This International Conference brings together renowned scientists, clinicians, researchers and scholars with a common interest and concern in the global dengue situation, and provides an opportunity to professionals in the field of health and allied health sciences to share the latest research findings, build new relationships and to discuss dengue and its management, prevention and control strategies.

The Conference is organized by the Epidemiology Unit, Ministry of Health, Sri Lanka, in collaboration with the Centre for Global Health Research at the University of Umeå, Sweden with its 14 partners from Europe, Asia and South America and the Partnership for Dengue Control (PDC) of Fondation Mérieux (FMx), France.

The broad aim of the conference is to celebrate the end of European Community’s DengueTools Project and to translate this information directly into improved tools for surveillance, better diagnosis, as well as prediction and prevention of the spread of Dengue to previously uninfected regions (including Europe) in the context of climate change.

The local Organizing Committee is confident that this event is an ideal platform of learning and collaboration and hope this will be a significant milestone of international events in Dengue in 2016.
International Conference on Dengue and Dengue Haemorrhagic Fever 2016

DENGUE: TO STEM THE TIDE

24 – 26 FEBRUARY 2016

BMICH
Colombo - Sri Lanka

Organized by
EPIDEMIOLOGY UNIT
Ministry of Health
International Conference on Dengue and Dengue Haemorrhagic Fever 2016

Scientific Committee

Dr. Paba Palihawadana
Dr. Hasitha Tissera
Dr. Ananda Amarasinghe
Prof. Annelies Wilder – Smith
Prof. Duane J Gubler
Prof. Aravinda de Silva
Dr. LakKumar Fernando
Dr. Ananda Wijewickrama
Dr. Jayantha Weeraman

Organizing Committee

Dr. Paba Palihawadana
Dr. Hasitha Tissera
Prof. Annelies Wilder – Smith
Prof. Duane J Gubler
Ms. Raman Preet
Dr. Samitha Ginige
Dr. Deepa Gamage
Dr. Jagath Amarasekera
Dr. Athula Liyanapathirana
Dr. Preshila Samaraweera
Dr. Azhar Ghouse

Dr. Miyuru Gamage
Dr. Sanjaya Nagasinghe
Dr. Oshen Chandrasoma
Dr. Sachini Gunawardane
Dr. Rajika Samarathunga
Mr. Sanka Ranawaka
Addressing Dengue as a major public health concern is among the topmost priorities of the infectious disease prevention agenda of the Government. This was evident in the past, present and will continue to be a frontline concern in the future as well.

During my tenure as Minister of Health, I strongly believed in the inter-sectoral approach in preventing and controlling the dengue epidemic. The National Task Force was established during this period where high-powered political and state officials were made responsible for spearheading prevention and control of dengue. As I clearly pointed out then that it was not solely a matter for the Ministry of Health alone to control Dengue, the prime objective was to establish a strong inter-sectoral collaboration incorporating relevant ministries in this task.

As the President, I pledge that the support and guidance from the highest offices will definitely be directed towards a coordinated and effective campaign aimed at sustainable control of Dengue. I affirm that the outcome of this conference will shed more light on understanding this disease and pave the way for better prevention and control measures to be carried out by the government and the people at large.

We are well poised to building the human and collateral resources, for a sustainable national programme. Human resources currently at our disposal includes number of our senior staff who have had experience abroad, and having horned their skills with those experts in dealing with such contingencies.
MESSAGE FROM HON. RAJITHA SENARATNE
MINISTER OF HEALTH, NUTRITION & INDIGENOUS MEDICINE

It gives me great pleasure to welcome all the International and local scientists, clinicians, researchers and scholars to this International Conference on Dengue. I feel that it is appropriately themed “Dengue: To Stem the Tide”, because we are at present facing a serious threat of increasing dengue patients day by day.

Due to the problems of urbanization, climate change and many other factors, Dengue is becoming an emerging/re-emerging disease not only in the traditionally previously identified tropics and sub tropics but in the entire global scenario. Despite the extensive measures taken over the years and the unflawing commitment of the governments, Dengue still remains at large in the entire world including Sri Lanka.

This conference is therefore, a timely platform to discuss and share the knowledge to combat Dengue, which has now become a socio-political issue. The updated knowledge will definitely guide the Health Ministry in formulating new strategies and policies towards control and prevention of Dengue in Sri Lanka.

