DENGUE INFECTION IN ASIA; A REGIONAL CONCERN

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Dengue fever is making headlines these days in Pakistan. Considering the havoc that it has caused in many countries of the region in general and lately in Pakistan in particular, this editorial is an effort to educate our readers on the topic and highlight the issue through this academic forum to raise awareness on the subject specially for the policy makers.

The global epidemiology of dengue fever (DF) and dengue haemorrhagic fever (DHF) is fast changing. Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. An estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries[1]. Furthermore in recent years the disease regularly manifests as DHF with increasing frequency of out-breaks.

Pakistan has experience a number of dengue fever outbreaks since 1992. In the 2005 Karachi outbreak 4,500 dengue cases were registered. The epidemic continued to affect a large number of people in Azad Jammu & Kashmir in 2006 but went largely unreported. Over 21,204 people were reportedly infected in the country in 2010[2]. This year the massive outbreak in Punjab attracted the attention of the Government of Pakistan, especially the Punjab Government[3]. This latest outbreak has resulted in 18,000 cases nationwide. Punjab has borne the brunt of the infection with 16,000 cases and 350 deaths of which 14,000 cases and 300 deaths were reported from Lahore alone[4]. While these figures are concerning, given the difficulty in collecting data particularly from private health care settings, it is likely that they represent an under-estimate of the actual disease burden. To counter this threat, and to develop effective preventive measures, it is important to understand the origin and progress of this infection.

Geographic distribution and genetic diversity of dengue virus suggests its origin in Asia. The first reported out-break of DHF was from Philippine in 1953[5]. One of the characteristics notable in Asian regions, where the disease is endemic is that dengue hemorrhagic fever outbreaks occurs in repetitive cycles of 3-5 years[6]. The dengue virus (DEN virus); a member of the family Flavivirida, genus flavivirus has four antigenically related but distinct serotypes; DEN-1, DEN-2, DEN-3 and DEN-4. The incidence of disease and its severity varies between primary and secondary infections and possibly also across different dengue virus serotypes[7]. Due to a lack of in-vivo study models, there is little information about factors contributing to disease severity and its variation across dengue viruses. The cyclical nature of dengue outbreaks is also not well understood. In the South East Asian region dengue cases are thought to be associated with variables such as water, sanitation, population density and rate of literacy. This is in contrast to developed countries where ambient temperature, moisture and rainfall perhaps play a greater role. A better understanding of disease epidemiology and pathogenesis will help identify optimum control measures in the region. It will also develop systems for predicting the outcome of mass vaccination when the vaccine becomes available in this region.

The principal vector for dengue; Ades aegypti is thought to have originated from African tropical forests and introduced into the coastal cities of South East Asia around nineteenth century via the shipping industry. A less frequent vector; Ae. albopictus is known to be native to South East Asia, but has spread across the globe within past few decades primarily due to introduction of trade, and particularly trade of used tyres within which rain water can be retained. While temperate and humid climates are prerequisites for the optimum survival of both the vectors, Ae. albopictus is known to better acclimatize to the cold

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and dry weather due to its ability of efficient egg diapause during the extreme conditions, thus favoring its survival in the regions with exotic temperature ranges[8].

Ae. albopictus is semi domestic species that breeds on natural and man-made breeding sights; it feeds on variety of animals, birds and man. Ae. aegypti on the other hand is more acclimatized to urban set-up, once established the density of this mosquito is directly proportional to density of human population and artificial breeding sites[9], it feeds almost exclusively on humans. Ae. aegypti moreover is considered to be more competent vector for dengue virus. After the female mosquito feeds on a viraemic patient, viral replication occurs in the mosquito over a 1-2 weeks period before it can transmit the virus on subsequent feeding. Genetic traits that determine successful midgut infection by DEN virus have been mapped on several loci on Ae. aegypti chromosomes[10] and the findings suggest that vector competence for supporting multiplication of DEN virus is genetically determined.

Although the factors responsible for the rapid expansion of dengue in the South East Asian region are complex, vector-host-virus triad, socioeconomic stresses and climatic variations are thought to have a significant role. The distribution of DHF outbreaks in South East Asia correlates with emergence of mosquito Ae. aegypti in these countries perhaps due to displacement of indigenous Ae. albpictus in the region[11] and is considered to be associated with uncontrolled urbanization leading to shanty towns with inadequate pipe water supply and poor sanitation. The extent to which these mosquitoes compete with each other in the environment is not clear, nonetheless the balance of two species in the region is important, and the socioeconomic factors in South East Asia appear to be displacing Ae.albopictus in favour of Ae.aegypti leaving the population more susceptible.

