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Dengue Fever: Lessons from Epidemiology

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History of Dengue: Dengue fever (DF) is a disease caused by 4 serotypes of dengue virus. It is a disease of antiquity. The first few scientific descriptions in literature include epidemic of knee fever in 1779 in Cairo and its suburbs described by Aljabarti; an epidemic in Batavia (Djakart) described by David Bylon in 1779, and an epidemic in philadelphia in 1780 described by Benjamin Rush. Till the 1950's the disease was reported infrequently from various tropical and subtropical countries. DF has been reported with increasing frequency subsequently. At present more than 2.5 billion people live in dengue endemic areas of the world. Each year an estimated 50-100 million cases of dengue fever occur annually throughout the world.

DF acquired public health importance due to the increasing incidence of dengue hemorrhagic fever reported since 1950's. The epidemics of DHF first occured in South Asian region in 1950's, spread to South Pacific islands in the 1970's and reached the Caribbean basin in the 1980's.

In 1953-54 the first major outbreak of DHF was reported from Manila. Subsequently it became endemic in Philippines with increasing number of cases each year. From Philippines the disease spread to other South East Asian countries.

In 1958 an outbreak of DHF occured in Bangkok affecting 2706 patients with a case fatality rate of 10.94%, majority of affected patients being children below 10 years. In the next few years the disease spread to the suburbs of Bangkok. It involved adjacent provinces in the central region of Thailand in 1961 and by 1964 major outbreak occurred in big cities in northern and north eastern Thailand. Over next ten years DHF became endemic throughout Thailand. Now every year DHF cases are reported from all provinces of Thailand with periodic epidemics. With good case management the case fatality has decreased from 11% in 50's to less than 1% in 1990's. The experience from Thailand suggest that the disease first spread to adjacent areas and finally involved all major cities to make the whole country/province endemic for DHF. Outbreaks of DHF like illness were reported from Hanoi and Hochiminh city of Vietnam in 1958 and 1960 respectively. Dengue type 2 virus was isolated from these epidemics and there were serological evidence to suggest presence of dengue 1 virus also. The disease has become endemic in Vietnam with frequent epidemics from mid 70s.

In 1960 DHF was reported first time in Singapore. Subsequently it became endemic with frequent outbreaks. In 1969 a nationwide control programme was launched to decrease dengue by environmental control which gave encouraging results with sharp decline in DHF. However, from mid 80's there is resurgence of DHF in Singapore. Outbreaks of DHF/DSS were reported from Kampuchia in 1961 with isolation of dengue 1 and dengue 4. In Malaysia, DHF first occurred in 1962. In 1971 the disease was made notifiable. Subsequent to this the number of cases increased with epidemics every 4 years. Cases of DHF from Myanmar was reported in 1963 and subsequently more cases were reported, every alternate year with epidemics every 4-5 years.

In 1963-64 DHF outbreak was reported from Calcutta. Dengue 2 virus was isolated from affected patients. Subsequently DHF was reported from Vishakapatnam in 1964, Vellore between 1960-68 Kanpur in 1968, Ajmer in 1969, Jalore 1985, Delhi 1988 and Prabhani 1988. From 1990 onwards epidemics of DHF were reported from Jammu, Surat, Shajahanpur, Lucknow, Delhi, Ludhiana, Panipat, Hissar and Jaipur. Between 1969 to 1985 epidemics of DF were recorded from Delhi, Gwalior, Hardoi, Jaipur, Bangalore, Pune, Trichur and Amalner (Table I). All 4 serotypes were isolated from different parts of India. DHF epidemics/outbreaks have been reported from all the states except Bihar, Orissa & Kerala. In the first two decades after the philippines outbreak, DHF was localized to few countries in South East Asia. Then it spread to other regions. In the period 1974-1980 three epidemics occurred in Southern coastal area of Peoples Republic of China.

