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Review

Emergence of Dengue in Bangladesh a major international public health concern in recent years

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Dengue epidemic in developing countries is due to many reasons. This review paper highlights some events within the country. The prevention of dengue fever is largely based upon the identification of risk factors and awareness. Bibliometric analysis, literature and archival document reviewed and key informant interviews. Factors responsible are overpopulation, uncontrolled urbanization, and inadequate waste management. The general management of these patients needs teamwork and separate wards. The ward should have mosquito net to prevent nosocomial Dengue transmission. The patient needs special laboratory investigation when they are high-risk subjects. The participation and cooperation of general people with government agencies is essential for Aedes control programs.

Keywords: Epidermic; Risk factor; Overpopulation; Urbanization; Waste management.

INTRODUCTION

The reemergence of dengue viruses has been very dreadful in recent times. The term “Dengue” has its origin in Zanzibar, where the disease was called ‘Denga’ during 1870 epidemic. There are four entities, which comprises the Dengue syndrome. These are undifferentiated fever (UF). Dengue fever, Dengue haemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS) (Haq, 2001).

So far there are four virus serotypes (Type I, II, III, IV) and they are grouped under the family flaviviridae. Dengue viruses share many characteristics with other flaviviruses. These viruses are RNA viruses having capsid and envelope. The virion is 50nm in diameter. Infection in human by one serotype produces life-long immunity against re-infection by the same serotype, but only temporary and partial protection against the other serotypes (Aziz et al., 2001; WHO/SEARO, 1999).

Dengue fever is marked by a sudden onset of high fever, severe headache and pain behind the eyes and myalgia / arthralgia. The symptoms and signs may be very similar to other viral infections. It occurs in epidemic form in most countries of Asia and other pacific islands. Children below 15 years are the common susceptible victims. Two types of Aedes mosquitoes are the vectors of dengue virus, which are *Aedes aeogypti* and *Aedes albopictus*. A. aegypti is the vector in urban areas and the latter in rural areas. Aedes mosquitoes breed in clean still stagnant water. Usually discarded tins, water tanks, flowerpots are the ideal places for their breeding. Dengue epidemic in developing countries is due to many reasons. The disposal of sewage, method of water and most importantly nutritional status of general population are important reasons for these viral infections (WHO/SEARO, 1999; Thein, 1994; Nimmannitya, 1993).

Bangladesh at the moment has experienced this viral infection in a most horrific manner. This review paper highlights some events within the country. So far, in Bangladesh, only sporadic cases were diagnosed through small-scale surveys that actually failed to unearth the real situation in Bangladesh. The first scientifically designed survey was conducted in Chittagong in 1996-97. The positive rate was 7.1% among the selected patients (Nimmannitya, 1993). This survey shows an average ELISA positive rate of 17.5% that warrants public health warning in Bangladesh. Chittagong being the most industrialized city, showed 34.3% of all reactive samples (Kalayanarooj, 1998; Yunus et al., 1998). Khulna (compared as state) is another industrial area that

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presented the second highest number of reactive sample (31.45%), (Kalayanarooj, 1998).

Historical aspects

The classical form of Dengue has been known for more than a century in the tropical South East Asia, and Western Pacific Regions. Dengue Haemorrhagic fever was reported as a new disease for the first time in the Philippines in 1953. Serotypes 2, 3 and 4 were isolated in 1956. Multiple infections were followed in 1958 in Thailand, in 1970 in Myanmar and finally in India in 1963. In 1965 there was an outbreak of Dengue and 'Chikungunga' virus infection called 'Dhaka fever' which was the first documented out-break of Dengue in Bangladesh[10] followed by few scattered cases of 'Dhaka fever' during 1977-78. In 1996-97 dengue infections were confirmed in 13.7% of 255 fever patients screened at Chittagong Medical College. The first epidemic of dengue haemorrhagic fever occurred in mid 2000, when 5 551 dengue infections were reported from Dhaka, Chittagong and Khulna cities, occurring mainly among adults (See figure 1). Among the reported cases 4 385 (62.4%) were dengue fever infections and 1 186 (37.6%) cases were dengue haemorrhagic fever. The case fatality rate (CFR) was 1.7% with 93 deaths reported. Aedes aegypti was identified as the main vector responsible for the epidemic and Aedes albopictus was identified as a potential vector in Chittagong. The worst outbreak was in 2002 with 6,104 cases and 58 deaths(WHO, 2011).

