arboreal *Aedes* vector for enzootic transmission of the flavivirus genus which includes different essential pathogens such as yellow fever. Dengue viruses are the causative agent of a dengue fever. Its genome is about 11000 bases that the codes for three structural proteins (Membrane protein M, capsid protein C, and envelope protein E) and seven nonstructural proteins it is additionally consisting of the brief non-coding region on each the 5' and three ends. The dengue virus genome is 11644 nucleotides in length, and is composed of three structural protein genes encoding the core protein (C), envelope protein (E), a membrane-associated protein (M), and seven nonstructural protein (NS) genes. Non-structural proteins is enveloped by way of glycoprotein, NS1 is of diagnostic and pathological importance. It is a forty five kDa in dimension and related with viral haemagglutination and neutralization endeavor [2, 3]. drug for dengue treatments, and prevention majorly depends on vector control. Therefore, dengue vaccine improvement is urgently required for dengue prevention.

Dengue is an acute febrile disease caused by a single-stranded RNA virus with 4 carefully associated however antigenically special serotypes: DEN-1, DEN-2, DEN-3 and DEN-4.1 It has end up a major health problem in both the tropics and subtropics, and is presently viewed to be the most vital human arboviral disease.2 According to the World Health Organization, about 2.5 billion humans (approximately half of the world's population) are presently at threat of dengue. Every year, about 50 million human beings are estimated to go through from dengue virus, with about 55,000 people requiring hospitalization, many of whom are children.3 At least 2.5% of these humans die, however the dying fee may

additionally be twice as excessive as this. Five sorts of dengue vaccines have

been under investigation, including stay attenuated vaccine, inactivated vaccine, recombinant subunit vaccine, viral vectored vaccine, and DNA vaccine [4]. They act primarily by growing the immune responses against dengue virus (DENV) E protein and non-structural protein 1 (NS1). Careful studies of the immune responses to DENV help to form an effective method for dengue vaccine development NS[5].

Pakistan, a united states characterised through its geographical and climatic diversity, is placed in the north-west of South Asia. It is located between latitudes 23.45 and 36.75 north and longitudes 61 and 75.5 east. Administratively, it consists of Punjab, Sindh, Khyber Pakhtunkhwa (KP), Balochistan, Gilgit-Baltistan and Azad Jammu and Kashmir. Due to its subtropical area and climatic suitability for vectors, Pakistan is confronted with problems associated with many vectorborne illnesses which include malaria, leishmaniasis, Crimean Congo haemorrhagic fever, dengue haemorrhagic fever, West Nile virus, Japanese encephalitis and scrub typhus. Dengue fever is pretty recent. It has prolonged its vary at some point of the remaining few years, ensuing in morbidity in the heaps of deaths due to issues of dengue haemorrhagic fever and dengue shock syndrome. Two principal challenges in dengue vaccine improvement have been discussed. Firstly, even though DENV antibodies exhibit shielding consequences in opposition to homotypic or heterotypic DENV infection, the ADE impact ensuing from a 2d heterotypic contamination majorly bills for DHF and DSS [6]. However, the immune response and pathogenesis of DHF and DSS are now not totally understood, which hinders DENV vaccine improvement [7]. Secondly, in vaccine development, we lack a with ease accessible, cheap, and touchy animal mannequin successful of simulating the immune responses in people after infection. Since mice are naturally resistant to DENV infection, human mobile phone chimeric mice and immune deficient mice touchy to DENV contamination are mounted to be used as animal fashions [18]. Nonhuman primates (NHPs) are tremendously possible animal fashions because they produce a comparable immune response to DENV contamination as humans, however they are normally used following mouse exams due to the fact of the costliness [8].

