Dengue : An Emerging Public Health Challenge

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Introduction:

Epidemiological transition of the world with a focus on developing countries have resulted in the dual burden of diseases whereby non-communicable diseases (NCDs) are increasing without any significant reduction of communicable diseases.[1] Effective newer drugs and vaccines have played pivotal role in conquering/controlling communicable diseases like Smallpox, Poliomyelitis, Dracunculiosis, Yaws, Malaria, Leprosy, Tetanus (neonatal & maternal) etc. This decline is being compensated by unabated Tuberculosis and emergence of other vector borne diseases (VBDs) especially the arthropod borne viral (arboviral) diseases such as Dengue and Chikungunya Virus. Between the two, dengue attracts more attention because of the mortality associated which is rarely seen in Chikungunya Virus.

Dengue an emerging important VBD is caused by 4 closely related yet serologically distinct serotypes DEN 1, 2, 3 & 4) of RNA virus from group B arbovirus. Infection with one serotype (primary infection) provides lifelong immunity for that serotype but when the same person in hyperendemic areas is infected with another serotype (secondary infection), it can lead to a complicated case such as dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Number of annually reported dengue cases to WHO from the entire world increased from 0.4 million (1996) to 1.3 million (2005), 2.2 million (2010) to 3.2 million in 2015. With substantial under reporting inherent to the disease, reporting system and mathematical modelling, it is estimated that there have been 50 – 100 million symptomatic cases in 2015 across the world; largely from Asia, Latin America and Africa. In 2013 dengue was estimated to be responsible for approximately 9000 deaths, the majority occurring in lower middle income countries, and for 1.1 million disabilities adjusted life years (DALYs).[2]Global burden of disease (GBD) since 1990 have also documented 610% increase in dengue fever incidence, consistent with its widespread emergence in Asia, Africa, and the Americas; much beyond what would be expected due to changes in population demographics. [3] In short, the global burden of dengue is formidable and represents a growing challenge to public health officials and policy makers.[4] High dengue disease burden and frequent outbreaks result in a serious drain on economy and stress on the health systems.

History, Epidemiology, Changing scenario:

Distribution of dengue is the distribution of its principal vector Aedes aegypti - largely confined to 25 ^{0} N to 25 ^{0} S to equator where it also transmits yellow fever and chikungunya fever. However, it is known to cause outbreaks up to 30 ^{0} N and 40 ^{0} S depending on the favourable season and climatic conditions.

Dengue fever caused major epidemics from 17thto early 20th centuries.[5] First confirmed case of dengue was reported by Benjamin Rush in 1789 and he coined the term “Break bone fever” due to the myalgia and arthralgia associated with dengue fever. However, its viral aetiology and mosquito borne transmission was established only in 20th century. In most Central and South American countries, effective disease prevention was achieved during 1950s - 1960s by eliminating A. aegypti. In Asia, however, it was never achieved and a severe form i.e. dengue haemorrhagic fever (DHF) emerged post-World War II (between 1950 – 70) as periodic epidemics in a few countries. During 1980s, however, incidence increased dramatically, expanding distribution of the pathogen and vector to the Pacific islands and tropical America.[5] In the latter region, the A. aegypti

eradication program had been disbanded in the early 1970s and by 1980s, this species re-infested most tropical countries thus increasing the transmission and frequency of epidemics in Asia, resulting in a dramatic increase in epidemic dengue fever; hyperendemicity (co-circulation of multiple virus serotypes).

DHF a potentially lethal complication of Dengue, was first recognized in 1950s during the epidemic in Philippines and Thailand but today it affects most Asian countries and is a leading cause of childhood deaths. Globally it is showing rising trend as before 1970, only 9 countries were affected but now it is endemic in more than 100 countries. Globally, DHF has emerged as a major cause of hospitalization and death. The number of DHF cases reported between 1981 - 1995 is four times higher than that of the previous 30 years. Dengue is the second most important tropical disease (after malaria) with approximately 50 - 100 million and 500,000 cases of DHF each year. [5]

Factors responsible for the emergence/ resurgence of VBDs:

They are complex and multiple such as insecticide/ drug resistance, changes in public health policy, demographic/ societal changes, emphasis on emergency response, de-emphasis of vertical control programs and emergence of climatic factors (less amenable for conventional control strategies) influencing survival and/or multiplication of vectors. All these in turn influence vector habitat, its distribution, abundance, intensity and temporal pattern of vector activity (biting rates) and also the rates of development, survival and reproduction of pathogens within vector.

