Dengue Fever in the Western Hemisphere

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Dengue virus, an arthropod-borne viral agent, causes two distinct diseases: classic dengue fever (DF) and dengue hemorrhagic fever (DHF). There are four dengue virus serotypes: DEN-1, DEN-2, DEN-3, and DEN-4. Although infection with dengue stimulates immunologic response to a serotype, there is no cross-immunity conferred. Hence, a person can potentially be infected with each serotype during his or her lifetime. An infected female *Aedes* mosquito transmits the virus from person to person while feeding. The disease, now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and Western Pacific, is spreading to new areas and causing explosive outbreaks. Because of the major impact on lives and local economies epidemics produce, rapid detection of dengue infection has become an important public health research issue. Recently developed serological procedures to detect dengue infections have shown great potential for field use.

ABBREVIATIONS: DF =dengue fever; DHF= dengue hemorrhagic fever; DSS= dengue shock syndrome; ELISA = enzyme-linked immunosorbent assay; MAC=IgM antibody capture; PCR = polymerase chain reaction; RT-PCR= reverse transcriptase polymerase chain reaction; VHF = viral hemorrhagic fever.

INDEX TERMS: Dengue fever. dengue hemorrhagic fever; dengue virus.

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LEARNING OBJECTIVES

1. Describe the general viral characteristics of dengue viruses.
2. Describe how dengue fever is transmitted and the species of the vectors associated with dengue virus transmission.
3. List three factors that promote dengue virus infections in endemic areas.
4. Describe the two clinical syndromes produced by dengue fever virus.
5. Discuss three laboratory diagnostic methods used to detect dengue fever.

Dengue virus is one of the emerging arthropod-borne viral agents of the century. This virus causes two distinct diseases, classic dengue fever (DF) and dengue hemorrhagic fever (DHF). Worldwide, DF and DHF have become major public health issues.[1] Dengue infections may produce nonspecific viral symptoms, such as headache, severe bone or joint and muscular pains, and rash. However, a more serious, sometimes fatal form of dengue infection, (DHF) may occur. In patients with DHF, hypovolemic shock may develop because of plasma leakage. This clinical complication which could be fatal, is called dengue shock syndrome (DSS).[1,2] With

more than half of the world population at risk of infection due to geographical location, dengue infection is the most prevalent viral hemorrhagic fever (VHF) in the world.[2,3]

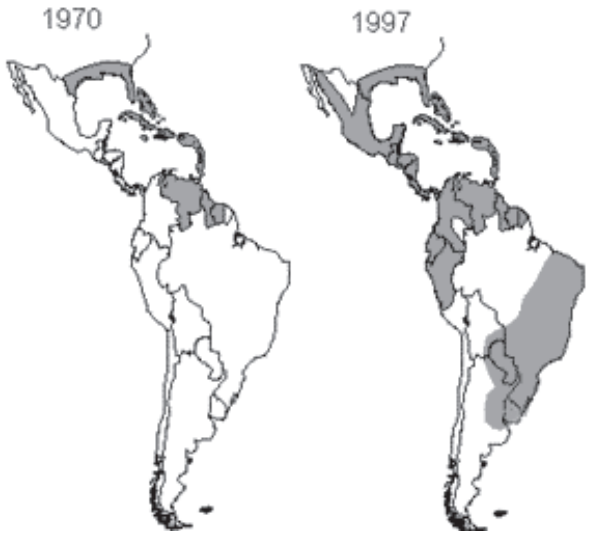
HISTORY AND DISTRIBUTION OF DENGUE

The word 'dengue' comes from the Spanish adaptation of the Swahili phrase 'ki denga pepo'. The phrase refers to a person who is believed to have been overtaken by a spirit.[4] However, it was an American physician, Benjamin Rush, who first referred to dengue as 'breakbone fever'. This reference was attributed to one of the major symptoms of the new disease, arthralgia and myalgia.[5]

Dengue was first reported, almost simultaneously as an epidemic, in Asia, North America, and Africa in the late eighteenth century.[2] In 1779, dengue was first described in Cairo, Egypt and in Jakarta, Indonesia. In 1780, a major epidemic of dengue occurred in Philadelphia.[4,5] At that time, dengue was considered a disease of tropical visitors and was not considered fatal when a person became infected. In addition, during this period, sailing vessels were the only means to transport the virus and the vector mosquito, hence, there were decades between major epidemics.[2,5]

