

Dengue a Worldwide Threat: Need to be Ceased with Systematic Scientific Measures to Stop its Fast Desolation Throughout the World

Muhammad Ibrahim^{*1,2}, Syeda Safia Hashmi², Syed Salman³, Syeda Jawariya Hashmi⁴, Syeda Asma Taskeen⁵, Muskan Shabbir⁶, Immad Khan⁷ and Muhammad Shabbir Ahmad⁸

¹Department of Biosciences, COMSATS University Islamabad, Pakistan, ²Department of Chemistry, Islamia College University Peshawar, Pakistan, ³Department of Chemistry and Biology “A. Zambelli” University of Salerno, Italy, ⁴Department of Botany Frontier College for Women Peshawar, Pakistan, ⁵Department of Botany, Islamia College University Peshawar, Pakistan, ⁶Department of Pathology University of Veterinary and Animal sciences (UVAS), Lahore Pakistan, ^{7,8}Institute of Chemical Sciences, University of Peshawar, Pakistan.

ABSTRACT

Dengue virus belongs to family Flaviviridae and genus Flavivirus, transmitted primarily in a cycle through human beings and mosquito vector. The rate of incidence of dengue fever epidemics has reached to the highest, since past few years. Over a geologically expanding area, the level of hyperendemic transmission has been established. The person with sequential dengue infection is also victim of dengue hemorrhagic fever (DHF) which is the most severe disease. The rate of incidence of DHF and the possibility of sequential infections, has increased intensely, first of all in Asian countries and currently in America. The wide spreading of mosquito *Aedes aegypti* is even more alarming. As a consequence of insufficiency of antiviral drugs and potential vaccine, a large number of individuals are infected with severe dengue virus every year which causes huge death cases.

Conclusion: Presently, to prevent epidemics, controlling the dengue mosquito is the only available method. New investigation for discovery of potential vaccine, evaluation of vector control tools and approaches are desirable.

Keywords: Dengue virus, *Aedes aegypti*, Dengue hemorrhagic fever, vaccine.

Introduction

Dengue is a mosquito-borne single stranded RNA virus (40-60 nm in size) in the genus Flavivirus and family Flaviviridae, responsible for causing fever and dengue hemorrhagic fever (DHF), both are universally severe diseases.¹ The total four antigenically different serotypes of the virus have been found i.e. DENV1, DENV2, DENV3, and DENV4 which are liable for causing the full spectrum of infection.² The more severe infection leads to DHF, which can be life threatening. There are numerous viral and host factors that have been linked with the severity of dengue infections. Generally, the secondary dengue infection is profoundly associated with DHF as compare to primary infections.³

Generally, dengue virus has a single-stranded having a diameter of 50 nm. It has a, positive-sense RNA genome and a globular shape, about 11 kb programming three structural proteins i.e. envelope, capsid, and a membrane and seven non-structural proteins i.e. NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. For virion assembly, virus replication and evasion of the host immune response, the non-structural proteins are prime essential.⁴ Genetically linked all types of dengue virus from DENV1 to DENV4 occur in nature that belong to the genus Flavivirus and family Flaviviridae. Each of them is further classified into various genotypes according to their nucleotide order. Presently, DENV1 consists of five genotypes (I) Southeast Asia, East Africa, China, Thailand; Sylvatic (Malaysia), Australia, and Western Pacific islands, America, West America, and Asia.²

The main symptoms of dengue virus infection are headache, high-grade fever, myalgia, severe pain in joints and muscle or retro-orbital pain. About 50-100 million dengue cases have been reported so far caused dengue vector in approximately 100 common countries including America, South-East Asia, Pacific Asia;

CORRESPONDENCE AUTHOR

Muhammad Ibrahim

Department of Biosciences,

COMSATS University Islamabad

Email: ibrahimattallah2347@gmail.com

however, countries in South Asia, including India, Bangladesh and most recently in Pakistan.⁵ In the year of 1994, the first dengue epidemic was reported in Pakistan. Later then, in different age groups, epidemics of dengue infection have been documented from various region of Pakistan. In the year of 2011 major dengue epidemic in Lahore, Peshawar, Islamabad and Multan, affected thousands of people and resulted hundreds of deaths. Some deaths raised due to morbidities that is, diabetes and absence of current awareness among the physicians for its supervision.

