

Evidence Based Decision Making Programme

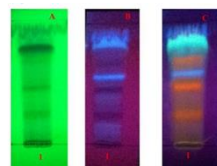
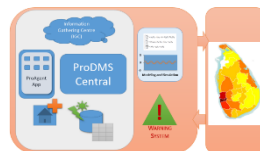
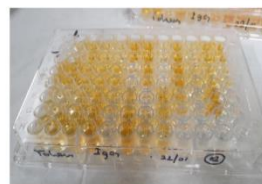
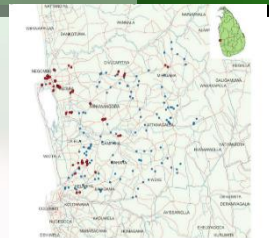


Research into Practice

Research Programme on Health Science: Dengue Projects

September 2023

Research Division | National Science Foundation



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Project Title : **Innovative tools and strategies for surveillance and control of dengue: 2017 – 2020**

Grant No : **RPHS/2016/D 01**

Principal Investigator : **Dr Hasitha Tissera**
Consultant Epidemiologist, Epidemiology Unit,
Ministry of Health

Background:

The burden of disease caused by dengue is challenging to be measured. Dengue endemic countries depend on passive disease surveillance systems which are known to underestimate the true dengue incidence and even deaths. In Sri Lanka the annual incidence of dengue has increased significantly during the last two decades with repeated outbreaks. Assessing dengue seroprevalence by detection of DENV-specific IgG will help to describe the true disease burden of dengue which in turn will facilitate future vaccination implementation policy decision- making.

Key Research Findings:

This is the first ever study on the seroprevalence of dengue carried out in Sri Lanka covering all age groups. The overall seroprevalence was 72.1%.

- An age-wise increase in seroconversion status was evident in the Colombo district with a significant difference in the disease burden in the metropolitan, urban and rural residential sectors. An early seroconversion rate was observed in the metropolitan sector compared to the urban and rural areas of the Colombo district. Different high-risk districts showed varying seroprevalence rates, with age-stratified changes not being remarkable among them.
- Previous exposure to dengue is an important factor in considering the efficacy and eligibility of a future vaccination strategy. These findings will facilitate the efforts for any future introduction of a vaccine against Dengue in Sri Lanka.
- The DALY assessment in this study was the first attempt to estimate the economic burden of dengue in Sri Lanka using this method. The DALYs for Sri Lanka were compared according to the non-epidemic and epidemic years with other South-east Asian regional countries. The economic burden of dengue as shown in the DALYs estimates showed a significant increasing trend over time due deaths rather than due to disability, whereas the Global Burden of Disease studies have illustrated a fall in mortality with an increasing disability contribution (from YLD) to dengue DALYs. The DALYs disease burden proportion in the Colombo district showed a decreasing trend, indicating a gradual increase in the Dengue burden in other districts. These findings also serve as catalysts for future studies on the impact of dengue vaccination costs.

Project Title : **Development of an early warning system, a risk map and a prediction model for dengue and establishment of roles of asymptomatic carriers and brackish water- derived mosquitoes in dengue transmission in Jaffna district**

Grant No : **RPHS/2016/D 02**

Principal Investigator : **Prof. S. N. Surendran**
Department of Zoology, Faculty of Science,
University of Jaffna

Background:

The Jaffna district, which is in the Northern Province of Sri Lanka, has been experiencing an increase in the number of dengue infections in recent years. Therefore, it is important to investigate larval bionomics of *Aedes* vectors, identify the emergence of different dengue virus (DENV) serotypes and develop a dengue risk map to understand the changing epidemiology of dengue and to initiate timely control measures. The habitats of the preimaginal stages of *Aedes* mosquitoes were surveyed, and ovitrap collections were carried out in selected localities in Jaffna district. *Aedes* larval productivity was analyzed in terms of habitat characteristics, rainfall and dengue incidence. Adults emerging from the collected larvae were tested for dengue virus (DENV). Blood samples were collected from NS1 positive patients admitted to Jaffna Teaching Hospital. Real- time PCR was performed to identify the DENV serotypes. Dengue specific IgM and IgG immunological assays were also performed, and patients were followed up throughout the duration of hospital admission to determine dengue disease severity. The DENV- positive samples were sent for sequencing and the results were analyzed. Dengue risk- related spatial-temporal factors were analyzed via multi- criteria analysis and a GIS-based dengue risk map was created. *Aedes aegypti*, *Ae. albopictus*, *Ae. vittatus* were collected and identified from their natural habitats and ovitraps.

Key Research Findings :

- Current dengue vector control guidelines target only freshwater habitats. However, the present study shows that the potential dengue vectors are undergoing atypical adaptation to salt and polluted environments. Therefore, this study recommends a policy change at the national level to accommodate fresh water, salt water and polluted water environments to target dengue vector preimaginal forms to control dengue transmission.
- Apart from destroying Aedes habitats, measures should be taken to establish proper waste management systems and regulations to reduce one-time use containers to reduce vector developing sites. The Health Ministry has to create model villages with dengue preventive measures to show the public that dengue can be prevented through proper control measures which prevent human vector contact.
- Due to logistic reasons and limited resources, the field study was restricted to only four places such as Gurunagar, Navanthurai, Thirunelvely and Uduvil. What is recommended here is to expand the survey area and increase the number of sample collection points in future studies to infer dengue transmission dynamics at the micro-habitat level. Further adult collection is recommended to study the feeding and resting behaviours of potential vectors. The Ovitrap survey, which is only restricted to the Jaffna Municipal Council area, should be extended to cover urban, semi-urban and rural areas to monitor the prevalence of dengue vectors. Focus should be laid on detecting DENV in vectors to understand the predominance of circulating serotypes over the period. Apart from screening the emerged adults from the larval survey, screening adults from the field for DENV is suggested. This will help to understand the changing epidemiology in terms of DENV serotypes and vector population dynamics. The results of these studies will be further useful to devise effective control measures.
- DENV serotyping was carried out in the Jaffna district from 2018 to 2019. This showed that DENV1 and DENV2 are the main circulating serotypes and shifting of the dengue serotype could lead to unprecedented dengue outbreaks. The study revealed that the >30 age group was the most affected by dengue. As young people are the main victims of dengue, vector control and awareness programs should be implemented in schools and workplaces where the young population is high.
- In this study only patients who were above 14 years of age participated; in future studies, the age group below 14 years should also be included in the associated

dengue transmission in children. Therefore, screening the pediatric cohort is highly recommended for future work to understand the prevalence of DENV serotypes and clinical outcomes in the pediatric cohort. In our study we collected the samples on admission to Jaffna Teaching Hospital on suspicion of dengue; therefore, asymptomatic dengue cases and serotype and genotype prevalence of DENV in the asymptomatic population were inadvertently excluded from this study. In the future, it is highly recommended that asymptomatic dengue cohorts be targeted via random sampling in dengue epidemic hot zones identified through GIS-based analysis. In this study, a single blood sampling was carried out. To study primary and secondary dengue infections, periodic blood sampling is suggested. Genotyping of serotypes is essential to study their epidemiology. It is the first time a study reports partial sequencing of the DENV1 and DENV serotypes. In future studies, it is highly recommended to perform frequent full genome sequencing of all four DENV serotypes to fully understand the circulating DENV.