In other words, this resurgence and expansion of endemic regions for dengue fever can be attributed to

1. Unplanned urban over population areas leading to inadequate public health systems (water, sewerage & waste management)
2. Poor vector control – stagnant water pools facilitating mosquito breeding
3. Climate change and viral evolution (increased viral transmission has been linked to El Nino effect)
4. Increased international travel to endemic areas

Indian Scenario:

The epidemiology of dengue in India was first reported in Chennai in 1780; outbreaks have been documented since 1950s but severity has increased only in the last two decades. First major outbreak associated with hemorrhagic manifestation occurred in Calcutta in 1963 followed by a major outbreak of DHF in Delhi in 1996 after which Dengue became a notifiable disease and a number of policies were formulated to bring the Dengue as well as its vector under control.[6]Delhi home to more than 13 million people, is endemic for sero type one.[7] City experienced another outbreak after 6 years in 2003 with one of the wettest monsoons in 25 years, leading to a spate of mosquito growth creating an alarming situation of mosquito borne diseases in many other states as well.[8] Despite hosting country's policy making institutions, Delhi found itself often paying a price on account of these diseases,[9] and faced this peak in 2003 after which all VBDs were put under single umbrella program - National Vector Borne Disease Control Program (NVBDCP). As per data of VBD (2010- 16), Delhi reported 34,052 cases (9.31 % of total cases).Despite the maximum number of cases during this period, it could contain deaths due to dengue while Maharashtra with 218 deaths (18.7% of the total deaths) occupied the top spot, [10]In 2017 maximum dengue cases were reported from Tamil Nadu not from Delhi followed by Kerala, Karnataka, Punjab, West Bengal, Andhra Pradesh, Assam, Gujarat, Haryana, Maharashtra, Odisha, Rajasthan, Delhi and other states. [11]

There have been no community-based studies reporting incidence of dengue. Monitoring and surveillance activities are generally geared up only at the time of epidemic though they carry more value for epidemic preparedness.

Changing scenario:

Dengue is the only VBD which affect all areas; urban, peri urban including slums and rural, all socioeconomic strata extremely poor to rich (incidentally famous film producer Mr.Yash Chopra died of dengue). Since mid-1990, epidemics have increased specially in urban areas and not only that it has quickly spread to new regions, such as Orissa. DF has been known to be endemic in India for over two centuries as a benign and self-limited disease but in recent years, the disease has changed its course manifesting in the severe form as DHF, or DSS with increasing frequencies.[12]

Epidemiological Determinants:

Transmission cycle is maintained by "human – mosquito – human" cycle and the principal vector is Aedes aegypti which is capable of quick adaptation to human habitation. Main mode of transmission is through the bite of a vector (got infected by biting a viraemic patient) to a vulnerable host. Transmission from other primates or through blood products or from infected mother to new-born are very rare. Therefore, determinants of Dengue incidence are those which determine high vector density include post rainy season collection of water facilitating breeding compounded with other climatic factors like high humidity and Optimum temperature favouring long survival.

Causative Agent & factors:

They playing a role in severity. Causative agent belongs to group B arbovirus, genus Flavivirus of family Flaviviridae and serotypes Den-1, Den-2, Den-3 andDen-4). When a person has had classic dengue (i.e. infection by one serotype), a second infection later by another serotype increases the likelihood of suffering from DHF. Infection with one serotype give immunity against that serotype and some partial immunity against other but as there is no cross resistance so person in endemic areas during life time can have infection with all 4 serotypes.

Host Determinants:

"**Vector breeds everywhere so everybody from everywhere is at risk"**

Dengue fever affects infants, young children and adult in fact everyone is at risk as no race/ traits (like in malaria) provide immunity against it. Especially school going children and young adults are the major group affected - may be due to more exposure to day biter, the severity of disease in India is still lower than that reported elsewhere in South-East Asia; and paediatric cases of dengue haemorrhagic fever have a high mortality. High prevalence of co morbidities attributes to high case fatalities in adults and vulnerable population.

