LARGEST DENGUE OUTBREAK (2022) IN NEPAL

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ABSTRACT

Dengue virus infection, transmitted by *Aedes aegypti* (also by *Ae. albopictus*) mosquito, is an increasing health problem. The number of dengue cases has increased over eight-fold over the last two decades, from 505,430 cases in 2000, to over 2.4 million in 2010, and 5.2 million in 2019 with deaths accounting in thousands. Currently, 3.9 billion people in 129 countries mainly in Asian countries are at the risk of dengue infection. Most of the new cases are reported from Brazil, Vietnam, Indonesia, the Philippines, Sri Lanka and others. First case of dengue was reported from Nepal in 2004 and in 2006 a small outbreak was reported with 32 cases throughout the country. In Nepal, dengue epidemic occurred in 2010, 2013, 2016, 2017, and 2019; of them 2019 epidemic was largest one with reported 17,992 cases. This year (2022) largest outbreak occurred with a total of 54,784 cases recorded from all 77 districts in 7 provinces. Of the 7 provinces Bagmati Province was hardest hit (77.4%) followed by Lumbini Province (9.2%), Province 1 (4.2%), Gandaki Province (3.6%), Sudur Pashchim Province (2.5%), Madhesh Province (1.8%) and Karnali Province (1.2%). Most of the patients were aged 15-59 years and slightly more than half were males. Of the four serotypes existed in Nepal, DENV-1 DENV-2 and DENV-3 were common this year's outbreak (DENV-1 was predominant: 57.1%). This demands a precise mapping of dengue through integrated disease surveillance and evaluation of the dynamics of population-level immunity on evidence-based policy-making in days to come.

KEYWORDS

Dengue virus, emerging infection, largest outbreak 2022, Nepal

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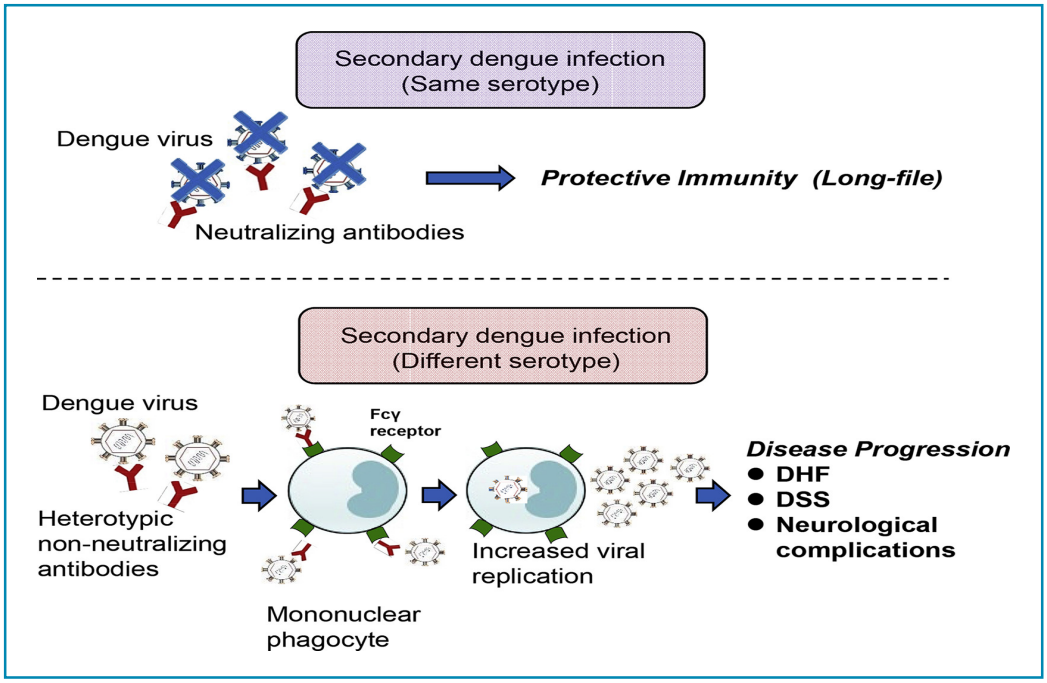
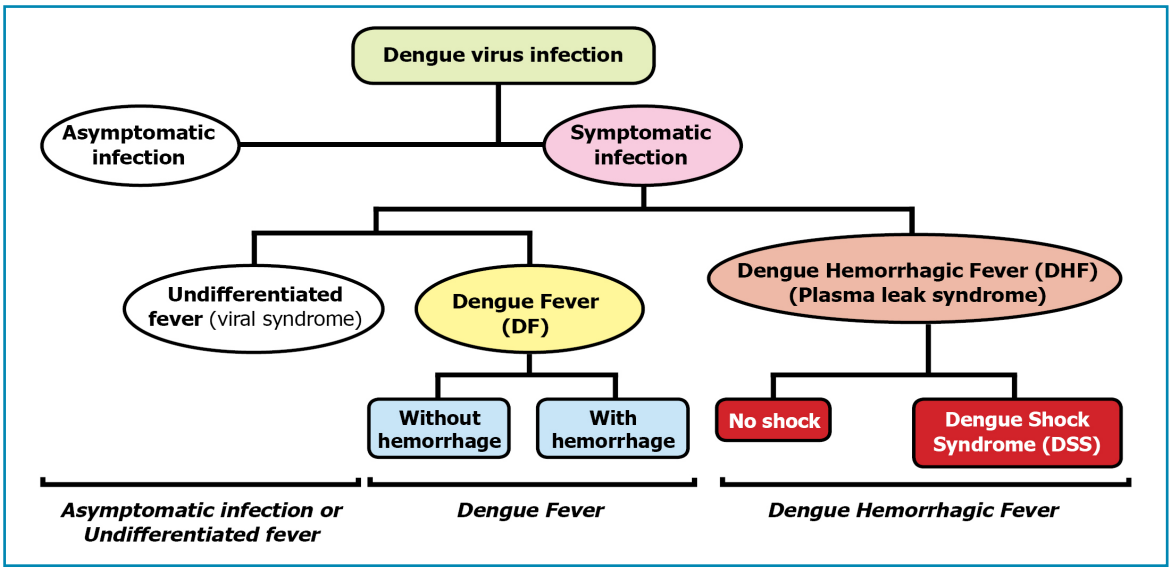
DENGUE VIRUS: INTRODUCTION