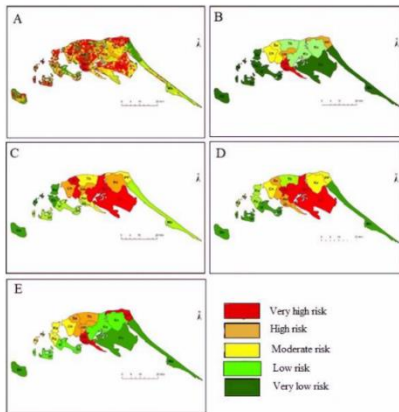


Figure 1 : Dengue risk map based on demography and land use risk categories A-E (A- Land use pattern B-Population density, C- Household type, D- Income based on Samurdhi, E-Schools)

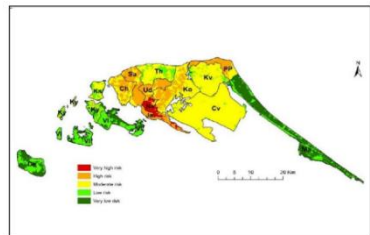


Figure 2 : GIS based dengue risk map for Jaffna district

Project Title : **Study of Risk factors affecting Transmission of Dengue in the District of Gampaha**

Grant No : **RPHS/2016/D 03**

Principal Investigator : **Prof. Menaka Hapugoda,**
Molecular Medicine Unit, Faculty of
Medicine, University of Kelaniya, Ragama

Background:

The second highest number of dengue cases has been reported in the District of Gampaha during the last ten decades. A broad knowledge of epidemiology and local disease transmission is lacking in the district. Epidemiology of dengue was studied covering three major areas (Area 1,2 & 3) as identified by the NSF.

Under Area 1 of the study, close monitoring of possible risk factors affecting transmission of dengue with regard to dengue high and low risk areas was performed for 18 months. Development of a hospital-based surveillance system for monitoring dengue incidence during pre, inter and post outbreak seasons will also be very useful. Further, identification DENV serotypes/strains circulating in humans and mosquitoes will also be very useful. These data will immensely contribute to the understanding of the nature of the virus circulating in the field. In Area 2 of the current study, a hospital-based surveillance for monitoring dengue cases was established and DENV serotypes/strains circulating in humans and mosquitoes were identified. Severity of dengue cases with circulating dengue serotypes/strains was identified.

Risk maps can be used to identify geographic areas with high disease prevalence. Such maps are particularly useful where disease surveillance data are poor or lacking. A mathematical model was developed to predict evolution of dengue epidemics with regard to these factors under Area 3 of the study. They are useful for guiding allocation of scarce public health resources for interventions.

Key Research Findings:

- Grama Niladhari (GN) Divisions with a high and a low transmission were monitored for 18 months. The entomological surveillance data showed the presence of high abundance of the secondary vector of dengue compared to the primary vector of dengue. It could be concluded that the major vector responsible for the disease transmission in the selected areas is *Ae. albopictus* compared to *Ae. aegypti*. Therefore, our control measures need to be directed against *Ae. albopictus*.
- From the statistical analysis of primary data, the presence of high densities of vector species, reporting dengue cases previously, cleanliness of premises, major mosquito prevention method, presence of potential mosquito breeding sites and

vegetation coverage may be the most important risk factors affecting transmission of dengue. Therefore, health authorities responsible for dengue control could focus on these risk factors in their vector control campaigns to eradicate dengue from these high-risk areas.

- Even though, the Municipal Council is responsible for removing solid waste weekly, a large number of breeding sites are available at both areas. As there is a significant difference between *Ae. albopictus* breeding sites at the dengue high and low risk areas, it is essential to specifically focus on removal of breeding sites for successful vector control measure
- The present study reveals that all serotypes of DENV had been circulating during the period from 2018 to 2019; DENV-2 was observed as the predominant serotype during 2018, which caused the largest dengue outbreak in Sri Lanka in 2017 and DENV-3 was the predominant serotype in 2019.
- This study has resulted in the identification of Zika infection in 5% (15/300) patients suspected of dengue infection during the period from 2018 to 2019. To the best of our knowledge, this is the first report of detection of Zika virus infection in Sri Lanka. Mismanagement of zika cases may happen due to overlapping of clinical symptoms.
- Pre-tested forecasting model using the random forest modelling method had resulted in fairly accurate forecasting for a number of incidence of dengue in the district of Gampaha. It will be further developed by fitting to reduce the MAPE parameter of the forecasted values to get the maximum accuracy

