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Dengue Fever as a Continuing Threat in Tropical and Subtropical Regions around the World and Strategy for Its Control and Prevention

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ABSTRACT

Dengue fever also known as break-bone fever has emerged as a worldwide problem afflicting millions of people each year in tropical and subtropical regions. Dengue viral infection is transmitted by the bite of an infected female Aedes mosquito and the symptoms appear on an average of 4-7 days after an infective bite of vector. The dengue virus of the genus Flavivirus, is a tiny spherical structure that can only replicate inside a host organism and comprising four types of viruses called serotypes due to different interactions with the antibodies in human blood serum. The present paper highlights the approaches having the potential to greatly reduce the global burden of this disease that solely depends on adoption of effective control measures, and its prevention and control. Urbanization, rapid movement of peoples and goods, favorable climatic conditions and lack of trained staff all have contributed to the global increase of dengue. Typical dengue is fatal in less than 1% of cases, and for helping in its recovery, healthcare experts recommend to take medicine to reduce fever. Dengue control strategy supports an integrated approach to sustain control measures, vector management and coordinated action among multi-sectoral partners at all levels. Its leading rule is to synchronize prevention, entomological and epidemiological surveillances, and case management within existing health systems, making sure that efforts to control disease are coherent, ecologically sound, cost-effective and sustainable.

INTRODUCTION

Dengue fever is a virus infection caused by the dengue virus of the genus Flavivirus within the family Flaviviridae. Other flaviviruses include Japanese encephalitis and yellow fever. Dengue virus is a leading cause of illness and death in the tropics and subtropics due to dengue disease. There are four distinct serotypes of dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4) all of which have the potential to cause either classic dengue fever or the more serious form of the disease, dengue haemorrhagic fever (DHF). There are also reported five strains of the virus, called serotypes, and because dengue is caused by one of five serotypes of virus, it is possible to get dengue fever multiple times [1]. Several reports have indicated that DENV-2 and DENV-3 may cause more severe disease than the other serotypes and that DENV-4 is responsible for a milder illness [2]. The dengue virus is carried and spread by mosquitoes in the genus Aedes, which include *Aedes aegypti* (Linnaeus) (principal dengue vector) and *Aedes albopictus* Skuse (have a limited ability to serve as dengue vector) of order Diptera in Family Culicidae, which are easily identifiable by distinctive black and white stripes on their body and their life-cycle averages about seven days. The male mosquitoes feed only on plant nectar, but, only the female mosquito feeds on blood because it needs the protein found in blood to produce eggs. The female mosquito is attracted by the body odors, carbon dioxide and heat emitted from the animal or humans [3].

Signs and symptoms of dengue

Dengue is an acute illness of sudden onset that usually follows a benign course with symptoms such as headache, fever, exhaustion, severe muscle and joint pain, swollen lymph nodes (lymphadenopathy) and rash. The presence of fever, rash, and headache are particularly characteristics of dengue. Other signs of dengue fever include bleeding gums, severe pain behind the eyes, and red palms and soles. Sometimes symptoms are mild and can be mistaken for those of the flu or another viral infection. The disease can be classified into five presentations including; non-specific febrile illness, classic dengue, dengue hemorrhagic fever, dengue hemorrhagic fever with dengue shock syndrome, and other unusual syndromes such as encephalopathy and fulminant liver damage. Clinical features vary with the age of the patient and between 15% and 90% of cases are asymptomatic or sub-clinical [4]. Dengue hemorrhagic fever is a specific syndrome that tends to affect children under 10 years of age that is a more severe form of the viral illness. The possible signs of hemorrhage fever are petechiae (small red or purple splotches or blisters under the skin), bleeding in the nose or gums, black stools, or easy bruising. This form of dengue fever can be life-threatening and may progress to the most severe form of the illness, dengue shock syndrome. Still, serious problems can develop and the symptoms may progress to massive bleeding, shock, and death which is called dengue shock syndrome.