In 2005 there were 1048 reported cases and 4 deaths (CFR 0.38%). The number of cases and deaths reduction is about 73 % and 69% as compared to 2004. In 2006 the number of cases and deaths increased by 2 fold as compared to 2005. The maximum transmission period is July to September each year since 2000. A WHO sponsored small scale survey also detected Dengue Haemorrhagic fever cases in 1982. It is difficult to predict why this virus was reactivated in Bangladesh. Probably seasonal occurrence such as monsoon-rain is ideal for breeding. The best environment conditions for mosquitoes breeding prevail during pre and post-monsoon periods in the tropical zones. Aedes eggs can survive in dry condition for a year (WHO/SEARO, 1995).

WHO currently estimated that there may be 50 million to 100 million cases of dengue infections worldwide every year. Two fifth of the world's population are at risk of infection. Bangladesh last year experienced the worst dengue outbreak, and the majority of cases being in the capital. It was estimated that 5,500 people were infected, with 98 deaths. Since 1995, a high percentage of the population in Dhaka and Chittagong has antibodies against type 3 and to a lesser extent to types 1 and 2. Reports show that there are about 500,000 cases of dengue haemorhagic fever (DHF) each year, which require hospitalization. Over the last 10 - 15 years, Dengue Fever and Dengue Haemorrhagic Fever has become a leading cause of hospitalization and death among children in South East Asian regions followed by Diarrhoeal diseases and Acute Respiratory infections (Thisyakorn, 1993).

METHODOLOGY

Information was retrieved from documents available mainly in electronic databases, and on the websites of specialized agencies, using the terms 'Dengue', and 'Bangladesh' with other researchers work was undertaken. The documents were retrieved from the databases (websites) of several national, and international agencies. The most important being online collection from different journals on dengue related issues. These sites housed a number of reports on quantitative and qualitative studies, estimates of Dengue cases, policy analysis of the existing dengue–situation. Histological observations were carried out and a cross-sectional prevalence study of dengue and Bangladesh was also held. A scrutiny of the abstract revealed that some presentation posted on the websites, which was presented in international conferences and few other presentations were published in journals. Collected documents were skim read to cases, whether they contained information on Bangladesh in conjunction with dengue.

Social and environmental aspects

Disease control unit of the Health Services of Bangladesh has documented that there are 5,575 cases of Dengue infections and 90 deaths have been reported (Koopman et al., 1991; Sabin et al., 1952). In comparison to Malaria, Tuberculosis, Leprosy, Filariasis, Diarrhoeal diseases, Leishmaniasis, there is no significant difference with Dengue infection in Bangladesh (Yunus, 2000). Dengue infection involves mostly the affluent section of the society indicating it is an urban disease. Usually there is a negative correlation between the infection and under nutrition.

The peculiarity of the vector has close links with human habitation. Female Aedes mosquitoes are the vector of the virus and are peridomestic in nature. The tropical zone of the world between 35^0N and 35^0 S latitude and area not over 1,000 ft. above sea level is the usual habitat; the area is marked by monsoon-rains. The breeding of the mosquitoes is highest during pre and post-monsoon periods.

Aedes breeds in clean, still and stagnant water usually discarded tyres; water tanks and storage appliances are the ideal sites for breeding. Aedes is a voracious bloodsucker, which aids more virus transmission during blood meal. Biting occurs throughout the day especially

