NICED Library Newsletter

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Editorial Board

DENGUE - A RAPIDLY EMERGING PUBLIC HEALTH PROBLEM

The word “dengue” probably originated from the Swahili phrase "Ka-dinga pepo", which means "cramp-like seizure caused by an evil spirit". The first mention of a probable dengue fever was found in a Chinese medical encyclopedia during the Jin Dynasty (265–420 AD) that referred to a “water poison” associated with flying insects. The earliest recognized dengue epidemics occurred almost simultaneously in Asia, Africa and North America during 1780s and the first confirmed case was reported in 1789 by Benjamin Rush, who coined the term "breakbone fever" because of the symptoms of myalgia and arthralgia associated with dengue.

Epidemiology:

Dengue is one of the most rapidly emerging pandemic-prone viral diseases in today’s world, especially in the tropical and subtropical countries. The incidence of dengue has increased 30-fold over the last 50 years. During 1996–2005, the decadal increase in the number of dengue cases reported to the World Health Organization (WHO) had been from 0.4 to 1.3 million; it increased further to 2.2 million in 2010 and 3.2 million in 2015. At present, dengue is endemic in more than 100 countries with an estimated 50-100 million infections occurring each year. However, these clinical dengue cases may represent only about 25% of all dengue virus infections due to substantial under-reporting. Moreover, around 40% of the world’s populations – i.e., about 2.5 billion people, are at risk of contracting the disease. WHO targets to reduce the overall dengue mortality and morbidity by 50% and 25%, respectively, by 2020.

In India, the occurrence of dengue fever was first reported from Vellore district in Tamil Nadu in 1956 and the first outbreak of dengue hemorrhagic fever (DHF) occurred in Kolkata, West Bengal in 1963. In 1996, the country experienced an outbreak of dengue with 16517 suspected cases and 545 deaths. A large number of cases and deaths (12754 and 215, respectively) had also been reported in 2003. Again, there was an upsurge in dengue cases in 2006, with a total of 11638 cases-

and 174 deaths reported by 21 states of the country. Fig.1 presents the number of cases and deaths due to dengue in India as reported to the National Vector Borne Disease Control Programme (NVBDCP) during 2010-2015. The Epidemiology of dengue is a complex phenomenon that depends upon an intricate relationship between the three factors: the agent (virus), the host (man and mosquito) and the environment (abiotic and biotic factors). The complexity of relationship among these factors eventually determines the level of endemicity in any area.

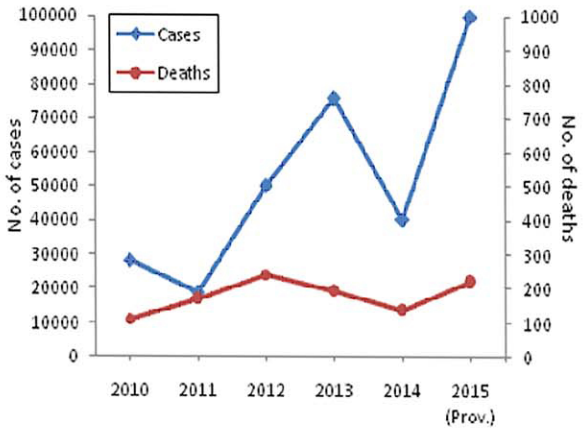


Fig. 1. Number of dengue cases and deaths in India, 2010-2015

Agent factors

Dengue is caused by single-stranded RNA viruses belonging to the genus Flavivirus. The 4 serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) of dengue viruses share only about 60%–75% identity at the amino acid level and thus pose as distinct viruses. All the four serotypes have been isolated in India.

Upon human inoculation, the virus replicates in local dendritic cells. Subsequently, it enters into the macrophages and activates lymphocytes, followed by entry into the bloodstream. Dengue viruses primarily infect cells of the myeloid lineage such as macrophages, monocytes, and dendritic cells. Hepatocytes and endothelial cells can be infected as well. Hematogenous spread is probably responsible for seeding of peripheral organs and the occasionally reported infection of the central nervous system.

Host factors

Dengue is not transmitted directly from person-to-person. The life cycle of dengue virus involves mosquito as a vector and humans as the main victim and the source of infection. Although dengue virus may infect humans as well as several species of lower primates, man is the only natural reservoir of infection in India. All ages and both sexes are susceptible to dengue. Travel to dengue endemic area is an important risk factor for acquiring the infection while migration of an infected person during viremia to a non-endemic area may introduce dengue into that area.

