**EMERGENCE OF DENGUE VIRUS INFECTION IN NEPAL**

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**Abstract**

This article reviews Dengue, a common viral disease in humans and is an emerging public health problem in Tarai Region of Nepal. The most affected are among the poorest populations living in remote, rural areas and urban slums who have even no access for medical treatment, acquired by bite of infected mosquito. Aedes Aegypti infected with dengue virus is the major source of infections for humans and cannot be transmitted from person-to-person because human are the dead end host. DENV-1 was first isolated by Ren Kimura and Susumu Hotta in Japan in 1943. An epidemic of DF involving at least 200,000 cases had occurred between 1942 and 1944 during World War II in Japanese port cities such as Nagasaki, Kobe, and Osaka. First case of dengue was reported in 2004 in Nepal. The seroprevalence study were done in different part of Nepal by IgM antibody capture ELISA and positive rate was highest (50.0%) in Biratnagar, and lowest (19.6%) in Chitwan male to female ratio was 2:1. IgM-positive rate was 29.0% at ages 21-30, 25.4% at ages 11-20 and 23.6% at ages 0-10, but 10.9% at ages 31-40, and ages over 40. There was not significant association between occupation of the patients and positive rate among farmer, labour, service, business and student. The epidemiological studies of Dengue virus infection and the knowledge of the pattern of the disease outbreak can guide therapy and effective preventive measures against this disease.

**Keywords***: Dengue virus, IgM ELISA, Aedes Aegypti.*

**Introduction**

Dengue viruses (DENVs), which belong to the genus *Flavivirus*, family *Flaviviridae*, comprise four serotype named dengue virus types 1, 2, 3, and 4 (DENV-1, -2, -3, and -4). Infection with any of these serotypes leads to a broad clinical spectrum, ranging from sub-clinical infection or an influenza-like disease known as dengue fever (DF) to a severe, sometimes fatal disease characterized by hemorrhage and shock, known as dengue hemorrhagic fever/dengue shock syndrome (DHF/ DSS). Dengue virus infection is a global health problem and its expanding endemicity towards new territories is a serious concern. Relatively a new disease in Nepalese context, dengue abruptly appeared as massive outbreak in 2010, merely four years after its first introduction. DENVs are transmitted to humans mainly by the bites of *Aedes aegypti* and *Aedes albopictus* mosquitoes. Dengue is the most important arthropod-borne virus in tropical and subtropical countries, with an estimated 50 million infections each year, resulting in 500,000 cases of DHF/DSS and 25,000 deaths.

 Like other flaviviruses, dengue virus has a single-stranded,Positive - sense RNA genome of ~10,700 nucleotides, surrounded by a nucleocapsid and covered by a lipid envelope that contains the viral glycoproteins. The RNA genome contains a single open reading frame (ORF) flanked by two untranslated regions (5’ and 3’UTRs). The single ORF encodes a precursor polyprotein, which is co- and post-translationally cleavaged resulting in the formation of three structural proteins, Capsid (C), membrane (M), and envelope (E), and seven nonstructural proteins, NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5. There is no specific antiviral therapy or vaccine in clinical use for dengue fever. Medical care is supportive in nature and focuses on monitoring and administration of fluids to prevent dehydration and shock, medications to lower fever and reduce pain, and management of bleeding complications.

**Global scenario of Dengue virus infection**

DENV-1 was first isolated by Ren Kimura and Susumu Hotta in Japan in 1943 (Kimura and Hotta, 1943). An epidemic of DF involving at least 200,000 cases had occurred between 1942 and 1944 during World War II in Japanese port cities such as Nagasaki, Kobe, and Osaka.The infections originated from persons returning from the tropics, in particular Southeast Asia and the Pacific islands (Hotta *et al*, 2000). A few months after the first isolation of DENV-1 in Japan, Albert Bruce Sabin and Walter Schlesinger isolated DENV-1 from Hawaiian and shortly thereafter, DENV-2 from Papua New Guinean samples (Sabin and Schlesinger, 1945). They demonstrated that these viruses were antigenically related, yet distinct, and they could be distinguished by the hemagglutination inhibition (HI) assay. In the late 1960s, DHF fatality has been reported to be as high as 41.3% (Sumarmo *et al*., 1987) when healthcare providers understandably were still unfamiliar with the disease. Today, DHF fatality rates can exceed 20% without proper treatment, but can be brought down to 1% with proper medical care (WHO, 1997).Although there were various speculations about the earliest description of *dengue-like* diseases in historical accounts (Halstead, 1980; Henchal and Putnak, 1990), the disease now known as DHF was first recognised in Manila, the Philippines in 1953 (Quinlos *et al.,* 1954). Viruses similar to DENV-1 and DENV-2 were isolated from Manila patients in 1956 by William Hammond and were called DENV-3 and DENV-4. Dengue viruses of multiple serotypes were subsequently isolated from patients of another DHF epidemic in Bangkok, Thailand in 1958 (Hammond *et al*, 1960). It is now known all four serotypes of dengue virus can cause DHF. DHF/DSS outbreaks were mainly restricted to Southeast Asia until the early 1980s (Halstead, 1980). Since then, dengue transmission has intensified and DHF/DSS outbreaks are now frequent in most tropical countries. To this day, DHF/DSS remains a leading cause of hospitalisation and death among children in Southeast Asia. Outside the region, the disease burden of dengue is most acutely felt in Central and South America where 24 countries have reported laboratory-confirmed DHF between 1981 and 1997 (Monath, 1994; Gubler and Clark, 1995; Gubler, 1998).