I wish all the very best for this International Conference and hope it will bring to light new ideas in successfully stemming the tide of Dengue.
MESSAGE FROM HON. FAIZER MUSTAPHA
MINISTER OF LOCAL GOVERNMENT & PROVINCIAL COUNCILS

Dengue prevention and control needs an effective inter-sectoral approach, requiring coordination between Ministry of Health and other relevant Ministries, government agencies, private sector and local communities. The Presidential Task Force for Prevention of Dengue Fever was set up with the aim of promoting environmental management through the collaboration of relevant Ministries for mosquito eradication than the isolated efforts of different sectors, the key to successful implementation of the vector control strategy.

In Sri Lanka, annually more than 30,000 patients are reported placing significant burdens on families, communities, health system and economy. Unfortunately, it can be seen that discarded receptacles are the major breeding source of dengue vectors. As an integrated approach, promoting garbage separation at the household level and solid wastemanagement for the elimination of containers are the strategies that can be adopted in this scenario to overcome the current crisis.

The Ministry of Local Government has pledged to strategize its activities to improve solid waste management practices with community participation coupled with behavioral change. Attempts to promote mosquito breeding free environment at household and institutional levels need to be endorsed by all key stakeholders at national, provincial, district and divisional levels with their active involvement.

I wish to acknowledge the officials at all levels of the Presidential Task Force for their continuous support and cooperation.
Dengue in Pakistan in 2011 spread out like an epidemic, in a very short span of time. I am proud of my experts, staff and their departments that not slowly and surely but rapidly, strengthened by the will and commitment we successfully handled possibly the largest epidemic of dengue in the history of mankind within a few months.

It has always been a moment of greater satisfaction that experts from Sri Lanka had been very close to us during the 2011 dengue epidemic and it was due to their joint efforts that we were able to manage the disease. As Chief Minister, Punjab and my government will always keep this gesture of scientific sharing as a memorable event whenever the history of dengue will be written, as perfecting clinical management saved many lives.

Today we have adopted effective strategies for combating the disease to make it a success story in Punjab, Pakistan. Our teams and professionals are working with the same pace as they did in 2011. Although, the worst ever epidemic of dengue is over, we are still working with the same professional engagement for serving the humanity. The participation of my team including the political representation and technical experts actually is a representation of the commitment of my government towards this global issue.

Lastly I would once again like to thank the Sri Lankan government and also congratulate experts like Dr. Paba Palihawadana, Dr. LakKumar Fernando and Dr. Hasitha Tissera for organizing such a wonderful scientific gathering and do wish that the findings of the experts will benefit the humanity as every life on this earth is precious.
“Dengue: To Stem the Tide” is an appropriate theme on which the proposed International Conference is scheduled to be held in Colombo.

It is opportune to take stock of the current Dengue situation which has apparently been on the increase despite numerous interventions undertaken by the National Dengue Control Unit and the Epidemiological Unit of the Ministry of Health with the collaboration of various stakeholders. It is, however, a cause for solace that mortality due to Dengue has been reduced substantially due to dedicated inputs to improve curative care.

A strategic plan was prepared by a core group of local and international experts with the aim of utilizing the currently available interventions optimally and effectively mobilizing inter-sectoral collaboration through sharing the leadership role and responsibilities with other liaised stakeholders like Ministries of Defence, Local Government and Provincial Council, Public Administration, Media and Information, Disaster Management and Education.

I wish my best for this international conference where experts meet sharing and exchanging knowledge will pave the way for further strengthen our efforts to control Dengue and benefit of our society.
MESSAGE FROM DR. PALITHA MAHIPALA
DIRECTOR GENERAL OF HEALTH SERVICES

It is indeed an immense pleasure to convey this message on the occasion of the ‘International Conference on Dengue & Dengue Haemorrhagic fever 2016’ with the participation of local and foreign experts. I consider it as a great opportunity for our health workforce to learn from the international experts and also to share what Sri Lanka has done, the progress made, in prevention and control of dengue fever and case management.

Today Dengue and Dengue Haemorrhagic Fever has become the most important public health issue globally; tropical countries in particular. Countries in South East Asia including Sri Lanka are facing the challenges of serious outbreak situations. In that respect, I am sure that the wealth of information shared in this workshop will be useful to combat this public health issues in Sri Lanka and in the region too.

Further, I am delighted to note that this will lead to many collaborative research works between Sri Lanka and other international agencies which I consider as a great global endeavour to upgrade the knowledge on this challenging issue. Let me wish a very successful workshop in Colombo which will set the platform for initiatives in better management of dengue fever and dengue haemorrhagic fever.
Epidemiological Unit of the Ministry of Health was established in 1959 with the aim of improving health of the public through collation, interpretation and provision of best possible information on communicable diseases. From its modest beginnings, it has evolved to become the premier institution in the country handling disease surveillance, Prevention and control of communicable diseases, immunization, epidemiological investigation into Emerging and re-emerging diseases and research and training in epidemiology.