It is the female Aedes mosquitoes that transmit dengue virus. The female mosquito usually becomes infected with the virus when it takes blood meal from a person during the acute febrile (viraemia) phase of the illness. Usually, an infected person with dengue becomes infective to mosquitoes 6 to 12 hours before the onset of the disease and remains so up to 3 to 5 days after the onset. After an extrinsic incubation period of 8 to 10 days, the mosquito becomes infected and the virus is transmitted to man through mosquito bites. There is evidence of vertical transmission of dengue virus from infected female mosquitoes to the next progeny through eggs - known as transovarian transmission.

In India, the primary vector is the *Aedes aegypti* mosquito, although *Ae. albopictus* has also been found as a vector in certain areas of southern India. As *Ae. aegypti* breeding is more common in urban areas, the disease used to be concentrated mostly in such areas. However, the trend is now changing due to socio-economic and man-made ecological changes, resulting in invasion of *Ae. aegypti* mosquitoes into the rural areas and thereby tremendously increasing the chances of spread of the disease to rural areas.

Ae. aegypti breeds almost entirely in domestic man-made water receptacles found in and around households, construction sites and factories; natural larval habitats are tree holes, leaf axils and coconut shells. In hot and dry regions, overhead tanks and ground water storage tanks become primary habitats. Unused tyres, flower pots and desert coolers are among the most common domestic breeding sites of *Ae. aegypti*. *Ae. aegypti* is a day time feeder; to get one full blood meal the mosquito has to feed on several persons, infecting all of them.

"Dengue is one of these neglected diseases diseases ... it's basically been ignored for many, many years".... Duane Gubler

Environmental factors

The population of *Ae. aegypti* mosquitoes fluctuates with rainfall and water storage. During rainy season survival of this mosquito is longer, resulting in higher risk of virus transmission. Its life span is influenced by temperature and humidity – the mosquito survives best with a temperature between 16-30°C and a relative humidity of 60-80%. Altitude also plays an important factor in the distribution of *Ae. aegypti*, which is limited between the sea level and 1000 ft above sea level. This mosquito is highly anthropophilic and rests in cool shady places. The rural spread of *Ae. aegypti* is a relatively recent phenomenon, associated with the development of rural water supply schemes, improved transport systems, growing urbanization, scarcity of water and lifestyle changes.

Clinical manifestations:

The majority of dengue virus infections are asymptomatic. For clinical cases, the incubation period is usually 4–7 days (range: 3–14 days). Commonly, the initial presentation includes sudden onset of fever accompanied by headache, retro-orbital pain, generalized myalgia and arthralgia, flushing of the face, anorexia, abdominal pain and nausea. Rash is frequently seen on the trunk, on the medial aspect of the arms and thighs, and on plantar and palmar surfaces and can be macular, maculopapular, morbilliform, scarlatiniform or petechial. While the first infection with one of the four dengue serotypes is typically non-severe or asymptomatic, individuals who are subsequently exposed in later years to one of the other serotypes are more likely to develop severe dengue. However, chronic infection with dengue virus or any carriage state is not known. Although there is no specific treatment for dengue, case fatality rates can be below 1% with proper case management. In its absence, the case fatality rate can be as high as 20% in patients with severe dengue. Early clinical diagnosis and careful clinical management increase the survival of patients. For the purpose of clinical management, WHO classifies dengue illness as (i) dengue with or without warning signs for progression towards severe dengue and (ii) severe dengue (Box 1).