 Recently, Messer and others have shown that the emergence of DHF in Sri Lanka in 1989 coincided with the appearance there of a new DENV-3, genotype III variant, which spread from the Indian subcontinent into Africa and then from Africa into Latin America. DENV-3 was re-introduced into the Americas in 1994, after an absence of 17 years, causing DF and DHF outbreaks in Nicaragua and Panama. Subsequently, DENV-3 spread into Central American countries and to Mexico. In 1998/1999, DENV-3 was introduced into Caribbean countries such as Puerto Rico, Barbados, Jamaica, and Martinique, and finally in 2000, into South America.

**Nepalese scenario of Dengue virus infection**

A study conducted by Central Department of Microbiology, Tribhuvan University, Kathmandu, Nepal ([Pandey](http://www.ncbi.nlm.nih.gov/pubmed?term=Pandey%20BD%5BAuthor%5D&cauthor=true&cauthor_uid=22335089)  *et al)* in between August 2007 and July 2008 in patients visiting hospitals of the western terai of Nepal with chief complains of fever. The sero-diagnosis of acute dengue infection was determined by enzyme linked immunosorbent assay among 239 patients visiting Lumbini Zone Hospital, Butwal; Bheri Zonal Hospital, Nepalgunj; Bardiya District Hospital, Bardiya and Mahakali Zonal Hospital, Mahendranagar. The anti-dengue IgM positivity was 29.3%. There was slight male preponderance with a male to female ratio of 1.2:1. Out of the total positive cases, the highest positive cases (75.7%) were from the age group 15 - 50 years followed by < 15 years old (15.7%). Out of four hospitals, the highest positive cases (54.3%) were in Lumbini Zonal Hospital, Butwal. The age and gender were independent predictors to dengue virus infection. The highest numbers of dengue positive cases were in October (52.6%). Similar study was conducted by Department of Microbiology, Nepal Medical College, Kathmandu, Nepal([Pandey](http://www.ncbi.nlm.nih.gov/pubmed?term=Pandey%20BD%5BAuthor%5D&cauthor=true&cauthor_uid=19968149)  *et al*). The study was conducted to determine dengue virus IgM-positive rate in Terai region, Nepal from August to December 2007. Serum samples were collected from 183 symptomatic cases. The samples were examined for dengue virus specific IgM using particle agglutination test. Out of 183 serum samples, 55 (30.0%) had positive for dengue IgM antibody. The positive rate was highest (50.0%) in Biratnagar, and lowest (19.6%) in Chitwan male to female ratio was 2:1 in IgM-positive populations. IgM-positive rate was 29.0% at ages 21-30, 25.4% at ages 11-20 and 23.6% at ages 0-10, but 10.9% at ages 31-40, and ages over 40. There was not significant association between occupation of the patients and positive rate among farmer, labour, service, business and student

**Outcome of Dengue Virus Infection**

A person could suffer from dengue infection four times throughout his/her lifetime, once for each of the four DENV serotypes. Both primary (first) and secondary (subsequent) infections with any serotype of DENV can result in either the clinically less severe DF or the more severe DHF (Rosen *et al*, 1977). A primary dengue infection confers the recovered patient life-long immunity against the infecting serotype and a brief protection against infection by other DENV serotypes (Sabin *et al*, 1952). However, epidemiological data and some studies suggest that the immunity thus gained, after the lapse of the temporary cross-serotypic protection, increases the probability of an individual developing DHF when infected by a second heterologous DENV serotype (Halstead *et al*., 1967; Halstead *et al*., 1970). A hypothesis to explain this phenomenon, called antibody-dependent enhancement (ADE), proposes that pre-existing sub-neutralizing antibodies from the primary infection and the second infecting DENV serotype form complexes that bind to cells bearing Fcγ receptor (FcγR) (monocytes and B cells) leading to increased virus uptake and replication. (Halstead *et al*, 1988).

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