Young children with dengue often have an undifferentiated febrile illness with a maculopapular rash, which typically spreads from the trunk to include the limbs and face and which occurs between days 3 and 5 of the illness. Upper respiratory tract infections are common and most infections in children are asymptomatic or minimally symptomatic. Classic dengue is more common amongst older children, adolescents and adults. It has an abrupt onset with a high fever which is often accompanied by a severe headache, myalgia, arthralgia, nausea, and vomiting. Most infections are self-limiting with improvement in symptoms and rapid recovery occurring in 3 to 4 days after the onset of the rash. Dengue hemorrhagic fever is primarily a disease of children under 15 years in hyperendemic areas. It is characterized by increased capillary permeability and haemostatic changes e.g., bleeding under the skin (purpura), from the gums and gastrointestinal tract. Mortality can be as high as 10-20% if case is left untreated. Dengue hemorrhagic fever with shock is accompanied by respiratory and or renal failure. Mortality, if case is left untreated, can be 40%. Survival rates are significantly higher if the patient is treated in hospital by experienced staff, leading to low mortality rates of 1% to 2% [5,6,7].

Information on dengue clinical classification has shown some confusion regarding the clinical classification of this disease. The current World Health Organization (WHO) classification used classifies dengue into dengue fever, dengue hemorrhagic fever and dengue shock syndrome. During 2009, a new classification of dengue proposed by WHO Tropical Disease Research (TDR) has been available as “Newly suggested classification for better clinical application” in the WHO TDR-2009 dengue guidelines. The current WHO classification is recommended for continuing use because the newly suggested TDR classification creates about 2 times the workload to health care personnel. In addition, the TDR classification needs dengue confirmatory tests. However, current WHO classification needs to be modified for more simple and friendly use. The suggested modification is to address plasma leakage as the major criteria, and Tourniquet test positive or bleeding symptoms can be considered as minor criteria. Unusual dengue is proposed to be added to the current WHO classification to cover those patients who do not fit with the current WHO classification.

Peoples and younger children who have never suffered the infection before are liable to have milder cases than adults and older children. Peoples with a second or subsequent dengue infection as well as those having weakened immune systems are understood to be at greater hazard for developing dengue hemorrhagic fever which is a rare complication characterized by high fever, damage to lymph and blood vessels, bleeding from the nose and gums, enlargement of the liver, and failure of the circulatory system. However, an attack of dengue produces immunity for a lifetime to that particular viral serotype to which the patient was exposed. Lifelong immunity to the infecting virus serotype occurs in those peoples who recover, however, infection with one serotype does not confer immunity to the other three serotypes or to other Flaviviruses. It is not certain what causes progression to the severe form, although it has been suggested that previous infections with a different serotype of the virus predisposes to dengue hemorrhagic fever when a person becomes re-infected. Infection with one serotype does not protect against the others, and sequential infections put people at greater risk for dengue hemorraghic fever and dengue shock syndrome.

Transmission of dengue

Among the actions which play an important role in the elimination of the dengue, is focusing on its transmission. Dengue does not spread directly from one person to another person, but its transmission occurs following a bite from an infected Aedes mosquito. It is most widely transmitted by *Aedes aegypti* and *Aedes albopictus* (Asia, Philippines and Japan), other *Aedes* species also transmit disease in specific areas; *A. polynesiensis*, *A. scutellaris* and *A. pseudoscutallaris* (Pacific Islands and New Guinea), *A. polynesiensis* (Society Islands) and *A. niveus* (Philippines) [8]. Dengue is mostly transmitted between people by the mosquitoes *A. aegypti* and *A. albopictus*, and symptoms of infection usually begin 4-7 days after the mosquito’s bite and typically last for 3-10 days. In order for transmission to occur, the mosquito must feed on a person during a 5 days period when large amounts of virus are in the blood; this period usually begins a little before the persons become symptomatic. After entering in the mosquito with the blood meal, the viruses require an additional of 8-12 days incubation before it can then be transmitted to another human. The mosquitoes remain infected for the remainder period of life, which might be days or a few weeks.