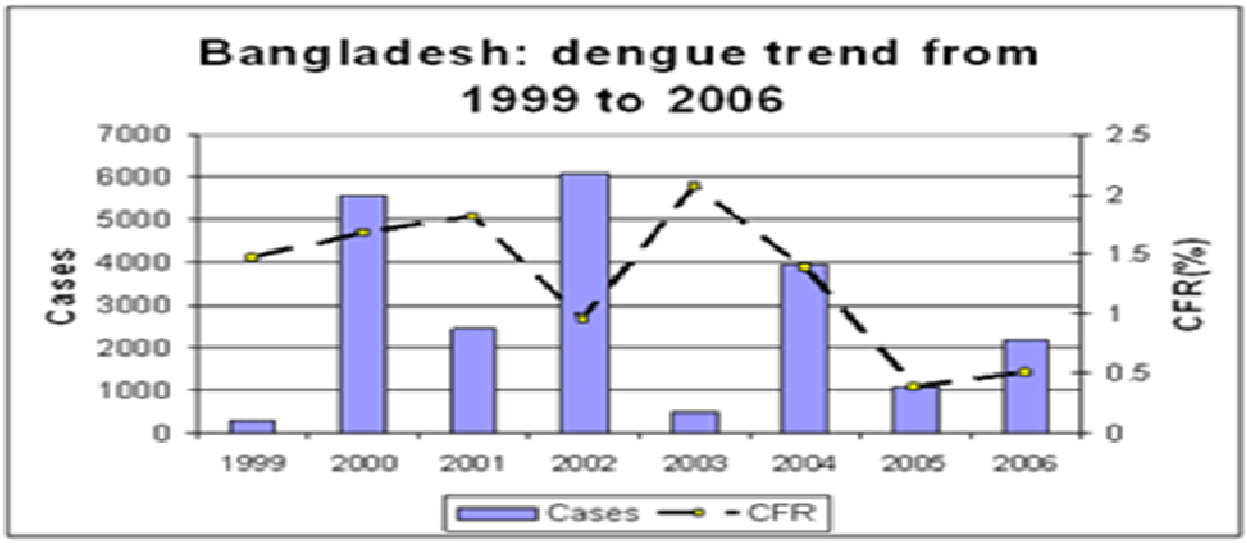

Figure 1: Bangladesh: Dengue trend from 1999 to 1996.
Source: http://www.searo.who.int/en/Section10/Section332/Section2277_11957.htm

Table 1 : Seasonal occurrences of positive cases

Season	Percentage of patients
PRE-MONSOON	28.5%
MONSOON	25.7%
POST-MONSOON	45.7%

marked at 8:00 A.M to 13:00 P.M and between 15:00 P.M to 17:00 P.M (Hussain et al., 2001). Therefore, late risers and late evening sleepers are more susceptible to mosquito bites. The mosquito sucks blood many times and therefore, it can infect many persons.

Like all vector-borne diseases, Dengue also needs conducive predisposing conditions for endemicity and outbreaks. The countries of South-East Asia share common features like large populations, rapid urbanization, development activities and monsoon rains. Urban human populations now constitute the natural reservoir, travelers are the only disseminating factor of the viruses from one country to another. The spreading mechanisms of the outbreaks are related to the dramatic increase of travels and the variable susceptibility of natural Aedes population to the virus. It has been found that the number of female *Aedes aegypti* per person is a very significant household risk factor (Amin et al., 2000).

A survey in Bangladesh, Dhaka city showed that independent houses were most likely to have high densities of Aedes mosquitoes. It appears those rooftops concrete water containers are one of the main breeding sources in independent houses (Chowdhury et al., 2000; Hussain et al., 2001). In one study in the city of Chittagong from September 1996 to June 1997 among255 positive cases shows a seasonal variation in Dengue Patients (Table 1)

Pathology and pathogenesis of Dengue virus

There are generalized haemorragic manifestation in skin, subcutaneous tissues, mucosa of gut, heart and liver, but cerebral or subarachnoid areas are rarely involved. The mechanisms involved are increased vascular permeability that gives rise to less of vascular compartment. As a result there is haemoconcentration, low pulse pressure and other signs of shock. Secondly there is disordering homeostasis leading to thrombocytopenia (Funahara et al., 1987). Dengue virus has inhibitory effects on bone marrow including megakaryocytes. It is mentioned earlier dengue virus binds primarily on the nuclei of megakaryocytec, causing inhibition of cell division (Funahara et al., 1987). The role of dengue virus antibody in the reduction of platelet count is also speculated. Platelet defects may be both qualitative & quantitative (Huang et al., 2001). Therefore patients with platelet count greater than 1,00,000 per mm^3 may still have a prolonged bleeding time (Nimmannitya, 1993). The virus replicates in macrophages by heterotypic antibodies. The other serotypes produce cross-reactive antibodies, which ultimately fail to neutralize the virus. As a result in infected monocytes increase in number.

Other factors that contribute to pathogenesis are cytokine production, chemical mediators and vascular defects. TNF-α is the most important cytokine production in monocytes which are infected with dengue virus.