At the end of World War II, a global pandemic of dengue, centered in Southeast Asia, began. DHF was first recognized in the Philippines in 1953 and by 1975, had become a leading cause of death and hospitalization among children in endemic countries in that region.[4,6] Epidemic DHF has not been reported in Africa (although epidemics of DF have) or the Middle East, but sporadic cases similar to DHF have been noted in that region.[4]

Figure 1. Distribution of *Aedes aegypti* (red shaded areas) in the Americas in 1970, at the end of the mosquito eradication program, and in 1997



Dengue fever and dengue hemorrhagic fever have emerged as a public health threat in the Americas when in 1970, the mosquito eradication program was terminated. *A. aegypti*, the vector for dengue, is also the vector for yellow fever. Because the goal of the Pan American Health Organization was to eliminate yellow fever, it organized the campaign that eradicated the vector from most Central and South American countries by the end of the 1960s. Since, however, the distribution of the *A. aegypti* has been wider than before the program began as shown in Figure 1.[2] The World Health Organization (WHO) estimates that there may be anywhere from 50 million to 100 million cases of classic dengue and about 500,000 cases of DHF each year. It also estimates that half of the world's population lives in areas where the disease is endemic.[7,8] Moreover, in 1970, only nine countries reported cases of DHF. Twenty five years later, forty one countries reported cases of the more serious form of the disease, an indicator of how this disease is rapidly emerging.[5,7,8]

DENGUE VIRUS AND DENGUE INFECTIONS

Dengue virus belongs to the family Flaviviridae. It is a single-stranded positive polarity RNA virus. There are four different serotypes of Dengue: DEN-1, DEN-2, DEN-3, DEN-4.[9,10] Although dengue infections result in serological immunity, there is no cross-protection between serotypes. Therefore, a patient can potentially become infected with each serotype in his or her lifetime. In addition, as the virus spreads to new geographical locations, the severity of the infections also increases. This phenomenon may be attributed to the ability of the dengue virus to produce two distinct infections. Dengue fever, also called classic dengue, a self-limiting benign infection, occurs because of a person's first exposure to the dengue virus. Individuals who are exposed to two or more dengue virus serotypes can develop dengue hemorrhagic fever, or dengue hemorrhagic shock syndrome.[6]

Classic dengue fever generally occurs in older children and adults. In countries such as Nicaragua, where the virus is endemic, greater than four percent of the population older than 15 years of age has antibodies to one of the dengue virus serotypes.[1] The incubation period is about 3 to 15 days. Once infected, patients experience a typical viral syndrome, similar to influenza. Patients develop fever, chills, myalgia,

headache, and bone pain (hence, the nickname 'breakbone fever').[5,9] The symptoms may persist for a few days and patients sometimes begin to feel better before the second phase of the disease follows. During the second phase, patients may develop macular rash, retro orbital pain, nausea, vomiting, and reappearance of fever. The infection may also be confused with rubella, measles, and mumps. The disease usually resolves within one to two weeks.[6,7]

DHF is a more serious form of dengue. Individuals are at risk for DHF when they become infected with one dengue serotype and live in an area in which other serotypes of the virus are endemic. If they become reinfected with another serotype, they may then develop DHF. Exposure to two different types of dengue virus serotypes is necessary for DHF to develop. Patients who develop DHF show symptoms of dengue fever, but in addition, they suffer from thrombocytopenia, hemorrhage, and shock; sometimes death occurs. DHF has four characteristic features: high fever, hemorrhage, enlargement of the liver, and in severe cases, signs of circulatory failure.[6,7] The severity of the infection may vary, and several stages of DHF have been identified as shown in Table 1.[10] Grades III and IV are often referred to as 'dengue shock syndrome' because of the remarkable circulatory collapse. This syndrome may occur in as many as 30% of patients with DHF. The danger of DHF stresses the possible consequence of living in a geographic area in which more than one strain of dengue virus is endemic.[10]

Table 1. **Clinical stages of dengue infection and the associated manifestations**

Stages	Clinical Manifestations
Grade I	Classical dengue fever; high fever, frontal headache, myalgias, arthalgias, nausea/vomiting, maculopapular rash, thrombocytopenia, and hemoconcentration due to capillary leakage.
Grade II	Signs of hemorrhaging and circulatory failure, lethargy, petechiae, purpura or ecchymoses, bleeding gums, and melena.
Grade III	Circulatory collapse, severe abdominal pain, protracted vomiting, marked change in temperature (from fever to hypothermia), or change in mental status.
Grade IV	Pulse and blood pressure may be undetectable.