Box 1: WHO Classification of Dengue Cases and Levels of Severity

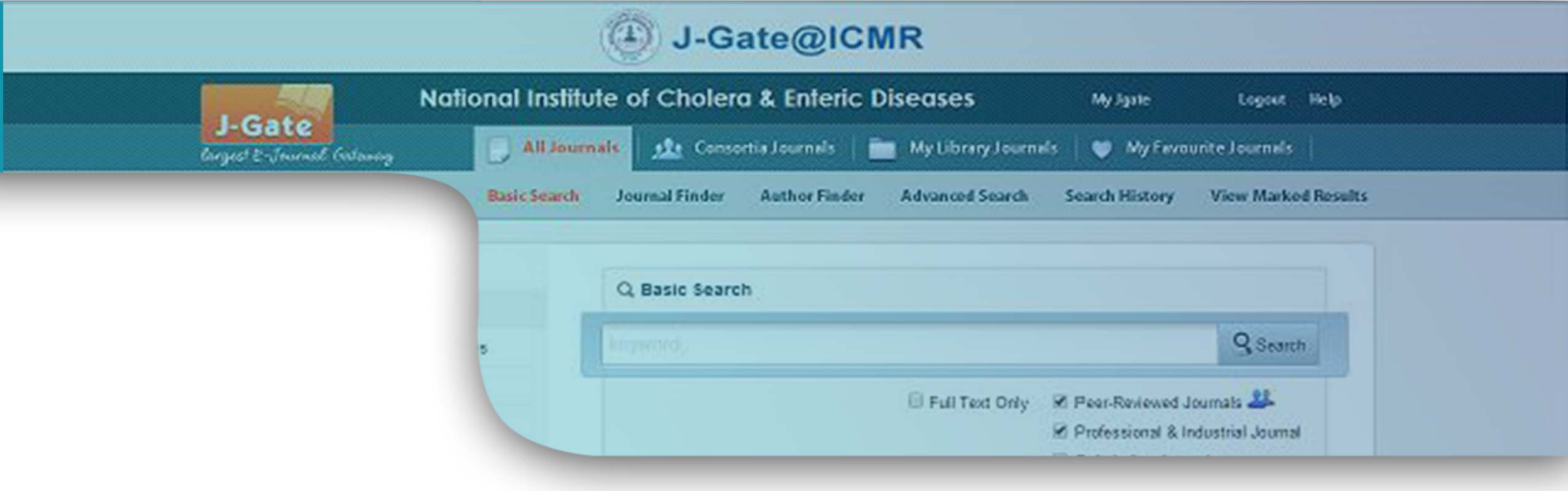
CRITERIA FOR DENGUE ± WARNING SIGNS		CRITERIA FOR SEVERE DENGUE
Probable dengue Live in / travel to dengue endemic area. Fever and 2 of the following criteria: • Nausea, vomiting • Rash • Aches and pains • Tourniquet test positive • Leukopenia • Any warning sign **Laboratory confirmed dengue** (Important when no sign of plasma leakage)	**Warning signs*** • Abdominal pain / tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • Lethargy, restlessness • Liver enlargement >2 cm • Laboratory: increase in hematocrit concurrent with rapid decrease in platelet count **Requiring strict observation and medical intervention*	**Severe plasma leakage** leading to: • Shock [Dengue shock syndrome (DSS)] • Fluid accumulation with respiratory distress **Severe bleeding** As evaluated by clinician **Severe organ involvement** • Liver: AST or ALT =1000 • CNS: Impaired consciousness • Heart and other organs

Immunity:

Dengue virus infection induces high-titre neutralizing antibody, which is believed to be an important component of a protective immune response. Following a primary infection with one dengue virus serotype, protection against the infecting serotype (homotypic protection) is considered long-lasting. Temporary short-lasting cross-protection is also induced to the other serotypes (heterotypic protection). Following waning of cross-neutralizing antibodies, severe illness is more likely to occur with a second dengue virus infection than with the first dengue virus infection. Following recovery from a second infection, broadly neutralizing antibodies are induced (multitypic protection), such that severe disease with subsequent infections is considered rare. The mechanism causing greater severity of the second dengue virus infection is not well understood, although antibody-dependent enhancement, cytokine storm, or cross-reactive T cells have been implicated in the pathogenesis.

Laboratory diagnosis:

Early symptoms of dengue infection mimic other diseases often prevalent in areas where it is endemic, such as chikungunya, malaria and leptospirosis. Hence, for proper management rapid differential diagnosis is very crucial. Laboratory confirmation of dengue virus infection is



sponging to keep temperature below 39°C, (c) oral rehydration therapy, specially for patients with excessive sweating and/or vomiting and (d) antipyretics, if required, to lower the body temperature. Non-steroidal anti-inflammatory drugs (NSAIDs) like Aspirin, Ibuprofen etc. should NOT be used. Paracetamol is the preferred drug for this purpose. Patients should be monitored in DHF endemic area until they become afebrile for at least one day without the use of antipyretics and after the haematocrit level is normal and platelet count is >50,000/ cmm. A drop in platelet count and rise in the hematocrit may be an early indication of DHF. Timely intravenous therapy with isotonic crystalloid solution can prevent shock and/or lessen its severity. Without improvement after one hour, crystalloid solution should be replaced by colloid solution (e.g. dextran or plasma) and as soon as improvement occurs, crystalloid solution is to be resumed. In case the hematocrit falls, blood transfusion should be given followed by crystalloid IV fluids. For severe bleeding, fresh blood transfusion is recommended, followed by crystalloid solutions. In addition, oxygen should be given for patients in shock and sodium bicarbonate for correction of acidosis. Antibiotics or steroids have no role in the clinical management of dengue infection.