TNF-α in turn activates IL-8, which stimulates histamine release from basophils. Studies have shown histamin mediates vascular permeability in DHF/DSS (Hober et al., 1993).

Previous studies have shown that complements are activated in Dengue haemorrhagic fever & Dengue shock syndrome (Aviratnan et al., 1998; Funahara et al., 1987). Complements such as C3a C5a may be involved in rapid leakage of plasma, leading to shock by stimulating mast cells and basophils. Further studies have shown that there is disseminated intravascular coagulation with progression of the disease. Partial thromboplastins time, prothrombin time thrombin time are all altered. During acute dengue virus infection, coagulation parameters such as platelet counts, activated partial thromboplastin time (APTT), tissue plasminogen, Plasminogen activator inhibitor are altered in severe form of DHF/DSS (Funahara et al., 1987; Huang et al., 2001).

Clinical diagnosis

The dengue virus can manifest itself in four ways. There are (1) undifferentiated fever. (2) Dengue fever, (3) Dengue haemorrhagic fever, and (4) Dengue shock syndrome (See figure 2). It can be asymptomatic as well. It is most common in older children and adults.

Common differential diagnosis of Dengue depending on the type of presentation and syndromes are influenza, Japanese-B encephalitis, Rubella, Malaria, Leptospirosis and Hepatitis. All these diseases are common in Bangladesh. Following an infection, a person develops immunity for that particular type of virus. In subsequent re-infection the patient develops spontaneous bleeding. This serious condition is called Dengue haemorrhagic Fever (WHO/SEARO, 1995). The other bleeding manifestations are: bleeding gum, haematemesis, epistaxis, malena, subconjuntival haemorrhage (+8.29%), cutaneous bleeding (44.83%).

Dengue Hemorrhagic fever (DHF)

DHF is not a complication of Dengue fever (DF); rather it can start from the very onset of the disease. The turning point between DF and DHF is an afebrile period, when DF progress to remit but DHF presents its morbid manifestations. One cannot differentiate between DHF and DF at the very beginning. Dengue Shock Syndrome is a complication of DHF. So, it is preferable to encompass all the entities as Dengue syndrome (DS) till differentiating manifestations are surfaced (Franklin and Brown, 1994). The clinical and laboratory criteria for diagnosis of Dengue haemorrhagic fever were developed by the children's hospital, Bangkok, which have been adopted by the WHO for worldwide distribution since 1975 and are based on the presence of major manifestations in order of appearance as follows(Thein, 1994): High continuous fever for 2-7 days; Positive tourniquet test; Enlargement of liver; Circulatory disturbance shock; Thrombocytopenia ≤100,000 cells/mm^3; Increased haematocrit by 20% (packed cell volume); Plasma leakage: Pleural effusion, Ascites; There are four cardinal signs, which help the diagnosis of DHF: High fever; Haemorrhagic phenomena; Hepatomegaly; Circulatory failure

Haematocrit value is the clue for the diagnosis and management of the dengue haemorrhagic fever. If there is leakage of plasma, the haematocrit value is elevated resulting into haemoconcentration, effusion or hypoproteinaemia. These clinical conditions differ markedly from Dengue fever (Aziz et al., 2001; Thein, 1994).

In children, the temperature rises above 39^0C and remains high for 2-7 days. Febrile convulsion may occur in infants. Some 96.8% of patients have infected pharynx and sore throat. Rhinitis and maculopapular rash /myalgia comprise about 12.0%.

The most common haemorrhagic phenomenon is positive tourniquet test. This test is performed by inflating a blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressure for about 5 minutes. A test is positive when 20 or more petechiae per 2.5 cm^2 are observed (Kalayanarooj, 1998).

The liver is usually palpable early in the febrile stage and is tender and jaundice is usually absent. The spleen may be prominent on the x-ray investigations (Nimmannitya, 1993). After 7 days, the fever falls followed by sweating and cool extremities.