Only the female mosquito transmits the dengue virus, which is a daytime biter, both inside and outside homes, and is most active in the hours after sunrise and before sunset. The cycle of transmission typically involves humans and mosquitoes. The virus is spread from an infected human to a mosquito and then to another human, often in areas where there are dense human populations. In parts of South East Asia and Africa, the transmission cycle may also involve jungle primates that act as a reservoir for the virus. The mosquito becomes infectious 8-10 days after feeding and remains infectious for life (2-3 months). In non-immune persons, dengue begins with a fever lasting 1 to 5 days. The risk is thought to be higher during periods of intense mosquito feeding activity in two to three hours after dawn and during the early evening. The incubation (time between becoming infected and developing symptoms) period is 5 to 8 days. After biting an infected person it takes 8-12 days before the mosquito can infect other people [9].

There are several genetic factors controlling the transmission of dengue virus strains in a natural population of mosquitoes. There has been indication that the transmission of these viruses in nature depends not only on mosquito genetic factors but also on their specific interaction with viral genetic factors. It has been discovered that a set of genetic factors making mosquitoes more or less able to transmit dengue viruses are present in the natural mosquito population. Surprisingly, the effects of some of these genetic factors depend on which strain of the virus the insect is exposed. Consequently, a genetic factor conferring resistance to one virus strain may turn into a susceptibility factor against another strain [10]. Therefore, these findings significantly would improve our understanding of dengue biology in nature and open new avenues such as developing strategies to inhibit dengue virus development in mosquitoes so that they can no longer transmit the virus. It is advocated that the effect of host genetic factors may vary depending on the genetic variations of the pathogenic agent itself. Therefore, genetic susceptibility to infectious diseases is not solely an intrinsic characteristic of the host but also a trait shared with the pathogen.

Epidemiology

Amongst the measures which take part in the elimination of the dengue, is dengue epidemiology which is the study of the patterns, causes, and effects of health and disease conditions in different populations. Dengue has been reported seeing as the hundreds of year ago and since that time major epidemics have been occurred at certain intervals in the world. The vectors Aedes mosquito and the dengue virus are dependent to transport from one to another population, on sailing vessels and when a new serotype is introduced, new epidemics occur [11]. The epidemiology of dengue changes when there are growth and the urbanizations where millions of peoples move to the cities, and then dengue virus spread rapidly and the disease develops into pandemic proportions [12].

The main dengue vector, *A. aegypti,* is found worldwide and epidemic of dengue has been increased, and all four serotypes have now been documented in certain localities. The factors influencing dengue vector densities and ultimately viral transmission are ecological and biological which tend to promote disease transmission or inhibit efforts at vector control. Vector breeding and the production of adult *A. aegypti* are influenced by a complex interplay of factors. Natural factors include climate (temperature, humidity and rainfall), and development of urban settlements and agriculture also have a profound impact. Biological factors relate to the behavior of the dengue vector *A. aegypti* and the transmission dynamics of the disease. In the ecological model, dengue risk is related to households situated in the ecotope of residential mixed with commercial and densely populated urban residential areas and, high historical dengue risk areas. Based on extensive research during the study, the incidence of dengue fever was found significantly associated with the following factors: - higher household index, higher container index, and higher Breteau index. The risk of dengue is also associated with elevated temperature, higher humidity and higher rainfall. The risk of dengue is inversely associated with duration of sunshine, where the numbers of dengue cases are lower as the sunshine increases. These data suggest that indices of mosquito and climate factors are main determinants of dengue fever and the global climate change will likely increase the burden of dengue fever infection. The intensified surveillance and control of mosquito during high temperature and rainfall seasons may be an important strategy for containing the burden of dengue fever. Incidence of dengue is reported to be influenced by climatic factors which propel increased emergence and transmission of vector-borne diseases [13]. While precipitation levels have an effect on dengue incidence, non-climatic factors such as presence of breeding sites, vector control and surveillance are important issues that need to be addressed. Only very limited environmental management can be undertaken and this will presumably affect the populations of *A. aegypti*. While climatic factors can not be controlled or modified, their monitoring can help to understand their effects on mosquito-transmitted diseases.

