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# Dengue – Changing Trends and the Need for Research.

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**ABSTRACT**

The potential threat of the dangerous re-emerging arboviral infection, Dengue is now recognized worldwide, with billions of people at risk. It is more prevalent in tropical and subtropical countries. The pattern of Dengue infection, its pathogenesis, risk factors and the clinical presentations are undergoing constant changes every now and then. There are changes in the survival, susceptibility to human and adaptability to climatic variations in the Aedes mosquito which is the vector involved in the transmission of the Dengue infection. This review article shows light into the changing patterns of Dengue infection and the various factors influencing such changes. Well planned research with clear objectives may help in Dengue control and prevention.

**Keywords**: Dengue, virus, Aedes mosquito

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## INTRODUCTION

Dengue fever is one of the reemerging mosquitos borne arbo viral infection. Dengue virus is the causative agent of this disease. This infection is endemic in South East Asia and Southern parts of Asia. Dengue fever and its dangerous complications, Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS) are spreading worldwide which may even cause death. Every year, approximately 50 million Dengue infections occur with more than 20000 deaths globally [1]. More than 70% cases of Dengue reside in Asian countries [2]. Hence, it has become a disease of public health importance.

Dengue infection is caused by a virus belonging to Flaviviridae family. Four serotypes namely DENV-1, DENV-2, DENV-3 and DENV-4 are known to cause the infection. All the serotypes are found worldwide, maintaining hyperendemicity [3]. Infection caused by one serotype provides lifelong immunity to that serotype only. Temporary cross immunity to the other serotypes is also observed. Secondary infection by another serotype may lead to Dengue complications like DHF. *Aedes aegypti* mosquito is the vector involved in the transmission of the Dengue virus. It is predominantly found in urban areas, usually feeds during day time, preferably early morning. *Aedes albopictus* is another vector involved. Dengue virus attacks mostly the circulatory system [4], causing more damage on the platelets. The disease usually presents as acute febrile illness, low platelet count and bleeding manifestations (4). No specific treatment is available for Dengue fever. Symptomatic treatment is recommended. Vaccines for the prevention of this infection are still under trial [5,6].

### Causes of Outbreaks

Several outbreaks of Dengue occur every year. The various causes anticipated for this include the viral etiology and no specific antiviral treatment available, transmission by mosquito which is difficult to control, low infective dose required for human infection, suitable climatic conditions, poor sanitation system, under diagnosis of the cases and few patients not fully treated continue spreading the infection.

### Clinical Presentations

Usually Dengue clinically presents with acute febrile illness, ranging from a mild fever to high grade fever with arthralgia, retro orbital pain, etc. Very rarely, it may even cause death. DHF and DSS are the life threatening complications of Dengue. DHF can cause hemorrhagic complications with decrease in platelet count and plasma leakage. DSS can even cause circulatory failure. But, sometimes there can be unusual presentations also [4]. This can cause difficulties in diagnosis. Also, the severity of the infection varies with different outbreaks.

### Pathogenesis of Dengue

The pathogenesis of DHF and DSS may involve both innate and acquired immunity. Both procoagulant and anticoagulant systems are activated simultaneously. The degree and the time at which each system is activated will determine the severity of the disease.

Various cytokines are involved in the pathogenesis of Dengue infection. The cytokine response may be associated with the cross recognition of the specific T cells. The cross reactive T cells cause increase in cytokine production. TNF- α has been found to be implicated in some of the hemorrhagic manifestations of Dengue fever in animal models [7]. The Dengue virus is found to be capable of activating many immune systems.

DHF may occur because of increased vascular permeability leading to vascular leak. The leakage occurs mostly in the pleural and peritoneal cavities. This will cause decrease in intravascular volume leading to shock. Usually there occurs, changes in the vascular integrity leading to rapid recovery from the shock. Rarely, in severe cases, this may lead to even death. During a secondary infection, sometimes the immune activation is more, leading to exaggerated cytokine response, changing the vascular permeability. The vascular permeability may also be regulated by some viral products like NS-1 [7,8]. Many studies have shown that the viral load and the NS-1 viral protein are found to be more in DHF patients than DF patients [9]. This shows that the viral load determines the severity of the infection. But the exact immune pathogenic mechanism of such activations is yet to be studied completely.

