

Journal of Coastal Life Medicine

journal homepage: www.jclmm.com



Review article

doi: 10.12980/jclm.3.2015j5-30

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Dengue fever in Pakistan: Challenges, priorities and measures

Javid Ali*

Pakistan Council of Scientific and Industrial Research, Laboratories Complex, Jamrud Road Peshawar, Islamabad, Pakistan

ARTICLE INFO

Article history:

Received 10 Apr 2015

Received in revised form 2 Jul 2015

Accepted 10 Aug 2015

Available online 30 Sep 2015

Keywords:

Dengue fever

Prevention

Vector control

Vaccine

ABSTRACT

Currently, there is no huge scale study on threat aspects and incidence of dengue fever in Pakistan, as a result it must be carried out on a priority source. It is the responsibility of the government to establish local community based laboratories and excellence research center for dengue cure, awareness and prevalence. The ailment could be cured in proper and better way. The treatment of dengue is extremely difficult due to lack of available vaccines. A developing country like Pakistan cannot handle the problems due to lake of awareness, behavior of people, terrorisms and other socioeconomic factors of the country as well as government interest to cope the other problems as compared to this one. Therefore, more measures should be carried out to prevent the disease.

1. Introduction

Pakistan is a developing country with limited resources and high population density, so it is difficult to afford high risk, prevalence, treatment and other problems associated with dengue fever. Presently, the most excellent means is supposed to identify the precise pervasiveness of dengue fever in the state and as well the chief hazard and rout aspects, thus they should be pointed out particularly. Pakistan has faced many natural disasters and problems in the last few years including water shortage, floods, earthquake and terrorism so as to damage the national resources that lead to endanger the health condition of general community. The dengue fever is also become an enormous problem due to no vaccination, inadequate sanitation facilities, unsafe drinking water, overcrowded cities and huge number of refugees.

According to World Health Organization (WHO), each year approximately 50 million dengue viral illnesses happen throughout the world and two fifths of the world's population is in the danger of dengue illness[1]. Dengue shock disease, dengue hemorrhagic fever and dengue fever have caused considerable and increasing morbidity and mortality in different localities of the world[2]. Dengue fever is among the 10 most important causes of death and hospitalization within kids in at least 8 tropical Asian countries[3].

1.1. Dengue history

In 1906, dengue fever seemed to be a viral illness. Dengue fever first recognized documented signs were cited in Chinese Encyclopedia in the Chin Dynasty (AD 265–420). This disease was connected by means of airborne arthropods close to H₂O and called as “the water poison”[2]. The word “dengue” is derivative from the Swahili saying Ka-dinga pepo, standing for “cramp-like seizure”. The first medically documented dengue outbreaks happened in the 1780s concurrently in Asia, Africa and North

*Corresponding author: Javid Ali, Pakistan Council of Scientific and Industrial Research, Laboratories Complex, Jamrud Road Peshawar, Islamabad, Pakistan.
Tel: +92-091-9216244
Fax: +92-091-9216233
E-mail: javedali_14@yahoo.com

America. The first clinical case report dating from 1789 of 1780 epidemic in Philadelphia was by Gupta *et al.*, who invented the word “break bone fever” due to indications of arthralgia and myalgia[4]. The common dengue fever symptoms include rash, vomiting, diarrhea, muscle and joints pains, mouth and nose bleeding, headache, and sudden onset of fever[5].

1.2. Dengue virus

Dengue is a speedy rising pandemic-prone viral illness in numerous countries of the world. Dengue fever virus (DENV) belongs to RNA virus of the Flaviviridae family[6]. The genetic material of DENV holds about 11 000 nucleotide bases[7]. The DENV composes of a nucleocapsid having cubic shape surrounded by a lipoprotein envelope. The length of DENV consists of 3 protein genes ((structural) which code the core protein (C) or nucleocapsid, a membrane-associated protein (M), an envelope protein (E), and seven non-structural protein (NS) genes. The envelope glycoprotein is related to viral neutralization and haemagglutination functions[8].

There are 4 types of DENV called as serotypes and to date 4 antigenically interrelated distinct virus serotypes (DENV-1, 2, 3 & 4) have been recognized[5]. The recent dengue outbreak has turned into a hot issue for global community health awareness. Dengue is different from malaria, as malaria is extra common in remote parts, but dengue is found in rural and urban areas, which makes dengue a special attention to control the epidemic. But unfortunately the DENV is difficult to control presently. Clinically no precise cure for DENV illness is available. Prevention of DENV by low cost, safe and long lasting vaccination has not been invented. Efforts are being in progress to produce several types of antiviral agent, including inhibitors against viral protein functions and replication.