Mode of Transmission

Dengue fever is found to be widespread mosquito-borne infection around the world. Universal visitors having dengue virus infection are the common means of virus transmission from one destination to another. Dengue virus is a vector-borne pathogen that is transferred by interaction amongst vectors and hosts. Dengue, the most severe universal viral pathogen that has established itself around the world in endemic and epidemic transmission cycles.⁶ In human population, Dengue virus infection is normally unapparent but can cause clinical manifestations in a wide range, from a minor fever to hypothetically serious dengue shock disorder. *Aedes. aegypti* and *Aedes. Albopictus* mosquitoes are the main vector of dengue viruses. Through the bites of infected female mosquitoes, the virus gets transmitted to human population with the incubation period of 8 to 12 days.⁷ *Aedes aegypti* and *Aedes albopictus* mosquitoes play an important role in the dispersion of dengue viral infection, mainly in tropical and subtropical districts of the whole world. The vertical transmission of the dengue virus in populations of *Aedes aegypti* and *Aedes albopictus* is found to be of great significance.⁸ By the symptoms of virus in fetal tissue, newborn serum, and placenta of pregnant women, the regular spread of dengue virus is certified.⁹

Male *Aedes albopictus* mosquitos were infected experimentally with dengue virus types 1, 2, 3, and 4 that transferred their infection sexually to female *Aedes Albopictus* mosquito. Such conduction was enhanced if the *Aedes aegypti* mosquito had occupied a blood meal II to VII days earlier to coupling. Male *Aedes albopictus* also spread dengue virus steeply to their female offspring. Interestingly it was also reported that male mosquitoes acquired their infection vertically as they are infected naturally with dengue virus.¹⁰ Transovarial transmission of all four types of

dengue serotypes was verified in *Aedes albopictus* mosquitoes. Overall, the supreme rates of causing infection were detected with strains of dengue type 1 and the lowermost with dengue type 3.¹¹

Mechanism of Pathogenesis of Dengue Virus

Although dengue is an ancient disease but recently an unexpected increase was seen in different geographical range, laterally with the severity of infection. The *Aedes Aegypti* mosquito inserts the virus into the blood stream after feeding on human being and spread infection all over the body. The virus primarily targets the immature Langerhans cells and keratinocytes. The infectious cells move towards lymph nodes, and attacks monocytes and macrophages. Thereby, the virus replicates and moves towards many parts of the body through the lymphatic system. The viral occurrence in the blood stream is known as viremia. those results infecting many other cells including blood-derived monocytes cells.¹² Both Macrophages and lymphocytes are mainly infected with the virus. Within two to six days of infection, viremia appears. As compared to DF patients, the level of viremia is found to be high in DHF patients. Plasma leakage into the abdominal and pleural cavities, is the most distinguishing feature causes low platelet counts that is below 100,000/mm³ within 1-2 days of infection and which remains low almost for 3-5 days in most cases while there is no plasma leakage found in case of DF.¹³ Dengue virus initially interact with the specific receptor(s) of the host cell. The provision of surface receptors facilitates the entry of viruses to the target cell thus initiates the signals for dispersion, intracellular transportation and causes infection in the host cell. The role of protein envelope of the disease (E-protein) shows a critical role in the supplement and the ultimate interaction with cellular responses.¹⁴

Proteomic Analysis of Dengue Virus

The dengue virus of NS1 protein is usually consisted of about 40-55 kDa in size and consisting 352 amino acids, liable on its glycosylation grade and is normally formed initially in pathological infection, before the opening of antibodies making in the septic host. Hence, in the patient's blood the discovery of dengue NS1 protein is seemed to be an appropriate sign for revealing in the primary days of the infection.¹⁵ Flavivirus, one of the main integrals of the viral replication complex, the non-structural protein NS2A

is that utilized in virion assembly and alienates the host immune response. The detailed topology of this protein has not been determined while it was known to be associated with the endoplasmic reticulum (ER) membrane (Falgout B, et al, 1993).¹⁶ In the nonstructural protein (NS) region, most of the proteolytic cleavages of the flavivirus polyprotein are affected due to virus-encoded protease which is comprised of two viral proteins i-e NS2B and NS3.¹⁷ NS4B, the highly hydrophobic transmembrane protein of the dengue virus, responsible for viral replication complexes formation which are typically necessary for the viral lifespan. The main non-structural hydrophobic proteins are DENV NS4B and NS4A if specially, involved in this assignment.¹⁸ Their purposes and hence their properties, must be similar to the other non-structural proteins of extra enclosed viruses which is involved in same purposes such as NS4B from hepatitis C infection.¹⁹ The most conserved protein in dengue virus known as NS5 protein, it has RNA-dependent RNA polymerase action at its C-terminal territory and methyltransferase activity at its N-terminal domains and also having important tasks for covering of the mRNA.²⁰ Throughout the lifetime of all viruses the cellular proteins play a key roles. In addition to, host cell nucleic acid-binding proteins forms interaction with the pathological mechanisms of positive-stranded RNA viruses and standardize pathological translation as well as replication of RNA.