In 1977 a dengue pandemic began in the Caribbean. Following outbreaks on many islands including Puerto Rico, classical dengue was introduced into Southern Eastern Mexico in 1978. In the Americas the first major epidemic of DHF/DSS occured in 1981 in Cuba. In recent years clinically compatible cases with DHF with or without laboratory confirmation has been reported from many countries including Mexico, El-Salvador, Nicaragua, Jamaica, Dominican Republic, Puerto Rico, St Luca, Aruba, Brazil, Surnam, Colombia, Haiti and the US.

The knowledge of dengue in Africa is incomplete. Dengue has been reported from coastal areas and islands of East and South Africa and from most of West Africa. There is no record of illness from central Africa. All four dengue serotypes have been involved, but to date, epidemic DHF has not been reported in Africa or the middle East. However, sporadic cases of disease clinically compatible with DHF have been reported from Mozambique, Djiboute and Saudi Arabia.

From review of DHF epidemics in various countries it seems that there is increasing number of cases from various parts of the world in last 2 decades. The disease got more attention due to the high case fatality rate when it occurs the first time. The disease first occurs as a small outbreak, becomes endemic and then periodic epidemics. The period between two epidemics decrease with time. In between the two epidemic in a geographic area there may be increased number of cases every alternate year.

Importance of Epidemiological information

The review of dengue infection in India suggests the disease has became endemic.

Attempts to control the DF/DHF problem should ideally be based on a good understanding of its determinants, the factors which affect disease spread. In a very simplistic model, if the vector (aedes aegypti mosquito) and the virus (multiple strains of dengue virus) are present and can proliferate and spread in a suitable environment with susceptible hosts (human beings), the disease is likely to occur and occur repeatedly. This disease may occur, if conditions permit, in an epidemic form. We have all the ingredients, susceptible hosts, the vector, the virus and the environmental conditions. Disease control theoretically should then be possible given the presence of political and technical commitment.

However, dengue fever epidemiology has many unanswered questions. While a review of publications reveal a large number of redundant epidemiological investigations which should be discarded, many important factors in transmission have been overlooked. These need to be studied in a planned manner. We shall briefly dwell upon the present knowledge about dengue epidemiology.

It is our belief, based on a review of available literature, that like malaria, factors important in dengue transmission have to be studied at a local/regional level. There can be no universal epidemiological pattern which explain transmission of this disease in various parts of the same country or continents. And therefore, if we wish to study and then control our own epidemics, we need to study our problem ourselves.

Epidemiological factors could be discussed under three headings: agent, host and environmental factors.

(a) Agent: The disease is caused by a virus. It is not firmly established what determines the occurrence of complications like DHF in areas where multiple strains of dengue virus are present. Is it that some strains are more pathogenic (and therefore lead to complications) or is it that the sequential infections with multiple strains that leads to this dreaded disease. However, one thing is clear that DHF occurs in an area where dengue is already established for some years.

The virus is transmitted by the female aedes aegypti during her blood feeding activity. Thus all factors which govern its survival, proliferation and feeding habits would assume

importance. Aedes is a domesticated mosquito, prefers clean water collections, rests indoors and does not like to move too much (25-50 metres). When it gets infected after feeding on a patient having virus in the blood, it remains infectious for its entire life span of around 10 days (range 8-42 days). Then it can bite vigorously and painlessly a large number of people in a small area. Since it is a day biting mosquito, it will bite children when they are in school, day care centres, at home and adults at their workplace or other areas of congregation. It can travel in rails, buses, ships and aeroplanes and therefore spread over short and long distances.

The factors outlined above have been shown to play their role in some very interesting epidemiological investigations of outbreaks or in experimental designs. The mosquito needs a warm temperature to grow (and the virus too), but it is not clear which temperature, outdoor or indoor temperature. In the Ajmer epedemic of 1969, low grade transmission persisted even in December inspite of prevailing low temperature. This total dependence of Aedes on man allows it to persist in these `hot islands' (indoors) in cold weather. Wherever man collects fresh water (for drinking, washing, cooking or for holding flowers/plants), Aedes can proliferate. Most human dwellings in developing countries have high population density-especially in urban areas. This suits aedes-which has a short flight range and can bite multiple hosts to spread the disease.