Environmental Determinants:

During the past century, surface temperatures have increased by a global average of 0.75°C per year warm, humid and rainy seasons favour abundant mosquito growth and shorten the extrinsic incubation period leading to substantial increase in dengue epidemic potential.[13] In most of the countries, Health risks due to climatic changes will differ between countries that have developed health infrastructures and those that do not.[14] this global issue of vector borne disease was taken up by World Health Organization (WHO), 2014 by marking it as a theme of World Health Day (WHD) - '**small bite big threat.'**

Increasing Water Scarcity-tendency to store water-increases breeding: Apart from climatic factors (Temperature/ humidity/rainfall) favouring vector density and disease transmission, environmental determinants also include water scarcity leaving large number of water containers, high population density, poor sanitation and large number of manmade containers (construction site/coolers/domestic plants etc) as well as in rural areas where the environment is also mosquito friendly (storage water for cattle feeding & drinking).

Receptivity of the vector:

Female Aedes Aegypti gets infected by biting a

dengue (viraemic) patient - 1 day prior to onset of rash to 5 days of illness. Trans ovarian transmission helps in passing the virus to subsequent generations of the vector. Vectors can Survive up to 12 - 14 days (adequate for the disease transmission) when temperature of surroundings is around 30 ^{0} centigrade with 60% relative humidity. Receptiveness to pathogenic organisms by a vector depends on its anthropophilic nature. Closeness to reservoir of infection with presence of high population density and efficient biting species further facilitates the transmission.

Personal protection (Host): It's a day biter-how important for prevention?

Aedes aegypti is office (school?) time biter and bites in day between 9 am and 5 pm. Day biting nature is a challenge as it need protection from the vector not only at home but also at school/ workplace (practically everywhere). Mosquito control measures (good night/ coil/all out) at household level by community are usually practiced during night time due to lack of awareness that vector is a day biter. Vector control measures are neglected at work place/ schools/institutions/ hospital premises. Hence these premises need to have mosquito trapping electronic devices apart from other permanent vector control measure like wire mesh at window/doors. Wearing full sleeve shirts/ full pants during day time can prevent mosquito bite. Vulnerable population like pregnant women/ children/older people even when sleep during the daytime must use insecticide treated bed nets (ITBNs).

Role of travel especially international:

Disease disappeared from Europe mainly due to nearly universal use of piped water but is frequently introduced by travellers returning from dengue-endemic countries but no local transmission has been reported since it depends up on the reintroduction of Aedes aegypti which is adapted to urban environments. However, over the last 15 years another competent vector Aedesalbopictus (Asian tiger mosquito) has been introduced into Europe and expanded into several countries, raising the possibility of dengue transmission. Clinical symptoms develop after a 3 – 14 days incubation period with a usual of 4 – 7 days. If a person develops confirmed dengue infection 14 days after the visit to an endemic country, the attribution to travel shall be ruled out and an indigenous transmission should be suspected.

Community participation:

It is key to the success of any control program and must have the involvement of Panchayati Raj Institutions (PRIs), and Mahila Arogya Samiti (MAS), Students in the schools can be involved as effective change agent because of (1) their vulnerability for bite during school time and (2) their potentials to take the message to their respective homes. Community participation requires community sensitization, mobilization (through IEC and IPC) A good example of the IEC is given at figure 1 targeting the community in general and primary care providers. A media hype has been there in the community about the severity of dengue and its potential to kill. Every case of dengue is considered as serious while number of them are purely asymptomatic or self-limiting. This point should be highlighted while delivering the Information, Education and Communication (IEC).

As part of community participation, **National Dengue Day is** observed in India on **May 16** with the recommendation of Ministry of Health & Family Welfare (Mo H & FW), Government of India (GOI) to create awareness and to intensify preventive measures and preparedness for the control of disease in the country before transmission season starts.[15]

Delhi initiative:

National Capital Delhi has the eighth highest literacy rate in the country and high penetration of media, making it easier to achieve the intended results in public health campaigns through IEC. Delhi is also the most urbanised state in the country with

highest accessibility to healthcare.[16] Delhi government has taken a unique initiative in the form of Mohalla (community) Clinics to make basic healthcare accessible. Each clinic is staffed by a doctor, a nurse, a pharmacist and a laboratory technician.[17] This has helped to decongest higher level health facilities.