The spectrum of the dengue virus contamination encompasses asymptomatic types to extreme instances with shock, organ dysfunction and applicable bleeding. The suggestions proposed in this paper focal point on extreme dengue cases.[9]

Dengue fever (DF) and its extreme forms—dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS)—have turn out to be essential global public fitness concerns. Over the previous three decades, there has been a dramatic international expand in the frequency of dengue fever (DF), DHF and DSS and their epidemics, with a concomitant amplify in sickness incidence (Box 1). Dengue is located in tropical and subtropical areas round the world, predominantly in city and semi-urban areas. The ailment is precipitated by way of a virus belonging to household Flaviviradae that is unfold by means of *Aedes* (*Stegomyia*) mosquitoes. There is no unique therapy for dengue, however suitable scientific care often saves the lives of sufferers with the greater serious dengue haemorrhagic fever.[10]

According to the World Health Report 1996,1 the “re-emergence of infectious illnesses is a warning that growth done so a ways toward world safety in fitness and prosperity may additionally be wasted”. The document similarly indicated that: “infectious illnesses vary from these taking place in tropical areas (such as malaria and DHF, which are most frequent in creating countries) to ailments located international (such as hepatitis and sexually transmitted diseases, together with HIV/AIDS) and foodborne ailments that have an effect on massive numbers of human beings in each the richer and poorer nations.”

Dengue, the mosquito borne disease, transmitted via the bites of *Aedes* mosquitoes, chiefly *Aedes aegypti* and *Aedes albopictus*, is regarded the most ordinary human arboviral contamination global [11]. Approximately, 3.8 billion humans residing in 128 nations are perceived to be in chance of dengue infection. According to the WHO, each 12 months about 20,000 deaths came about on account of dengue globally [2,3]. The reason of dengue fever (DF) is the contamination with any one of the four serotypes (DENV-1, 2, 3, and 4) of dengue virus and the DF may additionally show up as deadly ailment characterized by way of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[12]

The first dengue virus contamination was once located in South-East Asia [6] and about 52% of the humans who are at danger of dengue globally stay in this section of the world. Bangladesh is located in South Asia and has turn out to be an splendid habitat for the dengue vector and its

transmission . In Bangladesh, the first dengue contagion used to be detected in 1964 [1]. The sporadic instances and small outbreaks clinically recommend that the dengue passed off throughout the usa from 1964 to 1999 however these have been no longer formally suggested [8,9]. In the 12 months 2000, a extreme outbreak of dengue happened in Bangladesh with ninety three mortality amongst 5551 morbidity instances [10]. In subsequent years dengue instances decreased remarkably to as low as 375 instances in 2014. However, in 2016, round 6100 dengue instances have been pronounced with a DENV-2 outbreak in Bangladesh [11]. Three years later, in 2019, Bangladesh skilled easiest annual dengue incidence ever stated with 1,12,000 instances and 129 deaths .

Dengue virus (DENV) is the most essential mosquito-borne viral pathogen worldwide. Each year, an estimated 400 million human beings are contaminated main to approximately 25 zero deaths [1]. Within the closing decades, the virus has drastically re-emerged inflicting giant outbreaks in Africa, South-east Asia, the Americas and even some components of Europe [2,3]. To date, the virus is endemic in greater than 100 nations global [1]. In endemic countries, most DENV instances are mentioned in kiddies and younger children. Given the excessive disorder burden and the lack of a broadly applicable vaccine, there is an pressing want for an effective antiviral compound to deal with DENV

This assessment will supply describe the present day popularity and challenges of antiviral improvement closer to DENV. The chapters are divided on the groundwork of direct-acting anti virals and host-directed antivirals and the lessons learned and challenges in advance of us.

The profitable participation largely relies upon on peoples’ knowledge, awareness and mind-set towards this ailment [14]. Effective dengue prevention and control is an vital concern these days in Bangladesh as there is an ongoing challenge to make sure proper remedy and prevention options regardless of having continued development in dengue research during the world [18,19]. Therefore, the objective of this learn about was to examine nationwide people’s knowledge, attitude and practices (KAP) on dengue.

We discuss the cognizance of dengue in Bangladesh and discover future disorder risk. Lacking prevention practices and therapy of the disorder are additionally considered, with a center of attention on populace density, human conduct and socio-demographic context.

Newly generated genomic RNA is packaged with the aid of more than one copies of the C protein and the nucleocapsid then buds into the endoplasmic reticulum (ER)

lumen to shape an enveloped immature virion. From there, virions are transported through the secretory pathway the place the E and M proteins endure post-translational adjustments and conformational changes, which includes the cleavage of pre-cursor M to its mature shape by using the host mobile protease furin. Progeny virus launch happens with the aid of exocytosis.