The DengueTools project which was initiated in 2011 as a laboratory based sentinel surveillance study in the Colombo district helps to better understand the epidemiology and disease dynamics of Dengue in the local scenario which has enables us to carry out control activities in a more scientific context.

This international scientific conference to celebrate the end of the DengueTools study and dissemination of the findings obtained thereof will further strengthen our efforts and guide for future research and policy decisions.
PROGRAMME

Wednesday, February 24, 2016 - Inauguration Session

6.00 pm    Arrival of Guests
6.30 pm    Arrival of the Chief Guest
6.40pm    Welcome Address - Dr. Palitha Mahipala
6.45 pm    Address by the Special Guest - Hon. Khawaja Salman Rafeque
6.50 pm    Address by the Guest of Honour - Hon. Faizer Mustapha
7.00 pm    Address by the Chief Guest - His Excellency Maithripala Sirisena
7.15pm    Keynote Address: Part I: Can we control Dengue? - Prof. Duane J Gubler

Part II: Overview of Dengue Vaccine Pipeline - Dr. In-Kyu Yoon
8.00pm    Vote of Thanks - Dr. Paba Palihawadana
8.10pm    Cultural Event

Day 1 – Thursday, February 25, 2016 - Technical Sessions

Plenary Session on DengueTools – Moderators: Prof. Duane Gubler and Dr. Palitha Mahipala

09.00am    EU Contribution to Dengue Research - Inmaculada Penas Jimenez
09.15am    An Overview of DengueTools Project - Prof. Annelies Wilder-Smith
09.40am    Enhanced Dengue Sentinel Surveillance in Colombo, Sri Lanka - Dr. Hasitha Tissera

10.00am    TEA

10.15am    Point of Care Diagnostics in the Field - Prof. Sazal Abu Bakar
10.30am    Mast Cell Degranulation and Severe Dengue - Dr. Ashly Lauren St John
10.45am    Costing of Dengue in Sri Lanka - Dr. Yesim Tozan
11.00am    Early warning system: Modelling and Prediction of Dengue - Dr. Joacin Rocklov
11.15am    Dengue virus sequencing from SL - Dr. October Sessions
11.30am    Aedes albopictus in Europe - Prof. Paul Reiter
11.45 am    Discussion
12.15 pm    LUNCH
01.15pm **Guest Lecture**  Classifying Dengue Haemorrhagic Fever: 
My Journey in Time - **Prof. Suchitra Nimmanitiya**

### Symposium 1 – Clinical Management
**Moderators:** Prof. Sanath Lamabadusooriya and Prof. S.A.M. Kularatne

02.00pm  Fluid Therapy in Dengue - **Dr. LakKumar Fernando**
Managing Bleeding in Dengue - **Dr. Ananda Wijewickrama**
Dengue Management in Singapore - **Prof. Yee Sin Leo**

02.45pm  Revising Dengue Case Classification-Evidence from DENC0 - **Prof. Bridget Wills**

03.00pm  Round Table Discussion on Case Classification

04.00p  TEA

### Symposium 2 – Vector Control
**Moderators:** Prof. Rajitha Wickramasinghe and Dr. Hasitha Tissera

04.15pm  *Aedes aegypti* Control: Where to Now? - **Prof. Paul Reiter**
Integrated Vector Management: Sri Lankan Perspective - **Dr. Paba Palihawadana**
Approaches and Tools: Dengue Epidemic in Punjab, Pakistan 2011 to 2015
Dr. Waseem Akram
Dengue Surveillance and Control in Singapore - **Wilson Tan Cheong Huat**

05.15pm  Discussion

05.45pm  Roundup and Close

---

**Day 2 – Friday, February 26, 2016 - Technical Sessions**

08.30am  **Guest Lectures on Dengue as a Platform for Building Partnerships and Advancing Biomedical Research**