Another issue is that 52 % of Indians indulge in self-medication.[18]This tendency of not consulting doctor in case of common symptoms like fever and seasonal flu coupled with Over The Counter (OTC) sale of prescription drugs makes the case worse in many instances. Once the case is out of hand due to misdiagnosis and delay in appropriate treatment, people then directly approach emergency care which also hampers health services for the less privileged who may actually need emergency care on an urgent basis.

Drawing lessons from the current and previous crises, governments should develop a multipronged strategy with focus on prevention of such outbreaks. One important takeaway from the recent outbreak of chikungunya is the need for an adequate surveillance mechanism, and governments should aim to put in place mechanisms that ensure round the year stringent surveillance of vector-borne diseases rather than doing it just during (rather after) the outbreak of the disease. State of Tamil Nadu presents a good example of such a strict surveillance mechanism that helped in reducing the number of chikungunya cases and preventing the outbreaks of vector-borne diseases.

The role of the community health worker is very important in the case of prevention of any infectious diseases at the local level. Therefore, their training and adequately capacity building towards preventing VBDs should be the primary focus of government. As these workers come from the local community, they are better aware of the problems in that particular area. This places them in an important position to act as a crucial link between policy makers and the local community, which can be helpful in taking timely actions by the public health authorities in spread of diseases.

Prevention and control:

In view of non-availability of any specific Treatment, prevention and control assumes importance and here the mainstay is vector control along with host protection (from mosquito bite). World Health Organization emphasizes on integrated vector management with environmental engineering and use of long-term sustainable insecticides.

Vaccination:

Development of a vaccine is in a very early stage. CYD-TDV or Dengvaxia® is a live attenuated (recombinant) tetravalent (all 4 serotypes) vaccine. It has been evaluated through the phase 3 randomized control trials (RCTs) in Asia and Latin America. Vaccination schedule consists of 3 injections of 0.5 mL administered at 6-month intervals for the prevention of dengue illness in individuals above 9 years of age and living in dengue endemic areas (lower limit of 9 years of age due to safety concern). Vaccine efficacy during 25 months post first doze period was around 50 – 60% showing variation depending on the age groups, previous exposure status and the geographical area. According to the WHO, countries should consider this vaccine CYD-TDV only in geographic settings (national or subnational) with a high burden of disease (prior infection with any serotype, as measured by seroprevalence, should be $\geqslant$ 70% to maximize health impact and cost effectiveness.

Lab Diagnosis:

It is made by detecting the virus and/ or any of its components (virus, genome, dengue antigen) or by serological responses after infection and the objectives are to (i) confirm the clinical diagnosis for individual case management and (ii) conduct surveillance from public health point of view. Laboratory diagnosis is not very crucial for clinical management except in atypical cases or during differential diagnosis with other infectious diseases.

Febrile phase (day 1 to days 4–5 of fever):

Acute infection with very high sensitivity and serotype identification can be done by isolation of virus by tissue culture and virus genome detection by real-time RT-PCR. NS1 Ag is a marker of acute dengue and can be detected by enzyme-linked immunosorbent assay (ELISA) and rapid commercial tests.

Critical and convalescent phases (after days 4–5 of illness):

Specific IgM is the best marker of a recent dengue infection (persist for almost 3 months) and is best detected by MAC-ELISA and rapid tests. High levels of specific IgG in sera collected early after fever onset and detected by ELISA and Hemagglutination Inhibition Assay (HIA) also suggest a recent dengue infection. Primary infections are characterized by high levels of IgM and low levels of IgG, while low levels of IgM with high levels of IgG characterize secondary infections. Classification into primary or secondary infection is also determined by IgM/IgG optical density ratio. Ratios >1:2 suggest a primary infection.[19] In addition, IgG titres higher than 1/1280 by HIA or ELISA are also suggestive of a secondary infection. In dengue endemic countries, acute clinical cases with a positive IgM are classified as probable dengue cases. A case is called confirmed by the detection of the virus, viral genome or NS1 Ag, or seroconversion of IgM or IgG (from negative to positive IgM/IgG or four-fold increase in the specific antibody titre) in paired sera. As patients access care some early and some late – a combination of both NS1 Ag and IgM markers is advisable. Figure 2 presents the time when a particular test is to be advised.[20]