Prevention and control:

Vector control

Preventing or reducing dengue virus transmission depends entirely in controlling the mosquito vectors or interruption of human–vector contact. To control mosquito vectors, WHO promotes Integrated Vector Management (IVM), defined as a 'rational decision-making process for the optimal use of resources for vector control." Vector transmission is reduced through the use of one or more of the three methods: (a) environmental management, (b) chemical control and (c) biological control.

Environmental management should be the mainstay of dengue vector control. It tries to prevent or minimize vector propagation and human contact with the vector by destroying, altering, removing or recycling containers that act as egg/larval/pupal habitats. Three types of actions are defined: (i) Environmental modification such as installation of a reliable piped water supply to communities, including household connections, (ii) Environmental manipulation such as frequent emptying and cleaning of water-storage vessels, flower vases and desert room coolers, cleaning

of gutters, recycling or proper disposal of discarded containers and tyres, management of plants close to homes that collect water in the leaf axils and (iii) Changes to human habitation or behaviour such as installing mosquito screening on windows, doors and other entry points, and using mosquito nets while sleeping during daytime.

Chemical control includes larvicides and adulticides. Larviciding should be considered only as complementary to environmental management. Control measures that target adult vectors (adulticides) are applied either as residual surface treatments or as space treatments. Perifocal treatment, applied with hand-operated compression sprayers, has both adulticiding and larviciding effects. Indoor residual spraying (IRS) is done with long-acting chemical insecticides on the walls and roofs of all houses and domestic animal shelters in a given area, in order to kill the adult vector mosquitoes. Space spraying, on the other hand, is recommended for control only in emergency situations to suppress an ongoing epidemic or to prevent an incipient one. When a rapid reduction in vector density is essential, space treatment should ideally be carried out every 2–3 days for 10 days. Further applications should then be made once or twice a week to sustain suppression of the adult vector population. Continuous entomological and epidemiological surveillance should be conducted to determine the appropriate application schedule and the effectiveness of the control strategy.

Biological control is based on the introduction of organisms that prey upon, parasitize, compete with or otherwise reduce populations of the target species. For Aedes, a selection of larvivorous fish species and predatory copepods (small freshwater crustaceans) are effective against the immature larval stages of vector mosquitoes. Among the fish, guppies adapt well to the confined water bodies and have been most commonly used. Various predatory copepod species (small crustaceans) have also proved effective against dengue vectors. For example, in northern Viet Nam copepods were used in large water-storage tanks along with source reduction, and this approach successfully eliminated Ae. aegypti in many communes and prevented dengue transmission for many years. To date, these successes have not been replicated in other countries.

Individual and household protection

Clothing that minimizes skin exposure during daylight hours when mosquitoes are most active affords some protection from the bites of dengue vectors and is encouraged particularly during outbreaks. Repellents may be applied to exposed skin or to clothing. Insecticide-treated mosquito nets afford good protection for those who sleep during the day (e.g. infants, the bedridden and night-shift workers). Where indoor biting occurs, household insecticide aerosol products, mosquito coils or other insecticide vaporizers may also reduce biting activity. Household fixtures such as window and door screens and air-conditioning can also reduce biting.