Dengue virus (DENV) is the causative agent of dengue fever or break-bone fever in tropical and sub-tropical areas which are characterized by sudden high-grade fever and flu-like symptoms including acute arthralgia (bone/joint pain). The name "dengue" originates from "Swahili" (language spoken in Tanzania, Kenya, Uganda and Democratic Republic of Congo) phrase "*Ka-dinga pepo*", meaning "cramp-like seizure". DENV is a positive sense single-stranded RNA virus belonging to Flaviviridae family. DENV contains 10,723 nucleotides which encodes a large polyprotein precursor of 3,391 amino-acid residues comprising of three structural proteins (C, prM and E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5).[1] DENV has four serotypes: DENV-1, DENV-2, DENV-3 and DENV-4 and infection can occur by any one or more than one of the four serotypes. Recently, it has emerged as an important pathogen. DENV is transmitted in human population by day-biting female *Aedes* mosquitos mainly by *Aedes aegypti* and also by *Ae. albopictus*,[2] and causes dengue fever (DF), and also a serious form called dengue hemorrhagic fever (DHF).[3]



The mechanism of antibody-dependent enhancement of dengue virus infection (*Upper*: secondary infection by same serotype and *Lower*: secondary infection by different serotype) (Wang *et al*, 2020)



Flow chart of the classification of dengue infection and clinical presentation (Adapted from Wang *et al*, 2020)

PATHOGENESIS

Although complex and somewhat obscured pathogenesis, the hallmark changes in dengue infection is leakage of plasma and deranged homeostasis as a result of complement activation and cytokine dysregulation. The non-structural protein 1 (NS1) of DENV is attributed as the key viral factor that directly damages endothelial cells of blood vessels resulting in plasma leakage. It is noted that the severity of infection is directly proportional to the role of host immune response in DENV clearance.[4-6] Antibody-dependent enhancement (ADE) in dengue infection explains how the protective neutralizing antibodies produced by the host during primary infection causes Fcγ receptor-mediated increment of viral load in secondary heterotypic infection.[3] Furthermore, DENV genome, anti-NS1 antibodies, autoimmunity, cross-reactive T-cells and defective T cells also lead to complement activation and cytokine dysregulation. It is noted that the severity of dengue infection is directly proportional to the role of host immune system in DENV clearance and not the DENV load.[4]