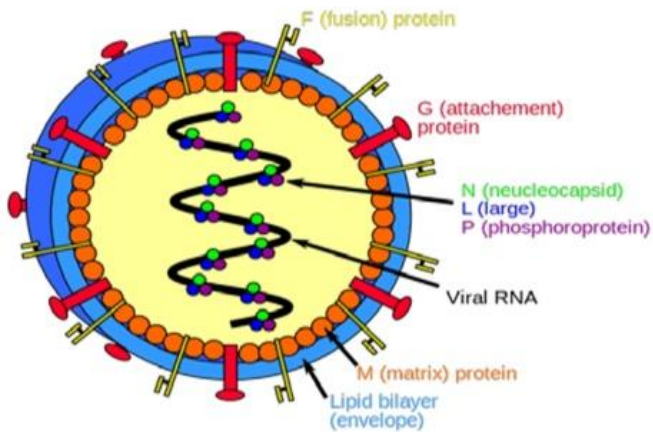


Fig. 1: Dengue virus

Two predominant challenges in dengue vaccine improvement have been discussed. Firstly, even though DENV antibodies exhibit defensive outcomes towards homotypic or heterotypic DENV infection, the ADE impact ensuing from a 2nd heterotypic contamination majorly debts for DHF and DSS [14–16]. However, the immune response and pathogenesis of DHF and DSS are no longer wholly understood, which hinders DENV vaccine improvement [17]. Secondly, in vaccine development, we lack a readily accessible, cheap, and touchy animal mannequin successful of simulating the immune responses in human beings after infection. Since mice are naturally resistant to DENV infection, human mobile phone chimeric mice and immune deficient mice touchy to DENV contamination are installed to be used as animal fashions [18]. Nonhuman primates (NHPs) are pretty possible animal fashions due to the fact they produce a comparable immune response to DENV contamination as humans, however they are commonly used following mouse exams due to the fact of the costliness [19]. two Live Attenuated Vacc.

History :

In the 18th century, dengue has brought about repeated epidemics international [2]. H. Graham in 1903 implicated *Aedesaegypti* as the vector for the ailment and the virus was once remoted in 1944 via Albert Sabin et al. Dengue haemorrhagic fever received nosologic reputation in 1954 and in consequence its grew to become

a endemic in many areas of tropical Asia. India belongs to class B, the place dengue is an rising ailment with cyclical epidemics turning into greater prevalent.[1,2]

Dengue fever :

Dengue fever (DF) and its severe types dengue hemorrhagic fevers (DHF) and dengue shock syndromes (DSS) have develop to be vital global public health concerns. Dengue is the most hooked up arthropod-borne viral illness in humans, with the half of the world populace at chance for illness and up to 50 million cases of dengue estimated each year. Dengue fever is moreover diagnosed as spoil bone fever is a mosquito borne tropical sickness it's precipitated with the useful resource of the dengue viruses. The dengue has transmitted by means of the pretty a few species of mosquito the genus is *Aedes*, The virus has 5 one-of-a-kind types, and normally it presents long-life immunity to that sort on the other hand fully non everlasting immunity to the one of a kind subsequent infection with a one-of-a-kind kinds .

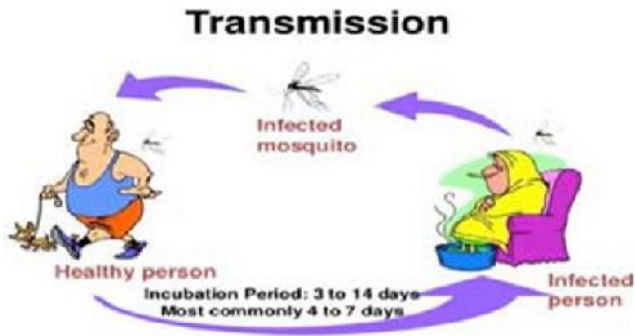


Cause: It is induced by using a virus (Dengue Virus), which has bought 4 exceptional kinds (Type I, II, III, IV). Common title of the ailment is 'break-bone fever'"(Haddi Tod Bukhar)" due to the fact of extreme physique and joint pains produced.[1]

Spread :