1.3. Dengue virus life cycle

The replication process of DENV consists of endocytosis through a cell surface receptor (Figure 1). After a specific process the virus uncoats intracellularly. In DENV situation, the coat protein places smoothly on the surface of DENV, making a smooth coat with icosahedral shape. When DENV is transferred in the host cell and lysosomes, the protein breaks into a diverse form due to acidic atmosphere and converts into trimeric spike. Numerous amino acids (hydrophobic) on the tip of the said spike add in the lysosomal membrane and cause the virus membrane to fuse with lysosome. At this point RNA discharges into the host cell and starts disease condition. The RNA genome of DENV in the disease cell is translated by the host ribosomes. The

resultant poly protein is then cut by cellular and viral proteases at precise recognition sites. The non structural viral proteins apply a negative-sense intermediate to replicate the positive-sense RNA genome, which afterwards links with capsid protein and is enclosed into individual virions. Replication of all positive-stranded RNA viruses occurs in close association with virus-induced intracellular membrane structures. DENV also induces such extensive rearrangements of intracellular membranes, called replication complex. These replication complex seem to hold viral RNA, viral proteins and host cell factors. The consequently produced immature virions are packed by budding of freshly produced nucleocapsids into the lumen of the endoplasmic reticulum, thereby acquiring a lipid bilayer envelope with the structural proteins prM and E. The virions grow up during transport through the acidic trans-Golgi network, where the prM proteins stabilize the E proteins to stop conformational alterations. Before discharge of the virions from the host body, the process of maturation is completed when prM is pieces to a soluble pr peptide and virion-associated M by the cellular protease furin. Outside the cell, the virus units come across a neutral pH, which supports dissociation of the pr peptides from the virus particles and generates infectious mature virions. This is the point in which the cycle repeats itself[9].

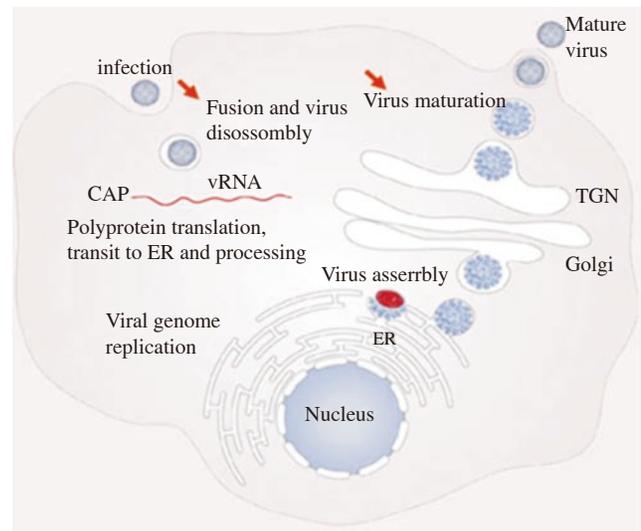


Figure 1. Dengue virus life cycle.

ER: endoplasmic reticulum. Available from: <http://www.denguevirusnet.com/dengue-virus.html>.

2. Dengue virus infection in Pakistan

Pakistan is facing a large number of water born and vectors related diseases (epidemics). Dengue fever is the most important and easily epidemic disease in the earth[1]. The first major epidemic of DENV fever in our country was noticed in 1994–1995 in Karachi[10]. For the last 4–5 years, circumstances of DENV epidemic are getting horrible in Pakistan, particularly

after monsoon phase and large cities like Lahore and Karachi are under harsh pressure of dengue outbreaks. These circumstances have been unfavorably affected by the current floods[1,11].

The dengue fever cases have consequently enlarged from 4 500 cases happened in Karachi in 2005 to 21 204 cases in the country in 2010. In 2011 only in Lahore 14 000 cases were reported and 300 deaths were from dengue fever. It is presumed by several experts that these numbers do not represent the real load of disease in Pakistan, the actual cases being higher than documented[12]. In 2003, another study reported 10 confirmed cases of dengue with 4 deaths from the north eastern city of Pakistan. It was concluded that in Lahore the dengue cases were rising since 2007. This year in the form of epidemic greater than 4 000 cases of dengue happened, a significant increase over previous years[13]. The WHO and United States Centers for Disease Control and Prevention have measured dengue fever a main health risk for Pakistan, Brazil and India[14].

2.1. Difficulties to deal with the problems

Laboratory diagnosis, clinical investigation and management against DENV fever in Pakistan have been quite complex due to simultaneous or super infection with malaria, typhoid and hepatitis. Highly variable mortality during various epidemics may also be attributed to more severe conditions, lack of proper management guidelines and training of health care professionals[2]. To date, there is no registered vaccine accessible for dengue fever[15].