Project Title : **Developing an effective epidemiological surveillance system for dengue in Southern Province of Sri Lanka.**

Grant No : **RPHS/2016/D 04**

Principal Investigator : **Prof. Ajith de Silva Nagahawatte,**
Department of Microbiology, Faculty of
Medicine, University of Ruhuna, Karapitiya,
Galle

Background:

The study proposed to develop a comprehensive dengue surveillance system that detects dengue hemorrhagic fever (DHF)/ dengue shock syndrome (DSS). A cross-sectional surveillance study of DHF/DSS was conducted. The study was performed in two phases: Phase 1 (sentinel surveillance of public hospitals in Galle District) and Phase 2 (sentinel surveillance of public hospitals in Southern Province). All patients with a diagnosis of presumed dengue and with signs of early plasma leakage were enrolled to determine risk factors for development of severe disease. Socio-demographic information, exposure and travel history, and clinical information from all patients were collected. An acute serum sample was collected from all patients at enrollment. Global Positioning System (GPS) coordinates were collected during the initial admission using Google Maps technology. Samples were tested at the Laboratory of the Department of Microbiology, Faculty of Medicine, University of Ruhuna. Testing for confirmation of dengue included dengue NS1 antigen rapid test, polymerase chain reaction (PCR) for dengue, and ELISA for dengue IgM and IgG.

Outputs included enhanced active dengue surveillance at public hospitals in Galle District and the Southern Province. Surveillance information was shared with the Ministry of Health and the Infection Control Unit of Teaching Hospital Karapitiya in order to enhance the existing surveillance system.

In addition, the research aimed to identify predictors of severe dengue to develop a triaging system for ambulatory versus inpatient care of acute dengue in Sri Lanka.

Key Research Findings:

- In conclusion, in this large, prospective cohort of patients hospitalized with acute dengue and the potential to develop severe disease, one half progressed to DHF and only a very small number developed DSS or severe dengue. Our findings suggest potential for triaging patients with acute dengue to ambulatory care versus in-hospital management. Identifying predictors of severe disease and

developing separate triaging algorithms for children and adults are our future goals to optimize utilization of healthcare systems in dengue endemic countries. Severe disease was more common among children than adults and ambulatory management is feasible in dengue. Separate triage algorithms for children and adults are a desired immediate goal to reduce hospitalization. The safety and impact of such triaging systems need to be identified prior to implementation.

- In conclusion, we found that the cases of dengue requiring hospitalization had a substantial economic burden on direct healthcare costs and indirect household costs. Sri Lanka, being endemic for dengue, is vulnerable to negative economic impacts from dengue, highlighting the need for strengthened dengue control activities and improved use of hospital-based resources for care. Dengue resulted in a significant economic burden to southern Sri Lankan community. These data highlight the need for preventative public health actions for dengue and may help decisions on vaccination or vector control activities.
- None of the serotypes were significantly associated with severe dengue. However, secondary dengue is more likely to be diagnosed with DEN2 than primary dengue. There is a significant association between the type of the virus and the age group affected. This highlights the importance of dengue surveillance and its influence on policy making on future vaccine approval and the potential need for different vaccine composition

Project Title : **Proactive Dengue Management System (ProDMS)**

Grant No : **RPHS/2016/D 05**

Principal investigator : **Prof. SSN Perera,**
Research Development Centre for Mathematical Modelling, Department of Mathematics, Faculty of Science, University of Colombo

Background:

In the past 10 years we have witnessed a dramatic increase in the incidence of dengue and its severe manifestations, making this infectious disease a major public health problem. Therefore, continuous monitoring, analysis, forecasting and controlling strategies are mandatory to control the spread of dengue and avoid further transmission. ProDMS is a multi-platformed informative and distributed system for monitoring, forecasting and controlling the dengue epidemics. Ultimately, ProDMS provides solution to eliminate the impediment created by lack of transparency and the liquidity of information flows among different communities involved with dengue control. The broad purpose of ProDMS is to provide an integrated environment to policy- makers, researchers and the general public to synergize the prevention of Dengue epidemics through sharing of information, knowledge enhancements, collaborations and community engagements. Thus, the system unites scattered information and works as one single entity with the objective of dengue prevention.