New Discoveries on the Human B-Cell Response to Dengue Infection - **Dr. Aravinda De Silva**
The Human T-Cell Response to Dengue: Impact of HLA Protein Variation on T-Cell Responses and Disease - **Dr. Alessandro Sette**
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.15am</td>
<td>Overview of Takedas Dengue Vaccine Candidate Development - Dr. Shibadas</td>
</tr>
<tr>
<td>09.40am</td>
<td>CYD TDV Dengue Vaccine: Sanofi Pasteur - Dr. Muruga Vadivale</td>
</tr>
<tr>
<td>09.55am</td>
<td>Vaccine CT Ethics in Developing Country Settings - Prof. Asita de Silva</td>
</tr>
<tr>
<td>10.10am</td>
<td>Round Table on Vaccines - Dr. Muruga Vadivale</td>
</tr>
<tr>
<td></td>
<td>Dr. Jeremy Brett</td>
</tr>
<tr>
<td></td>
<td>Dr. Alexander Schmidt</td>
</tr>
<tr>
<td></td>
<td>Dr. In-Kyu Yoon</td>
</tr>
<tr>
<td>10.45am</td>
<td>TEA</td>
</tr>
<tr>
<td>11.00am</td>
<td>Guest Lecture Wolbachia - Prof. Scott O'Neill</td>
</tr>
<tr>
<td>11.30am</td>
<td>Round Table on Control Strategies - Prof. W. Abeyewickrem</td>
</tr>
<tr>
<td></td>
<td>Dr. Deepthi Perera</td>
</tr>
<tr>
<td></td>
<td>Dr. Kevin Gorman</td>
</tr>
<tr>
<td></td>
<td>Dr. Rushika Perera</td>
</tr>
<tr>
<td></td>
<td>Prof. Scott O'Neill</td>
</tr>
<tr>
<td>12.30pm</td>
<td>LUNCH</td>
</tr>
<tr>
<td>01.15 pm</td>
<td>Asymptomatic Dengue Infections: Iceberg Under the Water - Prof. Anavaj</td>
</tr>
<tr>
<td></td>
<td>Sakuntabhai</td>
</tr>
<tr>
<td></td>
<td>Pathogenesis of Severe Dengue - Dr. Neelika Malavige</td>
</tr>
<tr>
<td></td>
<td>Next Gen Sequencing - Dr. October Sessions</td>
</tr>
<tr>
<td></td>
<td>Are Cytokines Good Markers for Dengue Prognosis? - Dr. Yie-Hoe Lee</td>
</tr>
<tr>
<td></td>
<td>Dengue Diagnostics: Dilemmas - Prof. Shamala Devi Sekaran</td>
</tr>
<tr>
<td>02.45pm</td>
<td>Discussion</td>
</tr>
<tr>
<td>03.00 pm</td>
<td>Considerations for Global Vaccine Recommendations and Use - Dr. Kirsten Vannice</td>
</tr>
<tr>
<td>03.15pm</td>
<td>Closing Session - Prof. Duane Gubler</td>
</tr>
<tr>
<td></td>
<td>Prof. Annelies Wilder-smith</td>
</tr>
<tr>
<td></td>
<td>Dr. Paba Palihawadana</td>
</tr>
<tr>
<td></td>
<td>Dr. Hasitha Tissera</td>
</tr>
<tr>
<td>04.15 pm</td>
<td>TEA</td>
</tr>
</tbody>
</table>
Prof Dr Duane J Gubler, ScD, FAAAS FIDSA, is Professor and founding director, Signature Research Program in Emerging Infectious Diseases at the Duke-NUS Medical School, Singapore. He is Adjunct Professor in his alma mater, Johns Hopkins Bloomberg School of Public Health and the Duke University School of Medicine. He has spent his entire career working on tropical infectious diseases with an emphasis on dengue and dengue haemorrhagic fever. He has extensive field experience in Asia, the Pacific, tropical America and Africa, and has published extensively in the area of dengue and other vector-borne infectious diseases. Prof Gubler was founding Chief of the Dengue Branch, United States Centers for Disease Control and Prevention (CDC) in Puerto Rico for 9 years, Director of the Division of Vector-Borne Infectious Diseases in Fort Collins, CDC for 15 years and as Chair, Department of Tropical Medicine, Medical Microbiology and Pharmacology, University of Hawaii School of Medicine, in Honolulu for 5 years. He has served on numerous WHO and national committees and study groups, and was founding Chair, Board of Councillors, Pediatric Dengue Vaccine Initiative. He currently serves on the Scientific Advisory Boards of a number of companies and institutions. Prof Gubler serves as Chairman of the Partnership for Dengue Control, a global alliance of experts in the dengue community. He is a Fellow of the Infectious Disease Society of America and the American Association for the Advancement of Science, and a Past President of the American Society of Tropical Medicine and Hygiene.

Dengue is one of the most important epidemic infectious diseases of humans. Current estimates of approximately 400 million people infected and 100 million symptomatic cases each year, vary with the frequency and magnitude of epidemic activity, but are likely conservative. Major epidemics in large tropical cities often result in high morbidity and mortality, causing hospitals and clinics to become overloaded. The disease thus imposes significant economic and public health costs in endemic countries. Public health efforts to control the disease in the past 40 years have failed, as both the mosquito vectors and the viruses have spread globally with increased frequency and magnitude of Dengue epidemics.