Poor socioeconomic conditions are an additional major contributing factor to sustained vector activity with severe form of disease in the South East Asia. The breeding habitats of Ae.aegypti have been strongly associated with squatter settlements, inadequate piped water supply and sewage facilities[12,13]. In addition, there is impact of higher environmental temperature in the region. High temperature is inversely related to the mosquito gonotropic cycle and viral extrinsic incubation period; this increases the egg laying episodes resulting in more blood meals and increased risk for viral transmission. Shortened extrinsic viral incubation period further results in increased virus load at time of inoculation[14]. These effects have been proven for dengue vectors in simulation studies[15] and it has been projected that increase in global temperature would increase the length of transmission season in temperate regions.

The word dengue is believed to have originated from Swahili language “ki denga pepo”, which describes sudden cramp like seizure. The clinical symptoms suggestive of dengue virus infection can be traced back to Chinese Chin Dynasty (265-420 AD) where disease was considered to be water poison and was known to be associated with water and insects[16]. There are reports that suggest possible epidemics of dengue like illness in three major continents (Asia, Africa and North America) as early as 1779 and 1780[12]. By early nineteenth century dengue fever was known to be endemic in the rural areas of South East Asia probably due to the indigenous vector Ae.albopictus. It manifested as self limiting disease to which native population developed immunity at early age. With the advent of Ae. aegypti at the Asian ports the disease spread to the main inland cities and towns. It is assumed that unlike rural population, the urban populations of South East Asia remained susceptible to dengue virus and were then infected by newly imported vector.

Dengue epidemics progressively became less frequent as urban population became immune to the disease[16], until 1953 when a new form of dengue fever was reported from Thailand and Manila, where children suffered from fever followed by bleeding diathesis; the disease was then called as Philippine Fever[17]. By 1960's the hemorrhagic form of disease had spread to Malaysia, Vietnam, Sri Lanka, Singapore and Indonesia[12]. The disease epidemiology extended and outbreaks of dengue hemorrhagic fever (DHF) were reported from India (1988) French Polynesia (1990), Pakistan (1992) and Bangladesh (2000). Over the past 2 decades, dengue infection and in particular dengue haemorrhagic fever has been regularly reported from Pakistan[18-21].

The incubation period of dengue infection is 4 to 7 days. The disease has a wide clinical spectrum with most infections being subclinical or with non-specific symptoms; fever, malaise upper respiratory symptoms and rash. Classic dengue fever however is an acute febrile illness with headaches, sever musculoskeletal pain and rash. The rash is generally macular, but as it fades or desquamates it is followed by petichae. A second episode of fever and symptoms (saddle back pattern) may occur. Recovery maybe prolonged with easy fatiguability.

There are two form of severe disease, namely dengue haemorragic fever (DHF) and dengue shock

syndrome (DSS) characterized by a haemorrhagic phenomena and hypovolemic shock due to increased vascular permeability and plasma leakage. Platelet count drops with appearance of petichae and ecchymosis as well as bleeding from mucosal surfaces. In populations with inadequate health support, mortality rate in these sever forms of the disease may reach 50%. Until recently, DHF was considered to be disease of childhood, especially in South East Asia where mean age of cases under fifteen, and the modal age of five or slightly higher was reported from countries such as Thailand, Philippines and Malaysia, however, recent reports are now documenting increasing number of DHF and DSS in adult population as well[22].

The devastating coagulation derangements seen in DHF/DSS are thought to be due to host immune response to the viral antigens leading to haemorrhage and shock. While infection with any serotype can lead to DHF-DSS, there is higher tendency in case of second infections, and particularly in infections with strains that have greater virulence[23]. In particular "Asian" genotypes of DEN-2 and DEN-3 have been associated with sever disease[24,25].

The concept of original antibody sin leading to immune enhancement is considered to be the main reason whereby infection with one type of dengue virus sensitizes an individual and that subsequent infection with different virus type elicits a hypersensitivity reaction (secondary infection). A number of studies have demonstrated elevated cytokine levels in patients presenting with DHF and DSS. Elevated serum levels of cytokine and chemokines such as IL-2, IL-8, IL-6, IL-10, IL-13, TNF and INF-γ have been found to be significantly associated with patients presenting with DHF and DSS in clinical setting[26-28]. It has also been proposed that the pro-inflammatory cytokines released by the cross reactive memory T-cells, induce plasma leakage through their effect on the endothelial cells[29]. In-vitro studies have demonstrated increased endothelial cell monolayers permeablity with chemokine such as IL-1β[30].