The Dengue virus is existing in the blood of the patient. Suffering from Dengue fever. Whenever an aedesmosquitoes bites a patient of dengue fever, it sucks blood and, the dengue virus is enters into its body. The virus undergoes similarly improvement of in the physique of the mosquito for a few days. When the virus

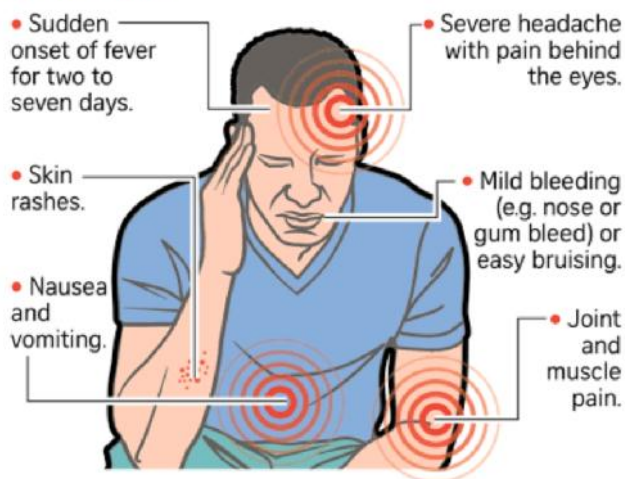
containing mosquito bites a everyday human being (Healthy person), the virus is injected into the Healthy character physique and he/she turns into contaminated and can boost the signs and symptoms of dengue fever.[1]



Symptoms :

- Severe Headache, Pains in muscle mass and joints.
- Pain at the back of the eyeballs mainly on urgent the eyes or on transferring the eyeballs.
- Sudden onset of excessive fever with feeling of chills (“Thandi Lagna”).
- Loss of appetite, feeling of nausea.
- Change in style sensations in mouth.
- Mild ache in throat. Rash on the pores and skin

SYMPTOMS



Dengue warning signs:

Dengue warning symptoms Warning signs and symptoms
No warning signs and symptoms Severe dengue.
1. Severe plasma transudation 2. Hemorrhage three 3
3.Organ dysfunction

Critical for dengue and warning signs

- 1) Probable dengue. Live or day trip to endemic area. Fever and 2 of the below criteria:
 - Nausea, vomiting.
 - Exanthema
 - Pain (myalgia, retro-orbital).
 - Capillary fragility test.
 - Leukopenia.
 - Any warning signal
- 2) Warning signs
 - Abdominal ache.
 - Persistent vomiting
 - Fluid accumulation.
 - Mucosal bleeding.
 - Lethargy, weak spot.
 - Sudden temperature drop.
 - >2 cm hepatomegaly
 - Laboratory tests: extended HT% concomitant with platelet drop Critical for several. Several plasma transudation
 - Shock
 - Fluid gathering with respiratory exertion

1) Hemorrhage

As assessed by the escalated care doctor



In this evolutionary form, there is widespread plasma leakage, which leads to shock and/or respiratory failure. Additionally, there can be clinically giant bleeding as regarded by using the attending physician, and/or development to organ dysfunction. analysis of dengue, with extra than 70% positivity on the seventh day from the commencing of symptoms, and a hundred percent positivity from the tenth day on.

Dengue vector :

Reports of Dengue vector in the region predate creation of Pakistan. In 1934, Barraud collected *A. aegypti*, the most important vector of dengue, from Peshawar, Dera Ismail Khan, Lahore, Larkana and Karachi [13]. In 1949, Qutubuddin reported *A. aegypti* from Kohat-Hangu valley in northern Pakistan [14]. The distribution of *A. aegypti* lowered notably after 1950 as a byproduct of a malaria vector eradication programme [15]. Dengue lower back in two episodes in Pakistan: one in the south in the Nineteen Eighties and one in the north in 1993. In the southern metropolis of Karachi, *A. aegypti* was once pronounced in a survey carried out in 1983 to decide the species of mosquitoes performing as vectors of distinctive diseases [16]. However, at that time, the distribution of *A. aegypti* was once restricted to the port metropolis of Karachi, and it was once now not accumulated from the neighbouring district of Thatta.