Dengue shock syndrome

Following the fever, there may be circulatory failure leading to shock. This may occur shortly after the fall of temperature. This circulatory failure may be manifested by cold, blotchy, congested skin; circumoral cyanosis is frequently observed, the pulse becomes rapid. Acute abdominal pain is a frequent complaint shortly before the onset of shock. The duration of shock is short; typically the patient dies within 12-24 hours. Pleural effusions, ascites, intracranial haemorrhage with the development of metabolic acidosis are the manifestations of Dengue shock syndrome. Intracranial haemorrhage with electrolyte disturbances can also be the important findings of Dengue shock syndrome (Nimmannitya, 1993). Good prognostic signs are adequate urine output and the return of appetite (Nimmannitya, 1993).

Laboratory diagnosis

Isolation of virus: During the period of viraemia, the dengue virus can be isolated in the following way:

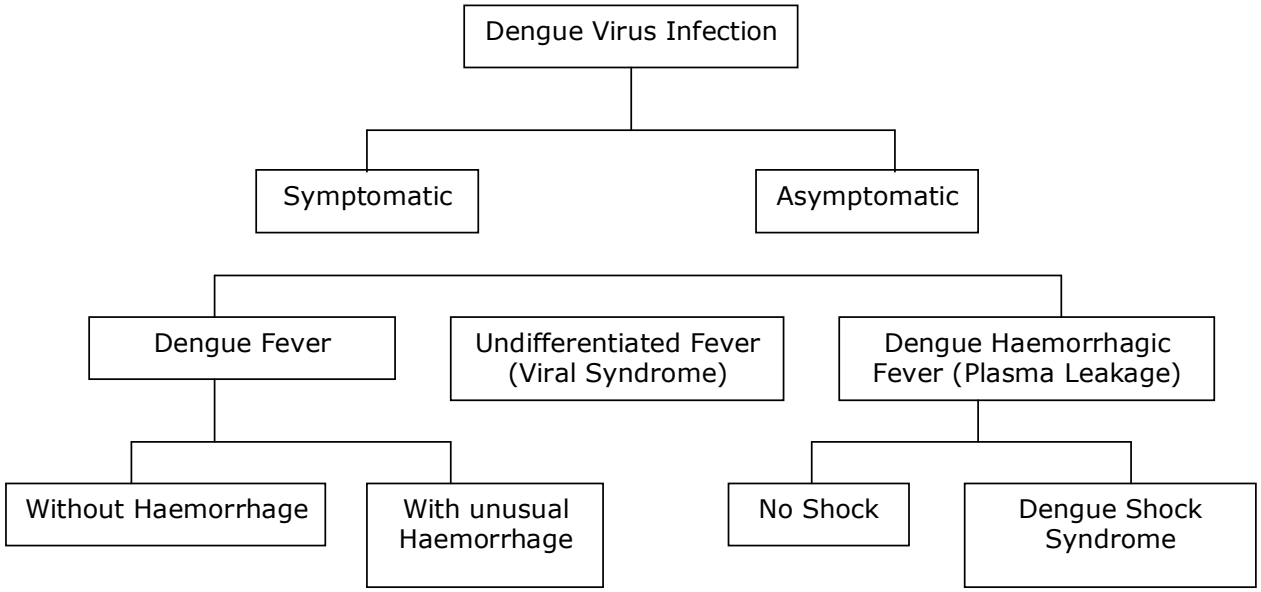

Figure 2: Manifestations of Dengue virus infection

Inoculation into mosquito. Antigen can be detected by immunoflourescence from mosquito.

Cell culture. Detection of antigen by antibody staining, cytopathic effects, and plaque formation.

Inoculation into suckling mice. Sign and symptom of encephalitis develop.

Antigen detection in fixed tissue. They can be detected in peripheral blood leukocytes especially during the febrile phase of illness. Dengue antigen can also be found in liver and lung at autopsy.

Serological tests: Reverse Transcriptase – *PCR* amplification of Dengue genotype RNA. The advantage is that during convalescence, when circulating antibodies interfere in the diagnosis, the dengue virus RNA genotypes in the blood circulation can be identified. But the test is highly prone to false positive results due to contaminations (Thisyakorn and Nimmannitya, 1993).

Mac ELISA. This test helps in diagnosis of primary and secondary dengue infection, where the haemogglutination inhabitation antibody is not confirmed. In addition, the detection of anti-flavored IgM in cerebrospinal fluid can be recognized. It is important that antiflavivirus IgM can be produced due to other virus such as West Nile virus. Therefore, there can be cross-reactivity. Mac-ELISA is a more sensitive test and the disadvantages are very little (Thisyakorn and Nimmannitya, 1993).