This 20th century pandemic of Dengue, driven by the global trends of population growth, urbanization, globalization and lack of effective mosquito control, shows no signs of abating in the second decade of the new millennium. However, new Dengue control tools developed in the past 10 years show great promise. The tools in the pipeline include at least three vaccines, antiviral drugs, therapeutic antibodies and a number of novel mosquito control methods. Unfortunately, none of these tools, when used alone, will likely be effective in reducing dengue transmission. When used together in an integrated and synergistic way, however, they should be able to control Dengue. This new paradigm for Dengue control will be discussed in the context of tools that should be available in the next two to three years.
Dr. In-Kyu Yoon received a Bachelor of Science degree from Yale University and an M.D. from the New York University School of Medicine. He completed his residency and fellowship training in Internal Medicine and Allergy/Immunology at the Walter Reed Army Medical Center, USA.

He is currently the Deputy Director General of Science and Director of the Dengue Vaccine Initiative at the International Vaccine Institute in Seoul, Korea. He was previously Chief of Virology at the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand where he investigated arbovirus and respiratory virus infections including clinical trials of candidate vaccines. He has conducted research on the epidemiology, pathophysiology and immunology of dengue virus and other emerging pathogens, and has authored over 80 publications. He has provided clinical care in a variety of civilian and military settings internationally.

Currently, six different dengue vaccine candidates are in active clinical development in various phases of human clinical trials. The most advanced candidate, CYD-TDV, sponsored by Sanofi Pasteur, is a tetravalent live attenuated chimeric vaccine consisting of a 17D yellow fever backbone with DENV pre-membrane and envelope proteins from the four different DENV serotypes. CYD-TDV has undergone phase III clinical trials in Asia and Latin America demonstrating good efficacy against serotype-3 and 4, moderate efficacy against serotype-1 and poor efficacy against serotype-2, despite having good immunogenicity to all four serotypes based on neutralization antibody assays.

In December 2015, CYD-TDV (trademarked as Dengvaxia®) was licensed in three countries (Mexico, Philippines, and Brazil) for use in 9 to 45 year olds in dengue endemic areas. Questions linger about the reasons for the mixed efficacy results and the safety signal in very young children which may have implications not only for CYD-TDV but also for other vaccine candidates. Two other dengue vaccine candidates in addition to CYD-TDV have entered or are close to entering phase III trials. TDV, sponsored by Takeda, is a tetravalent live attenuated chimeric vaccine that uses a DENV-2 backbone with pre-membrane and envelope proteins from the four serotypes. TV003/TV005, developed by U.S. NIH, is a tetravalent live attenuated vaccine which has undergone direct mutagenesis for three serotypes while the fourth serotype consists of a DENV-DENV chimera. DPIV, a tetravalent purified formalin-inactivated whole virus vaccine, being co-developed by GlaxoSmithKline, Fiocruz (Brazil) and the U.S. Army, is intended for use with several possible adjuvants. V180, sponsored by Merck, is a tetravalent recombinant protein subunit vaccine using truncated envelope gene expressed in Drosophila S2 cell expression system.
Inmaculada Peñas Jiménez is the scientific officer for malaria and Dengue fever in the Unit Fighting Infectious Diseases and Advancing Public Health of the Directorate General of Research and Innovation of the European Commission. Trained to protect consumers health by the University Complutense of Madrid (Spain), her career has been mainly dedicated to manage European funding grants, first in the Structural Funds and later on in the Directorate General of Research. She was responsible initially of the life sciences panel of the Marie Curie Research Fellowships (1994-2005) contributing to remove obstacles to the mobility of researchers and to develop the career of the researchers in this area. During 2006-2009 she was responsible of the human resources of the European Research Council executive agency before moving to her current position.

ABSTRACT

Aware of the growing risk of Dengue fever under changing climatic conditions, the European Commission published a call for research proposals to contribute to a comprehensive control of the disease, to develop innovative tools for better diagnosis, surveillance, development of treatment, prevention and vaccination strategies, as well as to predict and prevent the spread of dengue fever to previously uninfected regions. The call also addressed the host factors that can predict disease severity and prepare for further development of new vaccines, antiviral compounds, and more targeted treatment schemes.
Professor Annelies is the Scientific Coordinator of the European Commission funded consortium DengueTools with Umea University in Sweden as host institution. In addition to holding a professorship at Umea University, she is Professor for Infectious Diseases Research at the Lee Kong Chian School of Medicine (LKC), Singapore. Her research interests include vaccine preventable diseases, emerging infectious diseases, and travel medicine, with a strong focus on dengue. In 2015, Annelies Wilder-Smith was appointed Senior Advisor to the “Dengue Vaccine Initiative”, and she serves on the Executive Board of the “Partnership for Dengue Control”.