The 2nd re-emergence of *A. aegypti* befell in Landi Kotal, a border city of Khyber Agency positioned forty km from Peshawar and 10 km from the Afghan border. In 1993, there have been reviews of a high stage of uncommon diurnal human-biting mosquitoes in this area. A survey used to be carried out by means of a crew of entomologists from Peshawar University led with the aid of Dr Suleman. On surveying the area, *A. aegypti* mosquitoes had been amassed in person and immature forms. The mosquito used to be breeding in tyres stored in warehouses [15] and this was the first time that the unfold of this mosquito was once related with the tyre change in Pakistan.

In 2000, all 5 districts of Karachi were resurveyed for the presence of *A. aegypti*, and it was collected from all districts, indicating an increase in its distribution [17]. In some other survey of the district of Karachi in 2010, the presence of the vector mosquito was confirmed from all 18 towns of Karachi [18]. It is therefore clear that in spite of the eradication of this vector mosquito due to the malaria control programme in the 1950s [15], *A. aegypti* has re-established itself in Pakistan associated with the tyre trade. It is important to examine the link between the tyre exchange and the spread of the vector in more detail. This question will be examined elsewhere the use of genetic markers.

Dengue disease :

It is feasible that dengue virus may also have been endemic in Pakistan, and due to a lack of surveillance and diagnosis, no outbreaks have been stated till 1994. However, in accordance to a sero-epidemiological learn about carried out in the Sixties and the 1980s, full-size proportions of the

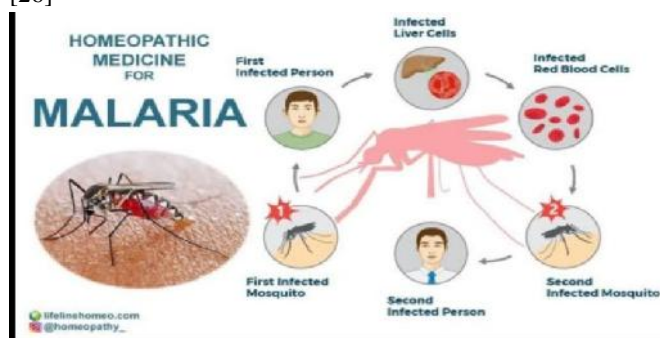
curiously healthful populace in Rawalpindi and Peshawar [19,20]. components of Punjab [21,22]. and Karachi [23]. examined nice for neutralization and haemagglutination inhibition antibodies for dengue virus. In every other find out about carried out between 1983 and 1985 on the occurrence of West Nile virus, Japanese encephalitis and dengue in the city of Karachi, 65% of the complete populace aged between 6 and sixty five years confirmed fantastic consequences for haemagglutination inhibition (HI) antibodies in opposition to one or extra of the three flaviviruses.

The first outbreak of dengue in Pakistan began in August 1994 and persisted thru November 1994 in Karachi, main to morbidity in the thousands. Epidemiological facts for this epidemic have been no longer recorded but the number of patients seen by physicians was in the thousands. There is no ideal estimate of the range of deadly cases, however at least two deaths came about in distinctive hospitals in Karachi [24].

A few unbiased small research had been performed to confirm this outbreak as dengue. In most of the investigations, the presence of dengue kind 1 and dengue kind two used to be tested by using detecting immune globulin M (IgM) the usage of an enzyme-linked immune sorbent assay (ELISA). These investigations were made on adults as well as children [24,25]. In one of the studies, Chan et al. used semi-nested polymerase chain response (PCR) to become aware of dengue virus in the sera of patients, and additionally isolated dengue kind 1 and kind two from these sera [20]. This used to be the solely learn about in which a molecular method used to be used and the virus used to be removed from the sera [24]. of contaminated patients. As such, there is restrained grasp of the extent and nature of this first epidemic.