Sign and Symptoms: In 2009, WHO stated that a case of high fever (104°F) should be suspected of dengue if there are any two additional features of severe headache, retro-orbital pain, myalgia, arthralgia, nausea, vomiting, swollen glands and rash.[7,8] Usually, after about 3-7 days of fever, the critical phase begins where some patients may deteriorate with development of warning signs such as severe abdominal pain, persistent vomiting, tachypnea (rapid and shallow breathing), bleeding disorders, hepatomegaly and fatigue. This potentially fatal complication, called severe dengue, results from plasma leakage, deranged haemostasis, respiratory distress and organ dysfunction.[5]

However, all dengue cases are not symptomatic or even the symptomatic infection can be represented as undifferentiated febrile illness (viral syndrome).[3] Symptomatic dengue can be characterized by fever with or without hemorrhage (bleeding). The most common bleeding manifestations are petechiae and other symptoms (epistaxis, gum bleeding, hematemesis, melena, hyper-menorrhea, hemoglobinuria).[5-7] While severe dengue and dengue hemorrhagic fever or plasma leak syndrome can be with or without shock. Severe plasma leakage leads to shock or fluid accumulation with respiratory distress which is accompanied by severe bleeding or severe organ impairment (as indicated by elevated transaminases ≥1,000 IU/L), impaired consciousness or heart impairment.[3]

From 1975 through 2009, symptomatic dengue virus infections were classified according to the WHO guidelines as dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (the most severe form of DHF). The case definition was changed to the 2009 clinical classification[7] as it failed to identify a substantial proportion of severe dengue cases, including cases of hepatic failure and encephalitis in resource limited settings. According to 2009 classification, dengue cases have been classified as dengue fever (DF)/dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS).[3] The 2009 clinical classification has been criticized for being overly inclusive, as it allows several different ways to qualify for severe dengue, and nonspecific warning signs are used as diagnostic criteria for dengue.[7,8] The warning signs of severe dengue fever - which is a life-threatening emergency - can develop quickly. The warning signs usually begin the first day or two after your fever goes away, and may include: severe stomach pain, persistent vomiting, bleeding from gums or nose, blood in urine, stools or vomit, bleeding under the skin, which might look like bruising, difficult or rapid breathing, fatigue, irritability or restlessness.

Laboratory Diagnosis: For the confirmatory laboratory diagnosis, virus can be cultured (and serotype identification can be done), nucleic acid detection, ELISA or hemagglutination inhibition test or neutralization tests and virus antigen detection can done.[9] Of these, anti-dengue virus IgM antibody positive in signle serum sample or IgG antibody positive serum sample with hemagglutination inhibition test titer with 12,80 or greater are highly suggestive of dengue. Virus culture positive, PCR test positive, IgM seroconversion (in paired sera) and IgG seroconversion (by four fold rise) (in paired sera) are the confirmatory tests. However, some of these tests are available only in peripheral laboratory except the rapid antigen test and antibody test by ELISA.