DengueTools is a global consortium of 14 partners, funded by the European Commission 7th framework. We identified several research gaps that we plan to address under 3 research areas.

Research area 1: Lack of understanding of individual or combined roles of viral, entomological, ecological, environmental and climate factors that influence dengue transmission dynamics and their respective outbreak predictive capability and the most cost-effective approach for surveillance and early warning systems. Early diagnostic assays at point-of-care and sensitive, reliable and simple field methods for vector surveillance are also lacking. To address those gaps we are setting up a comprehensive, early warning, laboratory-based sentinel disease surveillance system in Sri Lanka that has predictive capability for epidemic dengue.

Research area 2: Children are the most vulnerable group for dengue. Effective control strategies to protect children are lacking, in particular simple, cost-effective and scalable strategies. We hypothesize that insecticide treated school uniforms may be a target for school based intervention to reduce the incidence of dengue in school children. We are conducting a randomized placebo controlled school based trial in Thailand, complemented by laboratory-based studies at the London School of Tropical Medicine and Hygiene.

Research area 3: Gaps in understanding the risk of introduction of dengue to non-infected areas, including Europe, hampers effective preventive strategies. We currently have insufficient data on the magnitude and trends of importation and virus evolution over time and by geographic origin. We also only have a poor understanding of vector density, preferred breeding sites, and vectorial capacity of Aedes in temperate climates that are needed for predictive models under changing climate conditions. We will collect clinical and virological data in travellers returning to Europe from dengue endemic countries, explore the effectiveness of vector control programs against Aedes albopictus in Southern France, and develop predictive risk models and maps the introduction and establishment of dengue in Europe under different future climate scenarios in Europe.
Dr. Hasitha Tissera is a Consultant Epidemiologist leading the National Dengue Control Programme of Ministry of Health Sri Lanka. Dr. Tissera joined the Central Epidemiology Unit in 2002 after serving as a Regional Epidemiologist in the then war-torn Eastern Province of Sri Lanka. His responsibilities at the Epidemiology Unit encompass national surveillance of dengue, coordination of dengue case management based on national guidelines and training of all levels of clinical and public health staff.

Heading the National Dengue Control programme since late 2013 Dr. Tissera is involved in planning and implementation of all dengue control activities at national and sub-national levels. Dr. Tissera is the Principal Investigator of a number of International Research Projects on Dengue including the multi-region DengueTools Surveillance Project to develop a comprehensive early warning system supported under the Health Theme of the Seventh Framework Programme of the European Community. He received his Post-doctoral training in public health both at the Health Protection Agency – Centre for Infections (former Public Health Laboratory Services) and the Department of Health, London during 2006/08. Dr. Tissera has also been a researcher at the London School of Hygiene and Tropical Medicine, University of London.

**ABSTRACT**

The dramatic spread of epidemic dengue underscores the urgent need for better surveillance and control of this disease. The main purpose of surveillance is to provide timely and more accurate information to institute preventive or control measures for epidemic dengue. Dengue has emerged as a major public health problem in Sri Lanka. To obtain more data on the burden of dengue, a laboratory-based enhanced sentinel surveillance system was established in metropolitan Colombo.

How the sentinel sites were set up and reporting the results of enhanced surveillance (2012-2014) will be described. Out of 3,127 patients presenting with acute onset of fever, 43.6% had laboratory confirmed dengue (PCR or NS1 positive), mainly caused by dengue serotype-1. Clinicians’ diagnoses were associated with high sensitivity, but our findings also show that laboratory confirmation is required to enhance specificity.
Professor Sazaly Abu Bakar is currently the Director of the WHO Collaborating Center for Arbovirus Research and Reference at University of Malaya, Malaysia. He is also the Director and founding member of the Tropical Infectious Diseases Research and Education Centre (TIDREC), a center of excellence at University of Malaya. He received his training in virology from the University of Texas Medical Branch, Galveston, Texas, USA. His research interest is in emerging infectious diseases focusing especially on arboviruses including dengue.

Dengue continues to be the leading mosquito-borne disease of public health concern worldwide. The disease which manifests mostly as mild self-limiting febrile disease can also be contracted in its severe form, DHF/DSS, which has led to over 25,000 deaths annually. There is no specific treatment for severe dengue and prevention is the only currently available option. Studies have suggested that in most cases of dengue deaths, patients were late in getting the necessary medical attention. Early detection of dengue is critical to ensure that patients obtain immediate medical attention and immediate public health control measures can be taken to prevent further spread of the disease.