One reason for the 1994 and 1995 outbreaks may have been the introduction of any other serotype of dengue virus to the population. Only serotype two used to be proven by means of Sugamata et al. in 1987 [7] but serotype 1 was also detected in the patients in the 1990s. The presence of a couple of serotypes in a populace consequences in improved danger of antibody-dependent enhancement; a phenomenon in which the heterotypic antibodies from a previous dengue serotype infection result in promotion of viral replication inside the mononuclear leukocytes for the duration of secondary contamination of a special serotype [26]. It used to be at the beginning counseled by using S.B. Halstead in the Nineteen Seventies that dengue haemorrhagic fever is extra possibly to manifest in sufferers who have formerly been uncovered to dengue infection. The 1994 and 1995 outbreaks of dengue resulted in sickness in heaps of people, however no serious steps had been taken to forestall future epidemics. In

particular, no guidelines have been carried out to quarantine human beings coming from special dengue endemic areas, and the tyre exchange used to be now not monitored After a spoil of 10 years, any other serotype (serotype 3) of dengue virus was once said in Pakistan in 2005. During the intervening period, there have been no foremost outbreaks of dengue, even though instances have been nonetheless present. According to the National Institute of Health Islamabad, about 395 instances [26]



Control of Dengue :

Most of the disorder manipulate effort has been made to deal with dengue-infected human beings as quickly as possible, and consequently to decrease the range of deaths. However, no or very little effort has been made to stop or reduce the number of infected cases via vector breeding control. In all of the affected cities, solely thermal fumigation with delta methrine is carried out to kill grownup mosquitoes. Better manage might also be executed thru three essential routes: chemical control, organic manipulate and education. In phrases of chemical control, a aggregate of larvicide and fumigation with adult knock down effects has the potential to reduce the mosquito population. Chemical control is rapid and efficient, however its dangers encompass resistance to pesticides in mosquitoes[28]. However, it works properly in the case of *A. aegypti* when there is no rain.

aegypti when there is no rain. In phrases of organic control, small fish such as *Gambusiaaffinis* and *Tilapia* could be launched in water tanks, which may want to assist to limit mosquitoes by using consuming the larvae that are produced in the tanks. Biological manipulate is gradual but ought to show to be a accurate technique to manage mosquito populace growth. Finally, species of mosquito that breed in man-made containers are often aimed to decrease the variety of larval habitats (control with the aid of supply reduction). Such a approach will now not be profitable barring the involvement of the neighborhood community.



Overall characteristics:

Febrile phase :

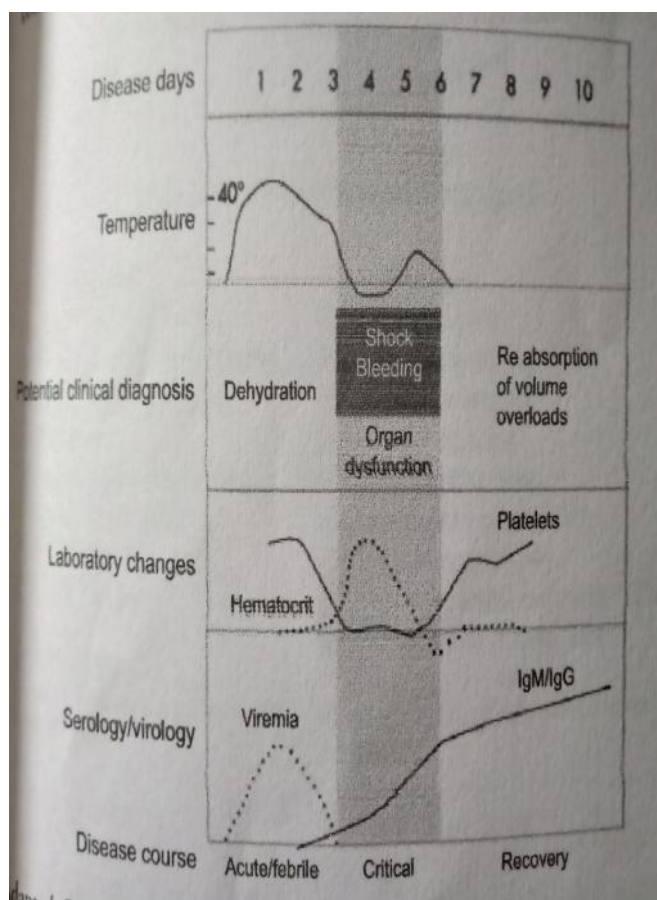
The signs encompass fever, myalgia, headache, arthralgia and exanthema, and it is often indistinguishable from different acute febrile diseases. Mild bleeding manifestations can appear as bleeding of the gums and epistaxis. The attention of development to extreme types may also be tough at some point of this phase. To decide whether or not development to greater extreme varieties of the disorder has occurred, the warning signs and symptoms need to be discovered (Figure 2). Duration of this section is typically 2-7 days.[29,39].