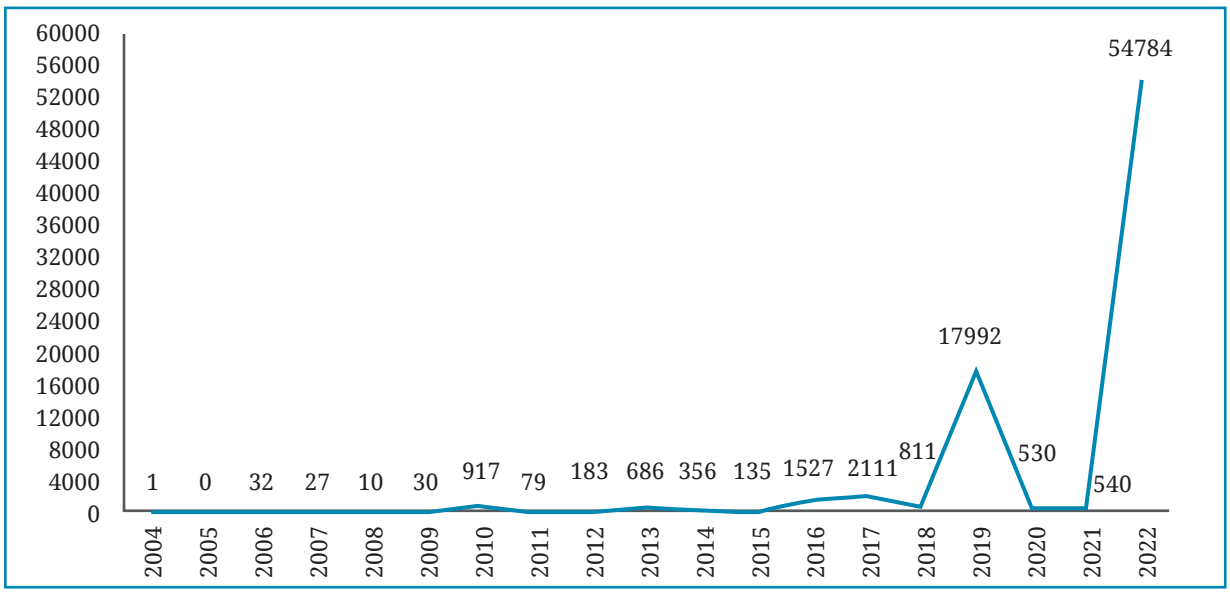
EPIDEMIOLOGY

The number of dengue cases reported to WHO increased over eight-fold over the last two decades, from 505,430 cases in 2000, to over 2.4 million in 2010, and 5.2 million in 2019. Reported deaths between the year 2000 and 2015 increased from 960 to 4032, affecting mostly younger age group.[5] Each year, up to 400 million people get infected with dengue.[5,10] Currently, 3.9 billion people in 129 countries mainly in Asian countries are at the risk of dengue infection.[11] This number must be higher as many cases are underreported due to mild and self-management or misdiagnosis of

infection. The total number of cases seemingly decreased during years 2020 and 2021, as well as for reported deaths. However, the data is not yet complete and COVID-19 pandemic might have also hampered case reporting in several countries. In the year 2022, a total of 4,110,465 cases of dengue and 4,099 deaths have been reported.[12] The majority of cases have been reported from Brazil (n=2,363,490) followed by Vietnam (n=367,729), the Philippines (n=220,705), Indonesia (n=125,888), India (n=110,473) and others. The majority of deaths have been reported from Indonesia (n=1,082), Brazil (n=991), the Philippines (n=722), Vietnam (n=140) and others. Most of the new cases are reported from Brazil (n=181,261), Vietnam (n=42,125), Indonesia (n=31,533), the Philippines (n=19,196), Sri Lanka (n=5,956) and others. According to Pan American Health Organization/World Health Organization (PAHO/WHO) 2,804,035 cases of dengue and 1,289 associated deaths occurred in the Americas in 2022.[13] The five countries reporting most cases include Brazil (n=2,363,490), Nicaragua (n=97,541), Peru (n=72,851), Colombia (n=69,497), and Mexico (n=59,918).

NEPALESE SCENARIO

Until year 2003, Nepal was free from DENV infection DENV. First case of DENV infection in Nepal was reported in 2004 in a Japanese national working in Chitwan District.[14] Two years later there was an outbreak of dengue in same district in 2006; with a total of 32 cases throughout the country. In 2007, 27 dengue cases were reported from four districts of Terai region. However, there was slight decrease in number of cases; with only 10 reported cases in 2008 and 30 cases in 2009. In 2010 Nepal faced a major outbreak of dengue, with 917 reported cases from six districts and 5 deaths. In 2011, a very low number of cases (79) were reported; however, there was an expansion in the distribution of cases (6 districts in 2010 to 15 districts in 2011). In 2012, the total number of cases reported was 183. There was another dengue epidemic in 2013 with a total of 686 cases reported from 25 districts. However, there were no cases of deaths in 2011, 2012 and 2013. In 2014, a total of 356 cases were reported of which, half (50.8%) of the cases were from Bagmati Province. In 2015, only 135 cases were reported with a death in Dang District, of which more than half (56.3%) were from Bagmati Province. The cases crossed four digits (1,527) in 2016 and this year the distribution further increased to 30 districts. This year also Bagmati Province reported 51.2% of total cases (Chitwan District was mostly commonly affected 44.8%). The number of cases increased further to 2,111 in 2017 and the highest numbers of cases were reported from Lumbini Province and least number was reported from Bagmati Province. First time, five digits alarming outbreak was reported in 2019 with 17,992 cases (largest dengue epidemic in the history of Nepal) from 68 districts in all seven provinces with 6 deaths.[15,16] In 2019, highest numbers of cases were reported from Bagmati Provice again and least was reported from Karnali Province. However, during the COVID-19 pandemic period dengue reporting was overshadowed (2020 and 2021, the cases were only 530 and 540, respectively)[16-18] however, this reduction in dengue incidence/ transmission might be attributed to movement restriction during COVID-19 pandemic.[19] This was against the expectation of health planners (much bigger epidemic of dengue in Kathmandu was expected).[20]