Key Research Findings:

Availability of the ProDMS System

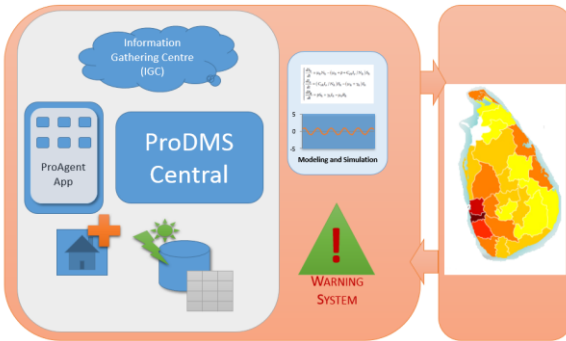


Figure 3: Proactive Dengue Management System — ProDMS



Figure 4: ProDMS Web-based system: Front view

Project Title : **Identification of the true burden and associated complications of dengue and related viral infections in Sri Lanka and finding long lasting solutions, through in depth understanding of the pathogenesis for development of therapeutic targets**

Grant No : **RPHS/2016/D 06**

Principal investigator : **Prof. Neelika Malavige**
Department of Immunology and Molecular
Medicine, Faculty of Medical Sciences, University
of Sri Jayawardenapura

Background:

Dengue viral infections is one of the most important mosquito- borne viral infections, which causes significant morbidity and mortality worldwide. Hospitalizations and costs due to dengue control activities were estimated to be US\$ 3.45 million in 2012 in Colombo, Sri Lanka. Despite taking active measures to control these epidemics, the number of cases is on the rise every year. Therefore, it is imperative that we find answers to key questions such as, identifying the true burden of dengue and related viruses, the consequences of infection during pregnancy, clinical spectrum of illnesses caused by the dengue virus including neurological manifestations, the mechanisms of occurrence of severe disease in order develop drugs, identify best management strategies to treat dengue- associated complications and also define the correlates of protection associated with protection against the dengue virus. In this project we were hoping to find answers to all of the key questions listed above so that we will be able to find long lasting solutions to the dengue menace in Sri Lanka.

Key Research Findings:

- Dengue infections accounted for 15.68% of febrile infections presented to the outpatient departments in the Kalutara and Galle districts and the majority of infections were due to DENV2 serotypes. 10.09% of cases were identified only by the NS1 antigen rapid assay while 11.53% cases were not detected.
- Flavivirus infection appears to be frequently associated with ?? (GBS) in Sri Lanka.

- Evidence of acute dengue infection of the central nervous system was seen in those with ?? (TM) suggesting a possible aetiological association between dengue and TM.
- Serum LPS levels were significantly higher in patients with dengue haemorrhagic fever
- Those with metabolic diseases and allergies were more likely to have detectable LPS
- Patients with detectable LPS were more likely to have elevated CRP levels
- Patients with high CRP in early illness were at higher risk of developing DHF
- Patients with high procalcitonin were more likely to have detectable LPS
- We found that urinary LTE4 levels were significantly higher in early illness in patients, who proceed to develop DHF. The LTE4 levels continued to rise during the course of illness in patients with DHF, whereas the levels remained unchanged in those with DF. As there are cysteinyl leukotriene receptor antagonists available, it would be important to evaluate if these drugs could reduce dengue disease severity.
- In this study we have shown that the leave extract of *T. hispida* which has been used for centuries to treat fever and inflammatory diseases in traditional medicine has potent sPLA2 inhibitory activity and in the cell cytotoxicity assays, it was shown to have minimum toxicity for mammalian cell lines. However, we could not isolate the exact compound in the extract of *T. hispida* that had these functions. Since the whole leave extract appears to be safe due to long term consumption and based on the evidence of in vitro studies, it would be important to carry out double-blind placebo controlled clinical trials to evaluate its efficacy in treating patients with acute dengue.
- The Tfh cells appear to significantly expand in acute dengue, which is associated with clinical disease severity and plasmablast expansion. This increase in frequency also 76?? correlated with DENV-specific IgG and Neut50 antibody titres. Since evaluation of Neut50 titres in the febrile phase (before patients developed either DF or DHF) did not appear to be associated with clinical disease