**Epidemiological Changes**

The Epidemiology of DF and DHF involves the human, virus and the mosquito which remains complex. Various social, economic and demographic factors are involved. Controversies have risen against the widely accepted epidemiological characteristics of Dengue fever.[10]. Dengue is no longer a infection of childhood, but has affected many adults of age 25-34 years [11]. Dengue occurs not only in tropical countries, but also in non tropical countries. New emerging Dengue is being reported from places, where it has never been existed so far. Further in depth studies on the changing pattern, cyclical epidemics and the epidemiology of Dengue infection is recommended.

**Changes in the Human Host**

In those days, the DF was typically found to occur in children, with adult infections being very rare. DHF and DSS were found to occur commonly in age group of 2-15 years. But, in the recent years, the incidence of Dengue infection in adult age groups is found to be increasing [11-14]. A study from Singapore by Yik Weng Yew *et al* has reported 17.2% cases of Dengue in adults between 18-24 years [15]. In Thailand, DHF cases have been reported even in infants [16]. In 1981, in Cuba, the outbreak of DF and DHF was found in both children and adults.

Many studies from asian countries have reported that the occurrence of DF and DHF were found to be more in males than females [17]. This could be due to the fact that men easily access health care facilities than females. Few studies done in South America reported no difference or the incidence was more in females [18]. Yaw *et al* from Singapore also reported no difference [19]. But most of the studies were hospital based which may not indicate the exact prevalence of the disease. A study by Shekar *et al* has shown that there is increase in mortality rate in females than males [20]. Further explorative studies in determining the sex difference is needed in order to understand the cause of such

difference and whether the immune response and the pathogenesis of Dengue infection is different in both sexes are not.

**Changes in Dengue Virus**

The severity of the Dengue infection depends on the sequential or secondary infection by another serotype of the virus. Various studies from Thailand have shown that the risk of Dengue infection increases to 500 fold if the infection is due to DENV-1 followed by secondary DENV-2 and the risk is 150 fold if DENV-3 followed by DENV-2 and it is only 50 fold risk of infection if due to DENV-4 followed by DENV-2 [21]. Another study by Messer *et al,* has reported that the genotypic changes in the virus may lead to DHF [22]. Sometimes, when the control measures are successful, it may lead to non immune children where Dengue infections if occur would even become severe.

**Changes in the Mosquito Vector**

Mosquito vector is needed for transmitting this infection [23]. Areas where water storage is done and where the waste disposal systems are inadequate are the favourite habitat of the vector. The Aedes mosquito is found to be more prevalent in urban environment. But now the disease has spread even to rural areas. Modern transport systems connecting rural to urban areas, water supply and storage system and solid waste disposal systems being introduced in rural areas are few of the causes which could have influenced in spread of the infection to rural areas [24]. The Socio economic status also plays a vital role in the incidence of the infection. Lower socio economic group people are at more risk of acquiring the disease. Breeding of the vector is more in stored water containers and it can maintain its life cycle there. Some studies have shown that the incidence of the infection is more in work places than the residential areas [25]. The incidence of Dengue infection is more in rainy seasons. Promprou *et al* have reported that climatic factors influence the incidence of DHF to a greater extent [26]. Studies have said that *Aedes aegypti* is a hygrophilic species. It is adapted to micro climatic conditions and is independent of macro climatic conditions. During the rainy seasons, the humidity increases as the temperature falls and this well suits the adaptation of this vector. Some studies have shown that there could be an association between the mosquito breeding site and increased infestations in the surrounding areas [27]. Further studies on the behavioural pattern of the vector and their influence on the occurrence of Dengue are recommended.

## CONCLUSION

Dengue has become one of the important public health threats. Measures to control and prevent this infection are of utmost importance today. However it is important to recognise the factors involved in the changing patterns of Dengue infection because these are the challenges which will be faced in planning any research in this field to prevent the dreadful infection. Studies on viral genotypes, vector ecology on different climatic conditions, viral load injected by the vector, time interval of infection influencing the severity of the disease and the immunity of the human are needed. Indepth research is recommended as Dengue has become global threat to the humanity. Urgent preventive and control measures are needed to save the people from this dangerous infection.

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