Haemagglutination-Inhibition Test (HIT). In this test, paired sera are used and it is the sera available upon hospital admission and second sera at the time of discharge. The advantage of this test is that it is sensitive, reproducible and local reagents can be used. The primary dengue infection is characterized by the slow production of the HIT antibody. The secondary response in contrast has rapid production of HIT antibody. Since this test does not differentiate among different immunoglobulin isotypes, therefore, the identification of primary antibody response is based on low level of antibody titre. The closely related flavivirus such as Dengue virus, Japanese encephalitis virus, and West Nile virus; can not be differentiated by this HIT.1(Thisyakorn and Nimmannitya, 1993).

Both Mac ELISA and HIT techniques are used in Dengue antibody detection. HIT is the gold standard test. It is rather difficult to perform. It has to be done in a well-set laboratory. It needs two sera specimens (at least 10-14 days apart) for making diagnosis. The definitive diagnosis is four-fold rising in the antibody. The ELISA test is easy to perform. There are many rapid slide tests (ELISA kit), which takes only 5-10 minutes for the results. The diagnosis is rising IgM antibody to more than 40 U.

Neutralization test. The most sensitive and specific test is the serum dilution, virus constant and plaque reduction tests. In early convalescence, specific neutralizing antibodies are detected, after primary infections. In secondary dengue infection, high titre neutralizing antibody is produced against all four dengue virus serotypes and other flaviviruses (Thisyakorn and Nimmannitya, 1993).

Dot-blot Immunoassay. This is a new technique and at least one blot immunoassay for dengue antibodies is available (Thisyakorn and Nimmannitya, 1993).

Complement fixation test. It is the least sensitive than other tests. Complement fixing antibody typically appears after IgM or HI antibody and it is usually more specific. The advantage is that it helps in the diagnosis in late dengue infection from paired serum(Thisyakorn and Nimmannitya, 1993).

Summary of laboratory diagnoses

The dengue fever can be established under the following guidelines:The dengue virus can be isolated from serum and autopsy; The detection of IgM titre (four fold greater) in paired serum sample; Detection of dengue virus antigen in autopsy tissue, serum or cerebrospinal fluid by ELISA, or immunofluorescence; Demonstration of dengue virus gene sequence by polymerase chain reaction.

The two basic methods for establishing a laboratory diagnosis of dengue infection are detection of the virus (e.g. culture) and detection of anti-dengue antibodies in serum (Nimmannitya, 1993).

The dengue virus causes viraemia, which last roughly 2-7 days. The virus infects the peripheral blood mononuclear cells. The antigen staining is usually 1-10 infected cells per 10,000 cells. The corresponding antibodies appear after several days of fever. IgM is the main isotype, which can be detected by Mac-ELISA. 80-90 % of IgM can be identified within 5-10 days. Anti dengue IgM appears shortly afterwards. Both IgM and IgG antibodies neutralize dengue virus. The neutralizing antibodies rapidly increase as fever subsides and can therefore interfere with isolation of the virus from serum (Kalayanarooj, 1998).

Management

The management of Dengue hemorrhagic fever is largely based upon fluid therapy (both oral and infusion) to which the laematocrit value is the key guide to fluid and infusion.

The general management of patients needs teamwork and separate wards. The wards should have mosquito nets to prevent nosocomial Dengue transmission. The patients need special laboratory investigation when they are high-risk subjects. Such individuals are young infants (<1 year old), DHI, overweight, encephalopathy, thalassemia, Glucose-6-Phosphate Dehydrogenase deficiency and congenital heart diseases (WHO/SEARO, 1999).

General guidelines in the treatment of Dengue Haemorrhagic Fever (DHF) are as follows(Yunus et al., 1998; WHO/SEARO, 1995): Hourly clinical assessment of the patient of DHI should be done; Haematocrit determination and platelet count are important for the early diagnosis of DHI; If the haematocrit is increasing, fluid should be changed to colloidal solution (Dextran). If the haematocrit is decreasing, the fresh whole blood transfusion is necessary; Oxygen can be administered for shock and sodium bicarbonate should be given for acidosis. Steroids and antibiotics should not be given in DHF; Aspirin or Ibuprofen is not indicated in DHF. Oral paracetamol can be given not more than + doses in 24 hours (Thisyakorn and Nimmannitya, 1993).

