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Review

Evolution of dengue in Sri Lanka—changes in the virus, vector, and climate

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SUMMARY

Despite the presence of dengue in Sri Lanka since the early 1960s, dengue has become a major public health issue, with a high morbidity and mortality. *Aedes aegypti* and *Aedes albopictus* are the vectors responsible for the transmission of dengue viruses (DENV). The four DENV serotypes (1, 2, 3, and 4) have been co-circulating in Sri Lanka for more than 30 years. The new genotype of DENV-1 has replaced an old genotype, and new clades of DENV-3 genotype III have replaced older clades. The emergence of new clades of DENV-3 in the recent past coincided with an abrupt increase in the number of dengue fever (DF)/dengue hemorrhagic fever (DHF) cases, implicating this serotype in severe epidemics. Climatic factors play a pivotal role in the epidemiological pattern of DF/DHF in terms of the number of cases, severity of illness, shifts in affected age groups, and the expansion of spread from urban to rural areas. There is a regular incidence of DF/DHF throughout the year, with the highest incidence during the rainy months. To reduce the morbidity and mortality associated with DF/DHF, it is important to implement effective vector control programs in the country. The economic impact of DF/DHF results from the expenditure on DF/DHF critical care units in several hospitals and the cost of case management.

1. Introduction

Dengue viruses (DENV) are mosquito-borne flaviviruses that have plagued humans for centuries. Urbanization and human population growth in the tropical regions of the world have produced favorable conditions for DENV transmission. Moreover, changes due to urbanization and human population growth have led to the current global dengue pandemic, characterized by a dramatic increase in DENV infections and an expanding geographic distribution of both DENV and the mosquito vectors,[1] *Aedes aegypti* and *Aedes albopictus*, which transmit DENV among humans.[2]

In Sri Lanka, 48 Aedes species belonging to 11 subgenera have been reported to date. The subgenera are Aedimorphus, Cancraedes, Christophersiomyia, Diceromyia, Finlaya, Mucidus, Neomelaniconion, Paraedes, Rhinoskusea, Stegomyia, and Verrallina. The established DENV vectors A. aegypti and A. albopictus belong to the subgenus Stegomyia.[3,4] However, nothing is known about the role of the remaining 46 Aedes species in DENV carriage and transmission, an area that might shed some light on how DENV survive the intra-epidemic periods.

Sri Lanka has been affected by dengue fever (DF)/dengue hemorrhagic fever (DHF) epidemics for over two decades. DENV infections have been endemic in Sri Lanka since the mid 1960s. DF was serologically confirmed in the island in 1962.[5] The presence of DF in all of the major towns situated below 1200 m elevation was confirmed in 1966 and in 1976–1978.[6]

In Sri Lanka, DF control efforts have been targeted at the disease and vector, including laboratory surveillance for DENV infections in patients and vectors, vector control, social mobilization, clinical management of DF/DHF patients, and the emergency response during outbreaks in terms of accelerated vector control and public awareness through the media. A national-level multidisciplinary task force on DF/DHF has been established to govern the DF/DHF control activities. Furthermore, there are provincial and district-level DF/DHF control activities in place. Training clinicians on clinical management has been carried out continually in an attempt to bring the DF/DHF mortality to zero, or to a minimum level. It is hoped that with the implementation of collective control programs in collaboration with other governmental and non-governmental organizations, with maximum cooperation from the community, the morbidity and mortality of DF/DHF will be reduced in the near future.[5]

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2. The virus

DENV is a flavivirus transmitted by *Aedes spp* mosquitoes. There are four antigenically distinct DENV serotypes, DENV 1–4. Infection with a single DENV serotype leads to long-term protective immunity against that particular serotype, but not against the other serotypes.[7] Thus prior infection with a single serotype of DENV only provides a homotypic protection.

The origin of DENV has been reported to be African, with the distribution of DENV around the world occurring as a result of the slave trade.[8,9] Conversely, it is believed that DENV may have originated in a forest cycle involving lower primates and canopy-dwelling mosquitoes in the Malay Peninsula.[9,10] It is possible that different DENV serotypes evolved in taxonomically related mosquito species in different geographical regions. All four DENV serotypes have been documented in a forest cycle in Asia, while only one (DENV-2) has been documented in Africa.[10] It is currently thought that DENV probably had an Asian origin, which is supported by serosurveys conducted in rural communities of Malaysia in the early 1950s.[9]

Biologically, DENV are highly adapted to their mosquito host and are maintained in the mosquito species responsible for forest cycles, with periodic amplification in lower primates.[10] In the past, due to the clearing of forests and the development of human settlements, DENV has moved out of the jungle and rural environment from where they were and still are transmitted to humans by mosquitoes. Due to the migration of people and commerce, DENV have ultimately moved into the villages, towns, and cities of tropical Asia, where these viruses are most likely to be transmitted sporadically by *A. albopictus* and other closely related peri-domestic *Stegomyia* species.[1]

The four serotypes of DENV have been co-circulating in Sri Lanka for more than three decades and their distribution has not changed drastically in the last 30 years. Although the Sri Lankan population had been exposed to DENV for a long time, the severe forms of DENV infection (DHF and dengue shock syndrome (DSS)) were rare before 1989. Studies have shown the existence of more than one DENV serotype in many parts of the country. There was an island-wide epidemic of DF associated with DENV serotypes 1 and 2 from 1965 to 1968. This epidemic caused 51 DHF cases and 15 deaths.[5] DENV-1 and DENV-2 were isolated from the outbreaks in 1965 and 1966.[11]