Dengue like other RNA viruses is prone to genetic mutations since it replicates using RNA-Polymerase; enzyme that lacks proof reading mechanism. The mutations result in genetic diversity within the 4 major dengue serotypes. Consequently, the viral linage is continually changing with the emergence of new variants. South East Asia displays greatest degree of genetic diversity, suggesting that it is the hub for the evolution of new epidemic strain particularly for DEN-3. The indigenous DEN-3 virus circulating up to 1992 in Thailand has been replaced by two new lineages perhaps from a common ancestor). While the relationship between changing strain types and disease severity/epidemic potential is not well understood evidence strongly suggests appearance of such new variants correlates with DHF/DSS epidemics. The 2002 outbreak in Bangladesh has been linked to the introduction of Thai isolates . Similarly studies from India report emergence of the dengue virus serotype-3 (subtype III) replacing the earlier circulating serotype-2 (subtype IV) linked with increase in DHF and DSS. Strains responsible for deadly outbreak in Karachi 2005-2006 were found to be similar to Indian strains of dengue serotype 3[19,22].

Laboratory diagnosis methods for confirming dengue virus infection may involve detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques. After the onset of illness, the virus can be detected in serum, plasma, circulating blood cells and other tissues for 4–5 days. During the early stages (first 5-7days) of the disease, virus isolation, nucleic acid or antigen (Non structural protein 1(NS1)) detection can be used to diagnose the infection however at the end of the acute phase of infection, serology is the method of choice for diagnosis.

In persons who have not previously been infected with a flavivirus or immunized with a flavivirus vaccine (e.g. for yellow fever, Japanese encephalitis, tick-borne encephalitis), IgM antibodies appear by days 3-5 with levels peak about two weeks after the onset of symptoms. Anti-dengue serum IgG is generally detectable at low titres at the end of the first week of illness, increasing slowly thereafter, with serum IgG still being detectable after several months[1]. In secondary dengue infection, IgG is the dominant immunoglobulin isotype and may persist for life. Early convalescent stage IgM levels are significantly lower in secondary infections than in primary ones and may be undetectable in some cases, depending on the test used. To distinguish primary and secondary dengue infections, IgM/IgG antibody ratios may be useful[33,34].

Careful monitoring and supportive care of patients with suspected DHF/DSS has reduced mortality rates by 50-100%. The World Health Organisation[1] recommends that activities at the first level of care for dengue should focus on the following steps:

i. Recognizing that the febrile patient could have dengue;

ii. Notifying early to the public health authorities that the patient is a suspected case of dengue;

iii. Managing patients in the early febrile phase;

iv. Recognizing the early stage of plasma leakage or critical phase and initiating fluid therapy;

v. Recognizing patients with warning signs who need to be referred for admission and/or intravenous fluid therapy to a secondary health care facility;

vi. Recognizing and managing severe plasma leakage and shock, severe bleeding and severe organ impairment promptly and adequately.

The critical activity is monitoring of circulation and vascular leakage by serial clinical assessments of pulse, blood pressure, skin perfusion, urine output, and haematocrit. An increase in haematocrit of greater than 20% indicates loss of intravascular volume and an urgent need for fluid resuscitation. Because vascular integrity is generally restored within 48 hours, over rehydration resulting in pulmonary oedema is a risk during fluid resuscitation and careful monitoring is thus essential.

Preventing or reducing dengue virus transmission depends primarily on control of the mosquito vectors or interruption of human–vector contact. Countries such as Pakistan which are endemic for dengue need to develop and implementing national preparedness plans including early warning systems, epidemiological, entomological and environmental surveillance. Establishment of laboratory support and a system for clinical case management are essential components of such preparedness. Determined effort is required to instigate long term preventive measures for vector control through controlled urbanization and appropriate piped water supply to the shanty towns and the elimination of pools of stagnant water that serve as mosquito breeding points. Programs for increasing community awareness together with social mobilization are key element of the control effort. National partnerships involving government bodies, research institutions and the private sector, as well as international collaborations will greatly strengthen national programs for dengue preparedness and response. The most vital component of such activity however is the leadership and political will to support preparedness planning, and to implement epidemic responses.

The Government of Pakistan and the Government of Punjab, Pakistan have introduced preventive measures to reduce the spread of the epidemic in the country. The Government of Punjab's "Punjab Health Line Project for Dengue" is designed to share information on disease recognition, provide help to suspected cases and identify affected areas. Spraying teams have been organized for fumigating, spraying and fogging. Mobile teams have been established which operate around the clock to treat affectees particularly in rural areas. Awareness programs have been launches and private hospitals have agreed to provide free treatment to dengue patients[35]. Despite these measures, Dr Muhammad Najeeb Durrani chief of the Dengue Eradication Programme, Pakistan has emphasized the urgent need for a comprehensive national plan of action against the virus, and warned that without such a plan, the deadly virus will continue to haunt Pakistan for several more years to come[4]. Given the high morbidity and mortality cost involved it is vital that this warning be taken seriously and a national plan be prepared and implemented without delay.

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