Both probable and confirmed dengue cases should be notified to health authorities.[20-23]

Management:

Symptomatic cases are around 25% of total infections and classical constellation of symptoms for an uncomplicated, yet symptomatic dengue case include fever associated with headache, retro-bulbar pain, prostration and extensive myalgia (responsible for its local name "KAMAR TOD BUKHAR" or break bone fever. These are self-limiting and complicated forms such as DHS and DSS only typically occur with second- or third-time infection with a different serotype. Further, the mortality is different between children and adults. Presence of co morbidities (hypertension, diabetes etc.) put the patients at a higher risk and complicate the management.

As it is difficult to differentiate dengue from other febrile illness during and immediately after monsoon, timely initiation of treatment is missed by health provider compounded by the treatment seeking behaviour leads to higher morbidities/ mortalities. As mentioned above, in absence of any specific therapy management is basically supportive type focussing on fluid management in complicated cases. Some of the below given points are worth considering during the management of dengue/ DHF cases.

1. **Rule of 20**: Following indicate high risk situation & require immediate medical attention
   a. Rise in pulse by > 20
   b. Fall of blood pressure by > 20
   c. Difference between upper & lower blood pressure < 20 mm of mercury
   d. Presence of haemorrhagic spots in an arm (after tourniquet test) > 20
2. Death in DHF or DSS does not occur due to platelets deficiency but due to capillary leakage of fluids leading to multi organ failure. Therefore, fluid replacement @ 20 ml/ kg / hour till pulse Pressure > 40 mm or patient passes urine is more important than platelet transfusion (needed only when platelet count < 10000/ mm^3),

In any developing country including India which is prone to the spread of many infectious diseases due to its geographical location, various

epidemiological, social demographic and climatic factors, prevention of dengue fever is the most cost effective and sustainable mechanism to ensure healthy lives to its population.

Figure 1: IEC material about dengue for treatment provider/ community [24]

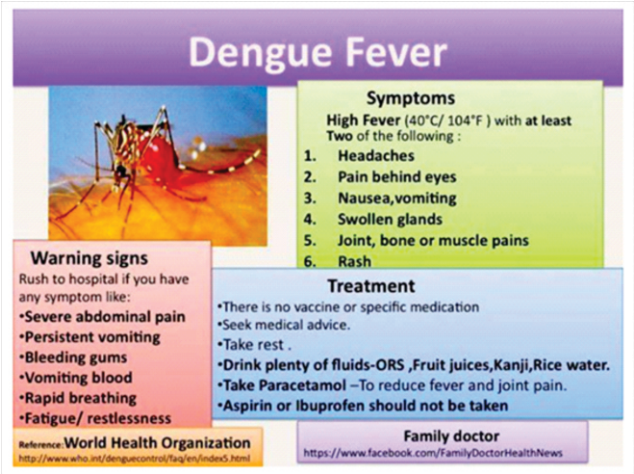
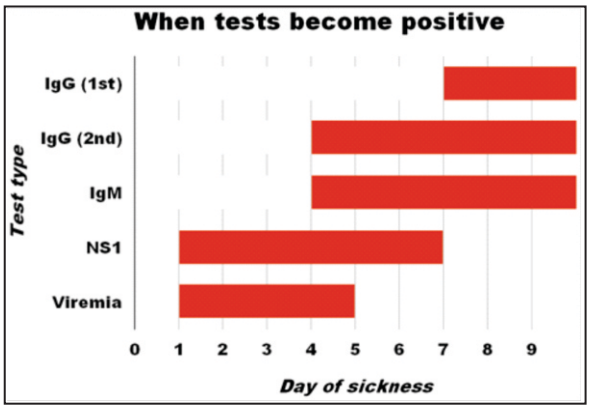


Figure 2: Diagnostic tests in dengue source [25]



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