A study conducted using mosquito pools in the Western and North-Western provinces of Sri Lanka, including the districts of Colombo, Gampaha, and Kurunegala, has indicated the circulation of multiple DENV serotypes within close proximity to each other.[12] Mosquito pools from Kurunegala district were positive for both DENV-2 and DENV-4, while mosquito pools from Gampaha and Colombo districts had DENV-2 and DENV-4. Higher numbers of positive pools of DENV-1 and DENV-4 have been reported in Kurunegala.[12]

The results of another study performed between 2003 and 2006, indicate the circulation of the DENV-1 serotype in the Colombo district of Sri Lanka.[13] However, this study showed a change in the genetic characteristics of the DENV-1 serotype during the study period. The two isolates of DENV-1 serotype from Sri Lanka obtained in 1983 and 1984 belonged to the South Pacific genotype, and it is believed that some time during the period 1984–1997, the Africa/America genotype of the DENV-1 serotype became established in Sri Lanka; this new genotype of the DENV-1 serotype continued to circulate through 2004. Moreover, the South Pacific genotype of the DENV-1 serotype has not been detected during the past 8 years in Sri Lanka.

In 2009, the largest epidemic of DF/DHF occurred in Sri Lanka (35 008 reported cases, 170 cases/100 000 population, and 346 deaths) and that outbreak was found to have been caused by a new strain of the DENV-1 serotype.[14] Results from DENV nucleic acid detection by reverse transcription (RT)-PCR in patients with DHF from August 2010 to December 2010 showed the predominance of the DENV-1 serotype, which accounted for more than 95% of DF/DHF cases in the Western Province of Sri Lanka;[15] this is similar to the observations made by the Epidemiology Unit of Sri Lanka during that period. Therefore, it appears that the serotype shift may have contributed in some way to the larger DF/DHF outbreaks in the last 2–3 years in the country.

All DENV-2 isolates from Sri Lanka are closely related and belong to the Indian subcontinent/Malaysia genotype. Moreover, there is no evidence of any recent introduction of a DENV-2 strain from outside the island, because the DENV-2 strains from Sri Lanka are more closely related to one another than to any other DENV-2 strain.[13]

DENV-3 strains from Sri Lanka isolated in the 1980s and 1990s belong to the Indian subcontinent genotype (III).[16,17] Genotype III of the DENV-3 strains from Sri Lanka are divided into two distinct clades linked to mild (IIIA) and severe (IIIB) disease epidemics in the island.[16] Moreover, the DENV-3 strains from Sri Lanka isolated in 2003 and 2004 form a new distinct clade that is closely related but different from the DENV-3 clade IIIB viruses that were isolated in the 1990s. This new 2003/2004 clade includes an isolate from 1993, which strongly suggests that the clade is derived from strains that have been circulating on the island for some time.[13]

Unlike group A viruses, the Sri Lankan group B viruses may be associated with severe disease, as the group B viruses are inherently more virulent. Alternatively, the ability of pre-existing antibodies against DENV to neutralize group A viruses but enhance group B viruses may account for the severe disease in group B DENV-3 infections but mild disease in group A DENV-3 re-infections. DENV-2 and DENV-3 are the common serotypes reported in many parts of Sri Lanka. Individuals with previous primary DENV-2 infections have been shown to neutralize the DENV-3 group A viruses better than the DENV-3 group B viruses, and this might be contributing to the severe disease in group B DENV-3 infections.[18]

In Sri Lanka, regular epidemics of DF/DHF have been observed only since 1989. DENV-3 is responsible for many of the infections that progress to DHF.[19,20] DENV-3 isolates obtained before and after the emergence of DHF are very closely related and belong to subtype III, indicating that the emergence of DHF in the island was not due to the introduction of a new subtype of DENV-3 from outside. During DENV surveillance studies in 1997, only DENV-3 was isolated from hospitalized DF cases, whereas DENV- 1, DENV-2, and DENV-3 were isolated from patients visiting outpatient clinics.[21] These observations suggest that DENV-3 is responsible for severe DF in Sri Lanka. However, further studies are required to establish the relative contribution of DENV-3 to severe DF/DHF in Sri Lanka.

The DENV-4 strain isolated in Sri Lanka in 1978 and in 2003/2004 was the Southeast Asian genotype, which indicates that this genotype is established and has been circulating in the island for decades. Two DENV-4 isolates from 1992 belong to the Indonesian genotype, which might represent a transient introduction to the island.[13]

In 2003, DENV-1 and DENV-4 showed a genotype switch, which is not observed in the phylogeny of DENV-2 and DENV-3. Instead, new clades of DENV-3 genotype III viruses have replaced older clades, and DENV-2 has also shown a similar trend. The emergence of new clades of DENV-3 in 1989 and 2000 coincided with abrupt increases in the numbers of reported DF cases, implicating this serotype in severe epidemics (Table 1).[16]

3. Changes in the epidemiology of DF/DHF and DENV infection in the vectors

Globally DF was initially an ‘urban’ disease, in that the epidemics mainly occurred in densely populated urban settings.