Prevalence

The global prevalence of dengue has grown dramatically in recent decades. The disease is now endemic in more than 100 countries in Africa, the Eastern Mediterranean, South-east Asia and the Western Pacific. Southeast Asia and the Western Pacific are most seriously affected. Before 1970 only nine countries had experienced DHF epidemics, the number had increased more than four-fold by 1995 (Mahmood and Mahmood, 1994).

Some 2500 million people – two fifths of the world's population – are now at risk of dengue fever. WHO currently estimates there may be 50 million cases of dengue infection worldwide every year (Mahmood and Mahmood, 1994).

In 2001 alone, there were more than 609 000 reported cases of dengue in the Americas, of which 15 000 cases were DHF. This greater than double the number of dengue cases which were recorded in the same region in 1995 (Mahmood and Mahmood, 1994).

Not only is the number of cases increasing as the disease is spreading to new areas, but explosive outbreaks are occurring. In 2001, Brazil reported over 390 000 cases including more than 670 cases of DHF (Mahmood and Mahmood, 1994).

Vector control

The most important vector of dengue virus is the mosquito *Aedes aegypti* that should be the main target of the vector control. There are several ways such as vector surveillance, improvement of water supply and storage, solid waste management and chemical controls. Besides DDT, organophosphate insecticides such as fenthion, malathion, can be used. Larvicidal agents can be used also in containers having drinking water. These chemicals are 1% temephos sand granules. All Larvicidal agents have extremely low biological toxicity (Franklin and Brown, 1994).

Transmission

Dengue viruses are transmitted to humans through the bites of infective female aedes mosquitoes. Mosquitoes generally acquire the virus while feeding on the blood of an infected person. After virus incubation for 8-10 days, an infected mosquito is capable through blood feeding of transmitting the virus, to susceptible individuals for the rest of its life. Infected female mosquitoes may also transmit the virus to their offspring by transovarial (via the eggs) transmission, in sustaining transmission of virus to humans has not yet been delineated (Mahmood and Mahmood, 1994).

Humans are the main amplifying host of the virus, although studies have shown that in some parts of the

world monkeys may become infected and perhaps serve as a source of virus for uninfected mosquitoes. The virus circulates in the blood of infected humans for two to seven days, at approximately the same time as they have fever; *aedes* mosquitoes may acquire the virus when they feed on an individual during this period (Mahmood and Mahmood, 1994).

Immunization

Vaccine development for dengue and DHF is difficult because any of four different viruses may cause the disease, and because protection against only one or two dengue viruses could actually increase the risk of more serious diseases. Nonetheless, progress is being made in the development of vaccines that may protect against all four dengue viruses. Such products may become available for public health use within several years (Mahmood and Mahmood, 1994).

CONCLUSION

The prevention of dengue fever is largely based upon the identification of risk factors and awareness. Factors responsible are overpopulation, uncontrolled urbanization, inadquate waste management.

Seroepidemiological survey showed that dengue infection has both primary and anamnestic infection. Studies have shown that the risk of developing of Dengue Shock Syndrome following anamnestic dengue infection with Dengue type-2 was 14 times greater than Dengue shock syndrome due to type 1,3 and 4. The role of complement, cytokines and IgG 1 in the pathogenesis of Dengue shock syndrome is under investigation, particularly to type-2, which is of epidemiological importance (Thein, 1994). Thus, series of experiments will aid in the development of an appropriate vaccine. It is important to bear in mind that Aedes mosquito is also a vector for Yellow Fever. The main threat of Yellow fever is the periodic invasion of the virus to densely populated urban areas where it can be transmitted by human biting species. Therefore, it can be anticipated the future impact of this tropical disease in Bangladesh. The foremost essential step regarding the prevention of this deadly dengue is the indentification and mode of Aedesmosquito breeding and the method of spraying insecticide/larvaecide at the appropriate sites (Mahmood and Mahmood, 1994).

It was recently found that papaya leaf juice and Papaya Juice could be given to the dengue patients as it may reduce the the fever (Not recommended by a physician or a journal publication). Most Aedes mosquitoes breed within houses where the reach of government investigations is limited. The participation and cooperation of general people with government agencies is essential for Aedes control programs.

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