The spread of the Aedes mosquito has been well documented by all means of communication. In fact, a unique way of transmission is by used automobile tyres - *Aedes albopictus* finds it very useful for transmission. Movement of viremic patients is a mechanism of spread. The Ajmer epidemic of 1969 referred to above, started at the time of annual `Urs Mela' in the central zone of the city and spread radially to peripheral zones along the busy routes of human movement. Probably pilgrims got the virus and the presence of high vector density caused an explosive outbreak. Pushkar, a nearby place which attracted an equally large number of pilgrims during the same period remained unaffected due to absence of *Aedes*.

The mosquito and the vector has spread widely now- Dengue/Aedes have been seen in Shahjahanpur, Vellore, Mangalore, Western Coast upto Pune, parts of Maharashtra, Surat, Jaipur and many other un-reported areas. So we have the disease/vector/virus in all the 4 zones of the country.

(b) Host factors: The most important host factor is clustering of human beings. Enormous rise in population of major cities (Delhi is more than 1 crore) and urbanization of rural areas in many developing countries including us, over last 20-40 years has undoubtedly contributed to frequent recrudescence of greater magnitude. Urbanization has clearly been shown in many analyses to be responsible as in Malaysia, Thailand. It is possible to get periods of intense transmission with epidemics of DF/DHF even in small populations e.g. islands, but endemicity does not typically occur. But if the population of an area is larger, the disease may linger between epidemics in an endemic form. It is very likely that the critical community size lies somewhere between 1.5 to 10 lakhs. All cities with population above this have a high chance to remain endemic once dengue reaches them.

Even within households, multiple infections is the rule. Secondary attack rate was 44% in households in a philipino outbreak. In Ajmer again, it was observed that in central wards practically all the family members of a house were affected.

How the epidemic will behave depends on the immunity of the people. It has been estimated that the basic reproductive rate of the disease is close to 2 in early part of an outbreak. This rate does not drop to below 1 (i.e, the epidemic starts dying down) until 50% of the population becomes immune (due to infection). How frequently epidemics occur in areas of dengue endemicity will depend on number and proportion of susceptible people and the level of herd immunity. If the growth rate of a population is rapid and there is a large significant population movement, the proportion of susceptible people will change with consequent effects on disease incidence.

Environmental factors: The larvae need water to grow and therefore epidemics are more likely to occur following or during rainy season. However, epidemics have been reported in hot

summers or during absent rain period if mosquitoes find water collections for drinking and other domestic purposes e.g, in Northeast Thailand, Ajmer.

The temperature issue has already been alluded to. However, in areas where seasonal changes in temperature are clear, dengue transmission usually declines with the approach of cold temperature.

Surveillence: In view of dramatic emergence of DHF in last 2 decades an effective surveillance system to monitor the disease in community is desirable. Dengue fever has some clinical features similar to other viral infections, a laboratory based surveillence system is more useful. The lab based surveillance system allows public health authorities to accurately monitor the activity of a number of infectious disease agents that present clinically as viral syndrome including dengue/dengue hemorrhagic fever.

In spite of the information mentioned above, we need to answer many questions:

(I) How frequently can epidemics of DF/DHF occur ?
(ii) Is there a correlation between vector density and dengue incidence ?
(iii) How does temperature affect the growth of mosquitoes ?
(iv) What determines DHF epidemics when multiple strains of dengue virus are present ?
(v) What is the best short term way of managing increased vector density ?