Annual trend of dengue cases in Nepal from 2004 to Dec. 31, 2022 (*Source*: EDCD, DoHS, Ministry of Health & Population, Nepal)

Currently, all four serotypes of Dengue virus (DENV-1, DENV-2, DENV-3 and CENV-4) are existed in Nepal. However, until 2017, major outbreaks in Nepal is associated with DENV-1 and DENV-2 serotypes.[21] In the past 10-12 years, demographical profiles suggest that dengue has migrated substantially to higher altitudes in Nepal resulting in the rise in the dengue cases.[22] This indicates that, *Aedes* mosquitos, which was not reported from Nepal until 1990,[23] has now been well adapted to higher altitudes and must be attributed to global warming.[24] First time *Ae. aegypti* in Nepal was reported in 2009, suggesting some coincidence between the invasion of this species and the first dengue outbreak in Nepal in 2006.[23] however, due to the lack of virus surveillance in mosquitoes and adequate molecular profiling of circulating DENV serotypes, it is difficult to precisely estimate the altitudes to which the virus has migrated.[18]

LARGEST DENGUE OUTBREAK

In Nepal, dengue outbreak occurred in 2010, 2013, 2016, 2017, and 2019; of them 2019 epidemic was largest one with reported 17,992 cases.[17] This year (January to December 2022), a total of 54,784 dengue cases have been recorded and this is the record highest number of cases since the first case was reported from Nepal in 2004.[14,19] This year, the cases increased significantly compared to the 540 cases reported during all of 2021 as well as the previous largest number (17,992 cases) reported in 2019.[17] All seven provinces have been affected with 88 total dengue related deaths. According to the Epidemiology and Disease Control Division (EDCD) of the Ministry of Health and Population,[17] all 77 districts in seven provinces have been affected with the highest number reported from Bagmati Province (n=42,428; 77.4%) followed by Lumbini Province (n=5,037; 9.2%), Province 1 (2,309; 4.2%), Gandaki Province (n=1,957; 3.6%), Sudur Pashchim Province (n=1,353; 2.5%), Madhesh Province (1,018; 1.8%) and Karnali Province (n=682; 1.2%). Among the districts highest number have been recorded from Kathmandu (altitude 1,300 m) (n=14,374; 26.2%), followed by Lalitpur (n=9,614; 12.0%), and Bhaktapur (n=6,145, 11.2%), Makwanpur (n=5,837; 10.6%), Chitwan (n=3,213; 5.9%) (all in Bagmati Province) and others. Highest numbers of cases have been recorded in between August to November (with the peak in the month of September) and the high altitude districts like Mugu, Manang, Humla, Dolpa, Mustang, Jajarkot have also been affected. Most of the patients were aged 15-59 years old and slightly more than half were males. Officials have reported disease activity nationwide, with Bagmati being the most affected province (n=42,428); within the province, Kathmandu (n=14,374), Lalitpur (n=9,614) were hardest hit followed by Bhaktapur, Makwanpur and Chitwan Districts. Of the four serotypes existed in Nepal, DENV-1 DENV-2 and DENV-3 were common this year's outbreak.[18,25] Of these three serotypes, DENV-1 was predominant (57.1%) and DENV-3 (32.1%).[18]

Significant increase in both the number of cases of dengue fever and the areas of outbreaks within Nepal in recent years has been attributed to global climate change and other associate factors.[26] As expected, this year an explosion of dengue particulalrly in Kathmandu occurred.[27] Nepal is one of the vulnerable countries from the climate change perspectives and the region has warmed up by 1.5C in the last 25 years[24] that has attributed in the spread of *Ae. aegypty* (as well as *Ae. albopictus*) mosquito (vector) and dengue cases in to higher altitudes.[26,28]

TACKLING DENGUE FEVER

Keeping in view of no specific treatment available for dengue and no dengue vaccines available in Nepal, the best measures for tackling this growing crisis are environmental / effective mosquito control and community mobilisation. This includes, removal of stagnant water collected on old tyre, coconut bark, no open water tank and frequent change of water in the flower pots inside the house ("search and destroy") as well as by strengthening our climate-resilient health systems. One study done by Khanal *et al*[29] has shown that 58% had good knowledge and 62% good practice regarding dengue fever in Nepal. In addition, a precise mapping of dengue and other related infections through integrated disease surveillance, evaluation of the dynamics of population-level immunity and virus evolution should be done for evidence-based policy-making[18] for the control of dengue infection in the country.

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