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Proteins of the DENV2 and their function

Protein Name	Function of protein
NS1	Immune evasion
NS2A	RNA synthesis, viral assembly
NS2B	Viral replication
NS3	Enzymatic activities
NS4A	RNA synthesis and assembly
NS4B	Formation of the viral replication complex
NS5	Enzymatic activities
E	Envelope protein

Discovery of Vaccine against Dengue Virus

The spreading of dengue virus-transmitting mosquitoes is one of the main reasons for the wide spread of dengue disease since the past 50 years, and in recent times outbreaks have also been detected in the United States. Development of drugs and vaccine against dengue virus is the most important worldwide health priority. The potential vaccine discovery is challenging because of the presence of all four serotypes of the dengue virus, which a vaccine must defend against.²² The first vaccine against dengue virus has been approved in December 2015 in many Asian countries and Latin American states for the defense against all four serotypes of the virus. The inoculation is a tetravalent, recombinant, live-attenuated with a yellow fever 17D vaccine virus strength and is ordered in a 3-dose plan at six-month intervals.²³ In dengue endemic areas, the vaccine has been permitted to patients between 9-45 years of age though the age bound influence vary by permit. For travellers this type of vaccine is not planned as a routine vaccination.²⁴ Presently, CYD-TDV is primarily accessible in private market not in Brazil and Philippines. The vaccine has been presented in subnational community-based programs.²⁵ The vaccine has not been examined as mediation for dengue epidemic control however the 3-dose vaccine might be presented during an epidemic as part of worldwide dengue control strategy.²⁶

Dengue virus might be treated by virus separation and serology i-e IgG, MAC-ELISA, ELISA, PRNT, and NS1 ELISA or by following molecular basis methodologies (RT-PCR. PCR) which are taken as standard for dengue, because serological assessments suffer from cross-reactivity, adjustable understanding by timing of sample collection, and the essential for various specimens which are IgG critical and convalescing samples.²⁷

Current dengue prospective, vaccine aspirants that are being studied in the different phases of medical trials.

Vaccine Name	Type of Vaccine	Stage	Earliest Licensure
CYD-TDV	Live reduced chimeric vaccine	Complete	2015
TV003/TV005	Live reduced chimeric vaccine	Stage III	2018-2019
TDV	Live reduced chimeric vaccine	Stage III	2017-2018
TDEN	Purified deactivated entire virus vaccine	Stage II	2018
V180	Sub unit protein vaccine	Stage I	...
D1ME100	DNA vaccine	Stage I	...

Prevention and Control

The improvement of dengue virus control tackles urgently need, which include potent vaccines and vector control. The dengue virus has infected population in more than 120 countries and has expanded since past decades.²⁸ Global forces will continue to contribute in the spreading of dengue viruses. They comprise of the population progression, unexpected urbanization, and suboptimal parasite control in municipal centres.²⁹ Dengue prevention depends upon control of the mosquito vector, while several novel potential vaccine candidates and new tools for vector elimination are under assessment and will be presented in the near future. A novel approach for dengue virus control and prevention is being employed for the period 2012–20.³⁰In the absence of effective tetravalent vaccine for dengue viruses, the vector control is the only approach to prevent viral infection. Besides this, reducing the area of skin exposed by wearing long pants, shirts with long sleeves, socks, and wearing a hat might be helpful to reduce the risk of infection. By applying pesticides on nets could be more effective as the mosquito can bite the person right beside to the net. The insecticide will either repel or kill the mosquito from biting human inside the net. Clean and staging water is most favorable habitat for breeding of *Aedes* mosquito. By covering clean water, we can avoid the possible damage caused by dengue virus.³¹

Conclusion

Almost 40% population of the sphere is under the threat of this viral contamination. Elimination of dengue virus signifies a proselytizer clash of the twenty-first century. Presently, to prevent epidemics, controlling the dengue mosquito is the only available method. On the other hand, new investigation for discovery of potential vaccine, evaluation of vector control tools and approaches are desirable. In conclusion, the modern research progresses on the prevention and treatment of dengue comprises different methods to control vector, vaccine identification and novel antiviral drugs discovery, since there are several under diagnosed cases of dengue virus infection due to unusual modes of transmission.

Conflict of Interest

No conflict of interest to be declared by any author.

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Abbreviations

DHF, **Dengue** Hemorrhagic Fever; NS, Non-structural Proteins; DV, Dengue Virus; PCR, Polymerase chain Reaction

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CONTRIBUTION OF AUTHORS	
AUTHOR	CONTRIBUTION
Muhammad Ibrahim	A
Syeda Safia Hashmi	B
Syed Salman	B
Syeda Asma Taskeen	B
Syeda Jawariya Hashmi	C
Muskan Shabbir	C
Immad Khan	C
Muhammad Shabbir Ahmad	C

KEY FOR CONTRIBUTION OF AUTHORS:

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