The lab based surveillance programme has three components -
1. Sentinel clinics/physicians
2. Fever alert
3. Sentinel hospitals

Sentinel Clinics/Physician: Some dispensaries, clinics, physicians can be identified from the existing system that provides primary health care to community. After a short training they may start keeping records of patients presenting with nonspecific viral syndrome and collect blood samples for further studies. The blood is sent for tests to central/regional laboratory for tests.

Fever alert: It relies on community health and sanitation workers. On observing an increase in fever cases they notify it to the designated authority responsible for monitoring. The outbreak may be investigated by public health department.

Sentinel Hospitals: These are hospitals which admit sick patients of infectious diseases. Patients admitted with various clinical symptoms suggestive of viral infections including DHF are investigated. The category of patients which need investigation for DHF and other infection include , patients with
1) any hemorrhagic manifestations
2) an admission diagnosis of viral encephalitis, aseptic meningitis and meningococcal shock.
3) a fatal outcome following a viral prodrome.

To the above list, patients presenting with other clinical manifestates thought to be associated with DHF may be added. These can be identified by clinical studies of confirmed dengue cases.

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More Musings on unknown Infectious Diseases

I am in complete agreement with Sridhar, not only because I am been on understanding Infections, or because I am a pediatrician presently working in an academic institution. Today I am convinced that finding answers to clinicial questions is as important an trying to understand the socio-economic determinants of discase.
Even though the information and knowledge available on infections is vast, there are so many unanswered questions. In the last four decades, the growth of knowledge about infectious

diseases has not been at the same rate as that in other spheres of human ill health. This could be the consequence ofthe West guiding the agenda for research for themselves and not necessarily for the benefit of developing countries. The time has come for us to take the 'bull by the horns' as it were and set our own agenda and attempt tofind answers to *our* questions.

For instance, what proportion of fever cases are due to malaria ? due to viral fever ? to urinary tract infections ? What is the correct definition of fever: axillary temperature of +1degree Fahrenheit equal to core temperature ? what is the natural history of a child with positive tuberculin test ? What proportion of acute dysentry in children is due to amoebiasis ? What are the causes and determinants of encephalitis - endemic or epidemic ?

The background papers for this meet, I notice, are many small attempts at understanding different aspects of various infectious diseases. A still more heartening fact is that most of these are based on individual experiences. It appears that we have been trying to grapple with many important clinical questions at an individual level. If answering these questions is considered essential at a collective level, then a forum for addressing these should be established. True, MFC has traditionally and essentially been a group fro sharing thoughts and personal experiences. But just the way the PHC cell and Women & Health cell have been established, we could think of doing something proactive about infectious diseases as well. We cannot leave it all to the existing academic institutions where the agenda is likely to be determined by other concern, or professional bodies like the API, IAP (which aften function more like clubs) to answer these questions. Individual attempts are important and will continue but sharing skills to ask the right questions, to design studies and to plan, conduct, and analyze the results in a collective manner has become the need of the day.

Another potential activity I envisage is to do regional surveillance. My epidemiologist friends could probably throw more light on this, but I am sure we could get member organizations to maintain regular surveillance of disease patterns, vital events, state of environment (water, sewage) vector density, etc. Is it necessary to wait for te NICD of some other institution to provide us the much needed information ? We have our own resources. For instance, Dr. BR Chatterjee's amazing laboratory at the Leprosy Field Research Unit, Jhalda, is capable of carrying out microbiology investigations of the highest order given a bit or financial inputs. I am also sure that certain governmental laboratory setups would be keen to collaborate in such work.

Microbiology as a discipline has been ignored for too long. Even in the 'conscious' and well meaning voluntary organizations it has taken a back seat. Cost considerations can only partially explain this attitude. The more likely reasons are (i) Most infections are still self limiting (ii) Most antimicrobials are by and large very safe (one can give penicillin in doses of 1000 units to 24 million units without causing any problems save an occasional anaphylaxis) and (iii) till recently most microbials had been affordable.

We could discuss the scope of establishing such a group within MFC on Day 3 of the annual meet.

Yogesh Jain.