3. Preventive strategies

There are three approaches to solve the problem of dengue fever. The first is to employ a preventive measure by keeping away from contact with infected mosquitoes. *Aedes* mosquitoes bite during daylight and its bites can be avoided by correctly managing waste materials and improving water storage, all sources of sluggish water should be removed, apply household mosquitoes avoiding items (pesticides, coils and nets), wearing long sleeved socks, shirts and trousers to avoid mosquitoes[15]. The Pakistan Government especially in Punjab is working on preventive measure through rising awareness of dengue fever among community. The second approach is vaccination, which is under preparation process and the third approach is drug therapy but unfortunately no antiviral drugs are available to target dengue virus[16]. However, sympathetic care and treatment can save a patient infected with dengue fever. Fever can be treated by antipyretics medicine, like paracetamol. Joint pain can be cured by painkiller or analgesics tablets. In case of dengue hemorrhagic fever and dengue shock syndrome, patients must be hospitalized.

Dehydration can be stopped by oral rehydration treatment and if oral intake is not possible, intravenous fluid replacement can be used to put off shock in patients. If platelet level drops below 20 000 or if there is large bleeding, platelet transfusion is suggested. Drugs such as brufen, aspirin and non-steroidal anti-inflammatory should not be used as they may worsen the bleeding tendency. The medicines which minimize the blood platelet count should be avoided[15].

It is essential to set up local laboratories in all union council of the country for counting and reporting the precise epidemic outbreak along with reason as well as quick precautionary measures in Pakistan. It is also suggested that one main research institute at district level in each province for dengue research, must be connected with every local unit along with hospitals, laboratories, centers and basic health units. The main aim of these dengue research institutes is to give quick response to the dengue patients, community and government on treatment and prevention measures of dengue.

To reduce dengue in our country, the national dengue control programmes must follow all WHO recommended dengue control guidelines. The important main points in WHO course of action are geographic referenced entomologic, public participation, identification of breeding spots, ecological managing through pesticide fogging, medical examination systems and community health education. The local, national and international level attempts are needed to control dengue fever. Furthermore, parallel researches must be encouraged on mega-scale in numerous cities of Pakistan. In addition, the institution will monitor and run the medical examinations with emerging and new cure which could be granted by patients in the future[14].

3.1. Prevention and control measures

Currently, the only way to control or prevent dengue fever is to fight against the vector mosquitoes. *Aedes aegypti* breeds are primarily in human-made containers like metal drums, earthenware containers and concrete cisterns utilized for household storage of water, used automobile tyres, as well as surplus plastic food jars and other objects that accumulate rainwater.

3.2. Vector control

It is employed using chemical methods and environmental management. Appropriate solid waste removal and enhanced water storage performance and covering pots are used to stop contact by egg laying female mosquitoes. Appropriate insecticides are applied. The main efficient way to manage the mosquitoes is the lessening of larva by cleaning or eliminating

aqueous holding places/pots as described over that act as the larval habitation for *Aedes aegypti*. Community participation is essential to execute mosquito control program. This is only possible by law enforcement and public education.

3.3. Vaccine research

No vaccine is available for DENV till to date. Though development is in progress, dengue vaccine synthesis is challenging. Till to date there is limited information of how the disease naturally behaves and how the virus works together with the immune system. Another complexity is that there is no trustworthy animal model for dengue hemorrhagic fever to trial immune responses to potential vaccines. In addition, achievement in vaccine advancement is sluggish mostly due to poor growth of dengue viruses in cell culture. Because there is no cross-protection between the four dengue serotypes and due to the possibility of immune enhancement by monotypic antibody leading to dengue hemorrhagic fever with subsequent natural infections, the control of dengue will be possible only after an efficient tetravalent vaccine has been developed. Attenuation was obtained by repeated passage of wild-type strains of DENV in cell culture. Additional methods are used for the preparation of vaccine classified as inactivated and subunit vaccines, DNA vaccines and recombinant vaccinia virus vectors. Currently, the new important advance method is to prepare a subunit, tetravalent vaccine by means of a mixture of the protein (E) from the DENV (1-4) and the non-structural NS1 protein of DV-2 as immunogens in a proprietary adjuvant.

4. Conclusion

Pakistan has required a multipurpose strategy to control DENV. For this purpose, Pakistan has learned lessons from other nations, utilizes standard of the art technologies to control vectors, gives quick response to dengue case reports and keeps adequate amount for DENV control in every financial budget. Dengue is a life-threatening disease and each year DENV infection has been increased. Till date, there is no licensed drug or vaccine available in the market, therefore, natural drugs possessing activity against dengue virus by their antiviral mechanism, larvicidal/mosquitocidal action and mosquito repellents property may be used effectively to control dengue fever. More research on the active compounds of the studied plants is suggested to develop medicines for the management of dengue fever. There is also required widespread coordination among academia, health professional and industries throughout the world. As a result, the latest research output can be circulated and finally converted into an effective drug against DENV.

Conflict of interest statement

I declare that I have no conflict of interest.

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