The point of care (POC) testing to rapidly detect dengue as early as on day one of fever is now widely available. This rapid strip format testing detects dengue virus non-structural protein-1 (NS1) in the patient’s blood. The test is relatively easy to perform as it does not require high level of expertise and no special equipment is needed. This testing method, hence, could become the preferred diagnostic method especially in the field and in resource limited environment.

In a recent study, we showed that the NS1 rapid strip test was sensitive to detect acute dengue especially in primary infection. Our findings also suggest that the IgM ELISA however, remained highly useful especially when complemented with the NS1 and nucleic acid tests for primary and secondary dengue, respectively. Recent development in non-thermal amplification of nucleic acids for detection of virus genome points to possible future direction of additional POC method for rapid and highly sensitive detection of dengue.
Ashley St. John is an Assistant Professor at Duke-NUS Graduate Medical School. Her work focuses on understanding host immune responses to virulent pathogens with the aim of developing novel vaccination strategies, diagnostics and therapeutics for infectious diseases. A major emphasis of her current studies is on understanding the role that mast cells play in promoting immune protection and pathology during dengue virus infection.

Dengue virus (DENV) is a mosquito-borne virus that causes a characteristic pathology in humans involving dysregulation of the vascular system. In some patients with dengue hemorrhagic fever (DHF), vascular pathology can become severe, resulting in extensive microvascular permeability and plasma leakage. The predominant view in the field is that vascular leakage during infection is the result of immune pathology that is induced by cytokines and other de novo transcribed vasoactive factors released from infected cells.

However, recent evidence has shown that mast cells (MCs), which are granulated immune cells that line blood vessels and regulate vascular function, are able to detect DENV particles in vivo and release pre-stored inflammatory mediators. We have identified the pre-stored MC products to be key for promoting endothelial cell permeability and vascular leakage during dengue infection. Mast cell proteases were identified as biomarkers of severe disease or DHF in multiple dengue patient populations.

These findings raised the possibility of repurposing MC stabilizers, which are drugs used to treat asthma and allergy, for treatment of vascular leakage during dengue infection.

**ABSTRACT**

Dengue virus (DENV) is a mosquito-borne virus that causes a characteristic pathology in humans involving dysregulation of the vascular system. In some patients with dengue hemorrhagic fever (DHF), vascular pathology can become severe, resulting in extensive microvascular permeability and plasma leakage. The predominant view in the field is that vascular leakage during infection is the result of immune pathology that is induced by cytokines and other de novo transcribed vasoactive factors released from infected cells.

However, recent evidence has shown that mast cells (MCs), which are granulated immune cells that line blood vessels and regulate vascular function, are able to detect DENV particles in vivo and release pre-stored inflammatory mediators. We have identified the pre-stored MC products to be key for promoting endothelial cell permeability and vascular leakage during dengue infection. Mast cell proteases were identified as biomarkers of severe disease or DHF in multiple dengue patient populations.

These findings raised the possibility of repurposing MC stabilizers, which are drugs used to treat asthma and allergy, for treatment of vascular leakage during dengue infection.
Dr. Tozan holds a Ph.D. and a M.A. in Public Affairs from Princeton University’s Woodrow Wilson School of Public and International Affairs, a M.Sc. in Environmental Technology from Bogazici University (Turkey) and a B.Sc. in Environmental Engineering from Istanbul Technical University (Turkey).

Dr. Tozan’s research centers on health decision science and priority setting and explores the costs and cost-effectiveness of health programs and interventions and the issues of health resource allocation in low- and middle-income countries. Her main focus has been on infectious disease prevention and control, with particular emphasis on malaria and dengue. Dr. Tozan is leading a work package on “Health Economics and Evidence Informed Policy-Making” in a European Union-funded research project on dengue, where the primary research emphasis is on the generation of information to support efficient resource allocation decisions on dengue surveillance and prevention through costing and cost-effectiveness studies. She is also serving as principal investigator for a prospective multi-country study on the cost of dengue illness in international travelers utilizing a network of travel clinics in Europe, the U.S., the Middle East, and Australia. Dr. Tozan is involved with multiple studies and clinical trials as a health economist. She has a broad background in applied health economics, global health policy, and health systems research.