Critical or deferve scence:

This segment is characterized by way of clinical and laboratorial proof of endothelial cell dysfunction prompted by the viral infection, ensuing in increased capillary permeability and plasma leakage to the extra vascular space. This segment is marked by surprising deferve scence, circulatory and perfusion changes (hypotension and hypovolemic shock), serosal effusions (pleural and ascites) and organ dysfunctions, such as liver failure, encephalitis, myocarditis and clotting disorders. Progressive leukopenia and surprising platelet count drop precedes plasma leakage, and the revolutionary hematocrit increase mirrors the magnitude of the quantity lost to the extra vascular compartment. However, it ought to be noted that extreme organ dysfunctions might be present, inclusive of hepatitis, encephalitis, my ocarditis and clinically significant bleedings, in the absence of medical signs of plasma leakage. The vital phase, which is evident in 10-15% of dengue cases, discloses the progression to extreme disease. The duration of this segment is 1-3 days.[29,30]

Recovery phase :

This section is characterized through progressive enhancement of endothelial function with gradual fluid resorption from the extra vascular space, hematocrit stabilization and innovative platelet recovery. A rash may exist as “white islands in a red sea”, alongside with pruritus and bradycardia. During this phase, due to the progressive recuperation of the endothelial function, fluid administration (and eventually diuretics) need to be prescribed with caution to forestall volume overload, congestive coronary heart failure and perpetuation of respiratory failure and serous effusions. The duration of this segment is 1-3 days.[29,30].



II. CONCLUSIONS

Dengue is rising as a global deal with and is an urgent public health precedence in many countries. The authorities and the pharmaceutical industries have been taking initiative to increase new techniques to enhance the prognosis and remedy of dengue. The project right here lies in how correctly the techniques developed are put into use. There additionally an obligatory want to globalize focus and precautionary measures amongst the hundreds in order to manipulate the incidence. Combined efforts of the

fitness care industries, governing our bodies and efforts at man or woman stage would assist us to handle the occurrence of dengue.

REFERENCES

- [1] IA Zybert, Rodenhuis, J Wilschut, JM Smit."Dengue virus life cycle: viral PMID 20372965; 2010.
- [2] Kuldeep Singh, Pragati Shakya. Prevention and control of dengue by herbal remedies. *J Chem Pharm Res* 2016;8:708-13.
- [3] DJ Gubler. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. *Trends Microbiol* 2002;10:100–3.
- [4] Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev* 1998;11:480e96.
- [5] Arunachalam N, Tewari SC, Theosophy V, Rajendran R, Paramasivan R, Manavalan R, et al. Natural vertical transmission of dengue viruses by *Aedes aegypti* in Chennai, Tamil Nadu, India. *Indian J Med Res* 2008;127:395e7.
- [6] World Health Organization. Prevention and control of dengue and dengue hemorrhagic fever-comprehensive guidelines. New Delhi: WHO Regional Office for South-East Asia; 1999.
- [7] World Health Organization. Dengue and dengue haemorrhagic fever. Geneva: WHO; 2008.
- [8] Sugamata M, Ahmed A, Kono R, Takasu T. studies of infections with Japanese encephalitis, West Nile and dengue viruses in Karachi-Pakistan in the year 1985: a neuroviro-patho-epidemiology-entomological study. Karachi encephalitis survey team secretarial, 2nd official report. Karachi: Karachi Encephalitis Survey Team Secretariat; 1987. p. 22e26.
- [9] Teixeira MG, Costa MCN, Barreto F, Barreto ML. Dengue: twenty-five years since reemergence in Brazil. *Cad Saude Pública = Rep Public Health*. 2009;25(Supl 1):S7-18. Guzmán MG, Kourí G. Dengue: an update. *Lancet Infect Dis*. 2002;2(1):33-42.
- [10] World Health Organization. Prevention and control of dengue and dengue hemorrhagic fever-comprehensive guidelines. New Delhi: WHO Regional Office for South-East Asia; 1999.
- [11] World Health Organization. Dengue and dengue haemorrhagic fever. Geneva: WHO; 2008.
- [12] Jahan F: Dengue Fever (DF) in Pakistan. *Asia Pac Fam Med* 2011, 10:1.
- [13] Barraud PJ. The fauna of British India, including Ceylon and Burma. Diptera. Family Culicidae. Tribe Megarhinini and Culicinae. London: Taylor and Francis; 1934.
- [14] Qutubuddin M. The mosquito fauna of Kohat-Hangu valley, West Pakistan. *Mosq News* 1960;20:355e61.