severity or the degree of viraemia, neutralizing titres alone do not appear to determine protection against severe clinical disease.

Scientific Impact

No.	Grant Number/ Title and Total expenditure	Capacity Building	Knowledge Creation & Dissemination	Infrastructure Development
01.	RPHS/2016/D 01 Innovative tools and strategies for surveillance and control of dengue: 2017 – 2020. Rs. 7,910,530/-	2 – Scientists 1 – Research Student 1 – MD	1 – International Collaborations 2 – Publications 7 – Communications	None
02.	RPHS/2016/D 02 Development of an early warning system, a risk map and a prediction model for dengue and establishment of roles of asymptomatic carriers and brackish water derived- mosquitoes in dengue transmission in Jaffna district. Rs. 9,999,135/-	5 – Scientists 5 – Research Student 2 – PhD	1 – International Collaborations 5 – Publications	Deep Freezer Centrifugal vacuum concentrator UPS Work station

03.	RPHS/2016/D/03 Study of Risk factors affecting Transmission of Dengue in the District of Gampaha Rs.6,869,000/-	6 – Scientists 1 – MPhil 1 – PhD	1 – International Collaboration 1 – Publication 5 – Communications	Nipichet Micropipette Two Computers
04.	RPHS/2016/D/04 Developing an effective epidemiological surveillance system for dengue in Southern Province of Sri Lanka Rs. 8,402,443/-	10 – Scientists	2 – International Collaborations 2 – Publications 7 – Communications	None
05.	RPHS/2016/D/05 Proactive Dengue Management System (ProDMS). Rs: 13,720,000/-	7 – Scientists 2 – Research Students 2 – PhD	2 – International Collaborations 16 – Publications 29 – Communications 7 – Book Chapter	Dell Server Note book & Laptops
06.	RPHS/2016/D/06 Identification of the true burden and associated	14 – Scientists 4 – Research Students	1 – International Collaboration 5 – publications 21 – communications	Circulation water baths - 2 Laboratory

	<p>complications of dengue and related viral infections in Sri Lanka and finding long lasting solutions, through in depth understanding of the pathogenesis for development of therapeutic targets.</p> <p>Rs. 27,417,000/-</p>	<p>2 – MPhil</p> <p>2 – PhD</p>		<p>Grade Refrigerator</p> <p>Micro Scale</p>
S U M M A R Y	<p>Total Spent</p> <p>Rs. 74,318,108/-</p>	<p>44 – Scientist</p> <p>12 – Research Students</p> <p>7 – PhDs</p> <p>3 – MPhils</p> <p>1 – MD</p>	<p>8 – International Collaborations</p> <p>31 – Publications (SCIE & Peer reviewed)</p> <p>69 – Communications</p> <p>7 – Book Chapters</p>	<p>Deep Freezer</p> <p>Centrifugal vacuum concentrator</p> <p>UPS</p> <p>Work station</p> <p>Nipichet</p> <p>Micropipette</p> <p>Two Computers</p> <p>Dell Server</p> <p>Note book & Laptops</p> <p>Circulation water baths - 2</p> <p>Laboratory</p>

				Grade Refrigerator Micro Scale
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