Vaccines

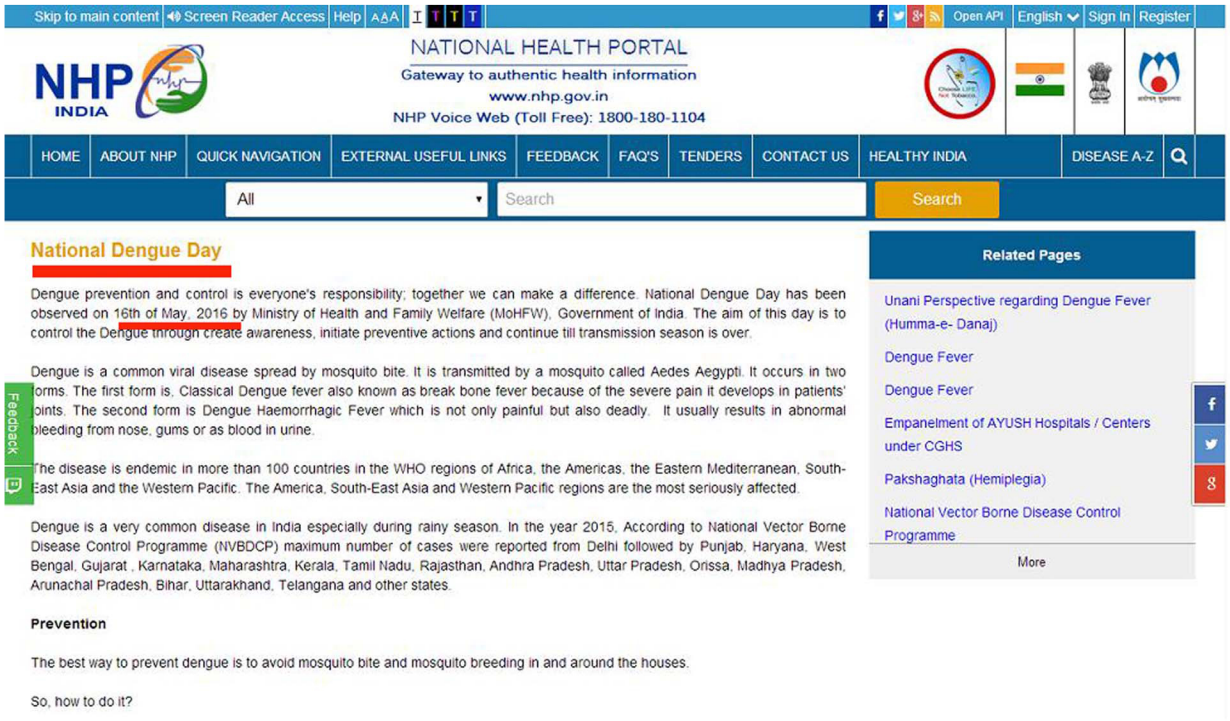
There are no WHO pre-qualified vaccines available against dengue. Very recently, one dengue vaccine (CYD-TDV or Dengvaxia) has been registered for use in some countries such as Mexico, Brazil and the Philippines. This live atten¬uated recombinant tetravalent vaccine is a 3-dose vaccine with 0/6/12 month schedule. Several other dengue vaccine candidates are in clinical

development, two of them are currently under evaluation in Phase 3 trials. Till date, no vaccine is licensed for use in India.

According to the WHO Position Paper issued in July 2016, countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease. In defining populations to be targeted for vaccination, prior infection with dengue virus of any serotype, as measured by seroprevalence, should be approximately 70% or greater in the age group targeted for vaccination in order to maximize public health impact and cost-effectiveness. Vaccination of populations with seropـrevalence between 50% and 70% is acceptable but the impact of the vaccination programme may be lower. The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination.