- [15] Suleman M, Arshad M, Khan K. Yellow fever mosquito (Diptera: Culicidae) introduced into Landi Kotal, Pakistan, by tire importation. *J Med Entomol* 1996;33:689e93.
- [16] Kamimura K, Takasu T, Ahmed A. A survey of mosquitoes in Karachi area, Pakistan. *J Pak Med Assoc* 1986;36:182e8.
- [17] Tariq RM, Zafar SMN. Why the population of dengue vector mosquitoes is increasing day-by-day in Karachi and other areas of Sindh, Pakistan? *Pak J Entomol* 2000;15:7e10.
- [18] Tariq RM, Ahmed I, Qadri SS. Population dynamics and mechanical control of dengue vector mosquitoes *Aedes aegypti* and *Aedes unilineatus* in seven towns of Karachi. *Pak J Entomol* 2010;25:21e6.
- [19] Burney MI. A report on the role of arthropod-borne viruses in human diseases in Rawalpindi and Peshawar areas. I. *Pak J Med Res* 1966;5:215e25.
- [20] Burney MI, Munir AH. Role of arthropod-borne viruses in human diseases in Rawalpindi and Peshawar areas. II. Isolation of West Nile virus from human blood and culicine mosquitoes in Rawalpindi area. *Pak J Med Res* 1966;5: 271e84.
- [21] Hayes CG, Baqar S, Ahmed T, Chowdhry MA, Reisen WK. West Nile virus in Pakistan I. Sero-epidemiological studies in Punjab province. *Trans R Soc Tropic Med Hyg* 1982;76:431e6.
- [22] Hayes CC, Burney MI. Arboviruses of public health importance in Pakistan. *J Pak Med Assoc* 1981;31:16e26.
- [23] Sugamata M, Khono R, Ahmed A, Takasu T. Seroepidemiological research on viral encephalitis in Karachi, Pakistan. Preliminary report. *J Pak Med Assoc* 1986;36:177e82.
- [24] Chan YC, Salahuddin NI, Khan J, Tan HC, Seah CL, Li J, et al. Dengue hemorrhagic fever outbreak in Karachi, Pakistan. *Trans R Soc Tropic Med Hyg* 1994;1995(89):619e20.
- [25] Qureshi JA, Notta NJ, Salahuddin N, Zaman V, Khan JA. An epidemic of dengue fever in Karachi. Associated clinical manifestations. *J Pak Med Assoc* 1997;47:178e81.
- [26] Cummings DAT, Schwartz IB, Billings L, Schaw LB, Burke DS. Dynamic effects of antibody-dependent enhancement on the fitness of viruses. *Proc Natl Acad Sci U SA* 2005;102:15259e64.
- [27] Halstead SB. In vivo enhancement of dengue virus infection in rhesus monkeys by passively transferred antibody. *J Infect Dis* 1979;140:527e33.
- [28] Kaunter I, Robinson MJ, Kuhnle U. Dengue virus infection: epidemiology, pathogenesis, clinical presentation, diagnosis and prevention. *J Pediatr* 1997;131:516e24.
- [29] diagnosis, treatment, prevention and control [Internet]. New edition. Geneva: WHO; 2009. [cited 2011 Mar 1]. Available from: http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf
- [30] Organización Panamericana de La Salud. Dengue: guías de atención para enfermos en la región de las Américas [Internet]. La Paz: OPS/OMS; 2010. [citado 2011 Mar 1]. Disponible en: <http://www.ops.org.bo/textocompleto/ndeng31482.pdf>