EPIDEMIOLOGY AND TRANSMISSION

Aedes aegypti and *Aedes albopictus* are the mosquito vectors that transmit dengue to humans. *A. aegypti*, a domesticated urban mosquito, has adapted to living close to humans. They breed in artificial containers such as old tires, water storage containers, and anything that collects rainwater. Although they are found primarily in the tropics, these mosquitoes are also common in the Southeastern United States, including parts of Texas. *A. aegypti* is also known to rarely migrate further than 100 yards from where it hatched. Because *A. aegypti* usually was not able to survive cold climates, most areas in the U.S., until recent years, have not been at risk for dengue fever. However, global warming has apparently allowed the mosquito to survive winters in areas that were once too cold for the mosquito.[6] In the late 1980s, the Asian tiger mosquito, *A. albopictus*, was introduced to the United States. This new mosquito was transported from China to Houston, Texas, in the wells of old tires containing mosquito larvae. Unlike *A. aegypti*, *A. albopictus*, is less domesticated and migrates further from its breeding sites.[11] There have been reported epidemics of dengue in northern Mexico, and in three separate years, cases of dengue have been reported in Texas, associated with those epidemics. Areas of the U.S. where these two mosquitoes are found are at risk of dengue outbreaks brought in by people returning from travel in tropical areas.[2]

Female mosquitoes become infected when they ingest blood during feeding from a viremic host. The virus multiplies in the salivary glands of the mosquito and then transmits the virus to the next host during the following feeding. Meanwhile, the mosquito vector suffers no harmful effects from the virus.[6]

The DEN-3 virus was the only Dengue virus known to exist in the Americas until 1977 when the DEN-1 virus emerged and for the next 16 years, caused major epidemics. In 1981, DEN-4 caused similar problems. The first cases of DHF were associated with the new strain of DEN-2 when it first appeared in Cuba. DHF is now considered endemic in many regions of the tropical and subtropical Americas.[2] In areas where dengue is endemic, the occurrence of epidemics of DF and DHF, such as in Puerto Rico in 1994–95, has been attributed to the introduction of a serotype that did not previously exist in the area.[1] Presumably, similar events occurred in Nicaragua in 1998.[12,13]

During recent years, the prevalence of dengue has significantly increased worldwide. The disease, now endemic in more than 100 countries in Africa , the Americas, the Eastern Mediterra-

nean, Southeast Asia, and the Western Pacific, is not only spreading to new areas but causing explosive outbreaks. Factors that have been attributed to the spread of dengue include 1) rapid increase in urban populations, 2) increased air travel, and 3) poverty. The growth in urban populations has brought greater numbers of people into contact with the urban mosquito, *A. aegypti.* Therefore, in areas where mosquito breeding is favorable, a wide spread of dengue is most likely to occur. Air travel provides the ideal means for dengue viruses to be carried anywhere in the world where the vector mosquitoes exist. The increased movement of persons around the world makes it possible to find dengue infections in any region or part of the world. Lastly, poverty promotes conditions favorable for mosquito breeding, e.g., water storage in various containers and inadequate solid waste disposal.[14]

HAITI AND THE ABSENCE OF DHF

Haiti offers a unique perspective on the effect of race in the severity of dengue infection. The Haitian population is almost entirely of African descent, about 95%; the rest are White and other ethnicities. When the United Nations was called upon to supervise the transition from a military to a civilian government, soldiers who were deployed to the island began to suffer almost immediately from DF. Researchers noted that DHF or DSS did not occur among the Haitian civilian population. In Haiti, there were no reported dengue cases among the indigenous population. DF-like symptoms were reported but those cases were mainly among non-indigenous patients.[9] There are no records of sporadic cases or outbreaks. This is not to say that the nation is without the virus. Indeed, in a survey of all public school children in grades one through four in the Carrefour borough of Port-au-Prince, only four out of 210 children had no evidence of dengue infection. Further analysis showed a 30% transmission rate in Port-au-Prince, although the rate of DHF and death among children is far lower than in Yangoon, Myanmar, where the rate of transmission is lower.[15]