Dengue diagnostic

The increasing frequency and intensity of dengue outbreaks in endemic and non-endemic areas require a rational, and evidence based response. Information of a country on dengue should be based on compulsory notification and reporting (surveillance), with laboratory confirmation or by using a clinical syndromic description. Several countries should have additionally sentinel sites with active dengue reporting, some also may have virological surveillance, and a formal definition of dengue outbreak to seasonal variations. The collected data by countries on a range of warning signs may identify outbreaks early, but should develop a systematic approach to identify and responding to the early stages of an outbreak. Outbreak response plans can vary in quality, particularly regarding the early response. The surge capacity of hospitals with dengue outbreaks varies; those that could mobilize additional staff, beds, laboratory support and resources can cope best in comparison to those improvising a coping strategy during the outbreak. Certain serological, virological and entomological investigations can be carried out to confirm the etiology of outbreak. A model contingency plan for dengue outbreak prediction, detection and response may help national disease control authorities to develop their own more detailed and functional context specific plans. There are numerous policy challenges to provide an effective public health response system in a fragile state, and a weak state has limited response capabilities. Disease surveillance and response plans need to be country-specific, consider state response capacity and the level of endemicity. Two feasible solutions for this purpose are (1) going upwards to regional collaboration for disease and vector surveillance, laboratory assistance and staff training; (2) going downwards to expand upon community mobilization, ensuring that vector control is anticipatory to outbreaks.

Laboratory confirmation of dengue infection relies on isolation of the virus in cell culture, the identification of viral nucleic acid or antigens, or the detection of virus-specific antibodies (from onset of fever to 10 days post-infection) or by molecular methods. Direct virus detection or virus components (RNA or antigens) can be detected in serum, plasma, whole blood and infected tissues (antigen detection), but serological tests (IgM or IgG) are more commonly used to diagnose dengue infections. Different patterns of antibody responses are observed when patients experience a first (primary) or subsequent (secondary) dengue infection. In primary infections, immunoglobulin M (IgM) is detected after 5 or more days subsequent to the onset of illness and immunoglobulin G (IgG) is detected from 10-15 days (IgM-positive and IgG-negative). In secondary infections, IgM appears earlier or in the same time frame, but are usually at lower titres than in primary infection. IgG is present from the previous infection and the titre increases rapidly. Haemagglutination inhibition (HAI) antibody titres in primary infections peaks at 1:640, whereas titres of 1:1280 or greater are common in secondary infections (IgG should be higher than 1,280 haemagglutination inhibition in serum). Acute infection with dengue virus is confirmed when the virus is isolated from serum or autopsy tissue specimens, or the specific dengue virus genome is identified by reverse transcription-polymerase chain reaction (RT–PCR) from serum or plasma, cerebrospinal fluid, or autopsy tissue specimens during an acute febrile illness. Methods such as one-step, real time RT–PCR or nested RT–PCR are now widely used to detect dengue viral genes in acute-phase serum samples [14, 15, 16, 17, 18].

Strategy for Dengue Control

As there is no specific treatment or vaccine yet available, the current dengue prevention methods are focused on eradicating breeding sites of vectors. The integrated strategy for dengue is expected to produce a qualitative leap forward in prevention and control through stronger partnerships among the state, its various ministries, and governing bodies, private companies, and the range of community and civil groups at all levels. This strategy, once implemented can reduce risk factors for dengue transmission, establish an integrated epidemiological surveillance system, decrease of Aedes mosquito populations, prepare laboratories to better detect and identify the virus, and optimize diagnosis and treatment. As a result of such actions, there can be decrease in frequency, severity and magnitude of dengue outbreaks and epidemics.