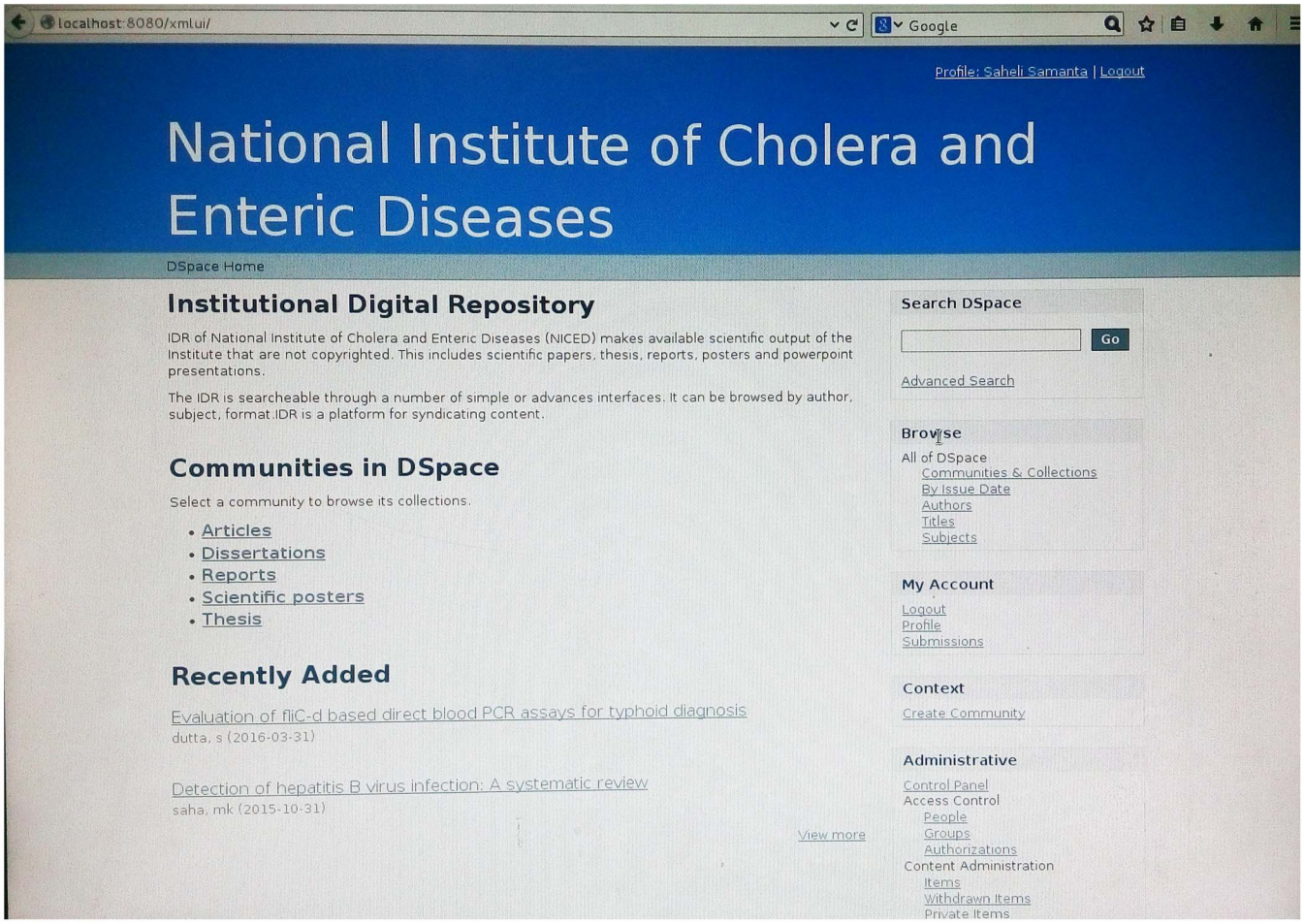
Dr. Aloke Deb, Scientist E
Epidemiology Division, NICED

Observation of National Dengue Day: Ministry of Health and Family Welfare, Government of India observed 16th of May 2016 as the Nationsl Dengue Day. The aim of this day is to control the Dengue through creating awareness, initiating preventive action and continue such activities till transmission season is over.



Institutional Digital Repository (IDR): NICED Library has set up IDR with DSpace, an open source software. Setting up of IDR in every sister Institute has been one of the priorities of Indian Council of Medical Research (ICMR), New Delhi and such an inititive at NICED Library is a step towards fulfilling the directive from ICMR. This is also a step forward towards making the digital resources of NICED library, that are not copyrighted, available to the scientific community at large through IDR. This will include articles published by the scientists in open access journals, posters presented by the scientists and their research fellows in different international and national conferences and seminars, dissertations submitted by the post-graduate students who got their training in different laboratories of the Institute, thesis, copyrights of which are with the Institute, reports that include Annual as well as Project reports etc. This will promote the visibility of scientific output of the Institute.

NICED library has started to upload digitally born documents in the database and these documents will be searcheable through simple and advanced search methods. The metadata of the resourcs of NICED will be made available to the National Digital Library, an initiative of the Ministry of Human Resource Development (MHRD), Govt. of India under its NMEICT mission.



Trainings and workshops attended by the NICED Library Professionals:

Mr. Tapas Pal, LIA, attended the 4th National Knowledge Network Workshop held during 21-22 January 2016 at Jawaharlal Nehru Technological University, Kukatpally, Hyderabad.

Ms. Saheli Samanta, ALIO, and Mr. Tapas Pal, LIA, attended a training workshop for Heads of ICMR librarues and senior library professionals organised by Indian Council of Medical Research, New Delhi at NIV Pune during 11-12 August 2016.

Ms. Saheli Samanta attended the workshop on "Institutional Digital Repository and Medical Metadata Engineering" at AIIMS, New Delhi held during 20-21 October 2016.