Moreover, in 1981, during an outbreak in Cuba, it was reported that black patients with DHF/DSS required hospitalization less frequently than white patients. The theory that the black population possessed a gene that limited the ability of the dengue virus to cause an infection and progress to the more severe forms began to arise.[15]

DENGUE IDENTIFICATION

The ability of the laboratory to detect dengue is certainly an important issue. Although dengue can be diagnosed by growing the virus in mosquito cell lines and in vivo with mosquito inoculation, clinical laboratories rarely carry these cell lines. Laboratory-based diagnosis is usually done with serological assays.[6] Acute-phase and convalescent-phase serum samples are tested for anti-dengue antibodies by enzyme-linked immunosorbent assay (ELISA). IgM antibody-capture ELISA (MAC-ELISA) can be used for diagnosis of dengue infections.[12,13,15,16] This standard assay has been modified to reduce time, with demonstrated comparable results.[1] IgG antibodies to the dengue viruses are also assayed by an ELISA technique.[12,13, 16] Because the MAC-ELISA test method may not detect antibodies to the virus in about five percent of secondary infections with dengue, the IgG assay is used to confirm a borderline result by the MAC-ELISA test method. Dengue infection is also confirmed by viral isolation from serum or autopsy tissue, seroconversion, or a four-fold increase in anti-dengue antibodies in a patient's paired sera.[12,13]

It is also possible to determine the serotype of a particular strain of dengue by polymerase chain reaction (PCR) or reverse transcriptase polymerase chain reaction (RT-PCR).[1,15] Jelinek, in his report, raised an important issue on the possible interference of the rheumatoid factor in detecting IgM antibodies.[16] In a rapid immunochromatogenic test for dengue infection detection, a 26% false-positive rate for IgM antibodies was reported, while the IgG had a 100% specificity. This report brought up the possibility of misdiagnosis in patients who have high levels of circulating rheumatoid factor when differential diagnosis includes dengue.[6]

During recent years, new tests that have potential applications for rapid diagnosis of dengue infection have been developed. One of these new tests is a rapid immunochromatographic assay. The test detects antibodies to all four serotypes of dengue viruses, and takes about five to seven minutes to perform. Because the test is simple to perform, it has potential applications in the field as a screening test on patients suspected of DHF/DSS. Test results may provide an early indication of dengue infection, and the opportunity to administer early intervention and treatment. The information may also be used to alert public health officials, and hopefully help reduce the fatality rate from DHF/DSS.[17]

In her study of dengue in Nicaragua, Harris demonstrated the need for rapid and accurate diagnosis. In her study, she reported that almost half of suspected DF cases were wrong when based solely on clinical suspicion. This can be understood when other prevalent diseases in the area are taken into consideration.[1] Rapid identification of dengue virus has become an important goal in the realm of public health re-

search. Recently, the specific binding epitope of the DEN-1 virus on B-cells was identified. The amino acid histidine was found to have a specific role in the B-cell epitope of DEN-1, similar to the role of leucine in the epitopes of DEN-2, DEN-3, and DEN-4. This epitope has been established with a 95% confidence level and with a 100% specificity. The epitope may eventually be used to develop serologic tests in the laboratory, and in the future, possibly even be utilized in the field diagnosis of dengue infections. This will permit the rapid treatment of patients with DF, and more important, DHF and DSS. Clinicians will be able to obtain a diagnostic result within minutes, as opposed to the hours or days which such diagnoses now require.[18]

CONCLUSION

The control and prevention of disease is one of the goals of medicine. Public health seeks to combat diseases which affect many people, not just a select few. The decision to end the mosquito eradication program in 1970 has not only allowed the *A. aegypti* mosquito to reclaim its old habitat, but expand into areas it did not inhabit before the initiation of the program.[4] The reemergence of the *A. aegypti* mosquito has contributed to the increase in the incidence of DHF beginning the latter half of the twentieth century.[4] DHF case fatality rate can exceed 20% without proper treatment. With intensive fluid replacement and supportive therapy, fatality rates can be greatly reduced. Although there are reports of relatively successful vaccine studies in the Far East, primarily in Thailand, no vaccine has been approved by the Food and Drug Administration for use in the U.S.[2] Therefore, the key to patient survival is early diagnosis and appropriate medical intervention. The need for a simple, cost effective screening tool for the early diagnosis of dengue infections and the requirement for continuing research in that area is recognized. [17,18]

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