Treatment of dengue

There is no definite antiviral treatment for dengue, however, severe dengue is a potentially lethal complication and its early clinical diagnosis and careful clinical management by experienced physicians can often save lives. Supportive nursing care and careful management of fever, electrolytes, and clotting parameters are the standard treatments. Other supportive care with analgesics, fluid replacement and bed rest is usually sufficient. For typical dengue fever, the treatment is directed toward relief of the symptoms (symptomatic treatment). Adequately management of dengue generally requires hospitalization and if a clinical diagnosis is made early, a health expertc can provide effective treatment using pain relievers. Management of severe dengue requires careful attention to fluid management to prevent dehydration and proactive treatment of hemorrhage.

As there is no any particlar medication for treatment of a dengue infection, vaccines are an important way to protect peoples from viral infections, which are prepared from weakened or inactive viruses or microorganisms that cause diseases. When a healthy person is given a vaccine, immune system of that person responds to the virus or microorganism and stimulates the body to produce antibodies against the disease-causing agent, which increases the immunity in individual to the disease. Beside to develop dengue vaccines, scientists are working to design antiviral drugs against dengue which are an alternative to vaccinations, and work by reducing the level of virus in an infected person, but research on antivirals is a relatively new field. As there is not yet any vaccine, medicine or antibiotic to prevent infection with dengue virus or to treat it, the most effective protective measures are those that avoid mosquito bites.

Prevention of dengue

The prevention of dengue requires control or eradication of the mosquitoes carrying the virus that causes dengue especially during daylight hours. When a mosquito bites a person who has dengue virus in his or her blood, the mosquito becomes infected with the dengue virus. An infected mosquito can later transmit that virus to healthy peoples by biting them. The transmission of the virus to mosquitoes must be interrupted to prevent the illness. To this end, patients are kept under mosquito netting until the second bout of fever is over and they are no longer contagious.

The Aedes mosquitoes breed in artificial containers and to prevent the spread of dengue fever, one must first prevent the breeding of its vectors, which prefer to breed in clean, stagnant water mainly found in homes. One can get rid of the Aedes mosquitoes by frequently checking and removing stagnant water in premises, turning over all water storage containers, changing water in vases and bowls, removing water from flower pots on alternate days, clearing blockages in roof gutters monthly, and empting stagnant water from old tires and trash cans. Governmental initiatives to decrease mosquitoes can also help to keep the disease in check and might be strongly effective.

The most effective protective measures are those that can avoid mosquito bites by wearing long pants and long sleeves shirts. For personal protection, mosquito repellant sprays that contain DEET can be used when visiting places where dengue is endemic. The *A. aegypti* mosquito is a daytime biter with peak periods of biting around sunrise and sunset. It may bite at any time of the day and is often hidden inside homes or other dwellings, but may also bite at any time during the day, especially indoors, in shady areas, or when the weather is cloudy. Limiting exposure to mosquitoes and staying indoors two hours after sunrise and before sunset can help to prevent mosquito bites. Use of other protection measure such as window screens (1mm insect screens), mosquito net, insecticide treated materials on house, boat, caravan or tent, an coils and vaporizers are imperative.

When any person is infected with dengue virus, an early recognition of disease and a timely helpful treatment may significantly lesser the jeopardy of medical complications and death cases. Physician can diagnose dengue infection with a blood test by checking the presence of the virus or antibodies in blood. If any one becomes sick after traveling to a tropical area, let the Physician to know the matter. This can allow Physician to evaluate the possibility that patient symptoms are caused by a dengue infection. Key strategy in dengue control is to tackle the root of the problem and breaking the source of transmission as quickly as possible when suspected and confirmed cases emerge. The primary preventative measure to reduce dengue infections is the control of mosquito populations in the regions where the threat of dengue is high. New chemical, biological and genetic approaches are also being developed and may provide promising alternatives to control mosquito populations and prevent dengue infections.

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