**ABSTRACT**

Reported as a public health problem since the 1960s in Sri Lanka, dengue has become a high priority disease for public health authorities. The involvement of large numbers of public health staff in dengue control activities year-around and the provision of free medical care to dengue patients at secondary care hospitals place a formidable financial burden on the public health sector.

We estimated the public sector costs of dengue control activities and the direct costs of hospitalizations in Colombo, the most heavily urbanized district in Sri Lanka, during the epidemic year of 2012 from the Ministry of Health’s perspective. The total cost of dengue control and reported hospitalizations was estimated at US$3.45 million (US$1.50 per capita) in Colombo district in 2012. Personnel costs accounted for the largest shares of the total costs of dengue control activities (79%) and hospitalizations (46%). The results indicated a per capita cost of US$0.42 for dengue control activities. The average costs per hospitalization ranged between US$216-609 for pediatric cases and between US$196-866 for adult cases according to disease severity and treatment setting.

This analysis is a first attempt to assess the economic burden of dengue response in the public health sector in Sri Lanka. Country-specific evidence is needed for setting public health priorities and deciding about the deployment of existing or new technologies as the results suggest that dengue poses a major economic burden on the public health sector in Sri Lanka.
Dr. Rocklöv is an Associate Professor in Epidemiology and Global Health. He has a B.Sc in Mathematics, an M.Sc in Statistics and a PhD in Environmental Medicine. He is the scientific leader for a research area within the Umeå Centre for Global Health Research, Umeå University.

Dr. Rocklöv’s group research the relationship between climate change and public health. The research group includes around 20 doctoral candidates, post-doctors, and mid-level and senior researchers. His research focuses on modeling, the relationships between weather, climate and climate change and health and making predictions of climate sensitive diseases for adaptation and preparedness purposes.

ABSTRACT

Infectious diseases are threatening with an increasing disease burden due to climate change, globalisation and population growth. Climate change is associated with changes in seasonal weather patterns with subsequent impacts on the suitability and temporal and spatial distribution of, in particular, water and vector-borne diseases. An early detection of a new establishment, or an outbreak, of an infectious agent is of great importance to limit its consequences on population health. At an operational level a simple and well functioning early warning are valuable to timely and well-informed response activities.

Weather and climate information, such as current and past weather, often impose patterns in the disease transmission chain, which can be used to understand coming disease rates, or abundance of host or vector animals. Similarly, weather forecasts and seasonal weather predictions can be used to inform stakeholders on the risk of introduction, or outbreaks.

Various differentially complex mathematical and statistical techniques can be applied to describe the disease propagation and outbreak risks. Analytical methods depend on its application in time and space and on the availability of quality data.

This presentation mainly focuses on Dengue and discusses various analytical methods that have been applied to make predictions and projections of risks related to this infectious agent. The strengths and limitations of the methodological approaches and the future developments may further improve weather and climate sensitive infectious disease predictions.
He earned his Bachelor of Science degree from the University of Arkansas in 2001. After college he worked as a research assistant in a gene therapy company in Raleigh, North Carolina before enrolling in the graduate program at Duke University. He received his PhD in molecular genetics and microbiology from Duke University in September of 2009 and did his post-doctoral studies in associate professor Ooi’s laboratory at the Duke-NUS Graduate Medical School in Singapore involved the application of high-throughput sequencing for the characterization of the interactions between dengue and its human and mosquito hosts. Currently, he is an assistant professor in the Emerging Infectious Diseases program at Duke-NUS.

**ABSTRACT**

Sri Lanka has experienced confirmed dengue outbreaks since the 1960s although severe dengue disease (DHF/DSS) didn’t appear until 1989. Since then, cyclical outbreaks associated with severe disease have occurred throughout the island. The most recent epidemic began in 2009 with the apparent introduction of a new genotype of DENV-1. To better understand the mechanisms underlying the persistence of this ongoing epidemic, a longitudinal study was conducted in hospitals in the Colombo district from April 2012 to March 2014. In order to glean as much information as possible about the viral genetics from this large cohort, a novel Next Generation Sequencing (NGS) platform that can function without any a priori knowledge of the target dengue genome was developed.

The principle problem encountered when employing NGS directly on patient samples is the high ratio of host to viral RNA. A developed hybridization-based enrichment strategy consisting of DENV-specific 120nt, biotinylated oligodeoxynucleotides to capture DENV genomic material from an NGS library prepared directly from patient sera.

The strategy developed here allowed us to enrich DENV genomic material over 5000 fold relative to unenriched material. Full genome data and phylogenetic analysis indicate that the DENV-1 are predominantly genotype 1 although a smaller number of genotype 5 isolates was also identified. The platform developed for this study has the inherent ability to capture all four serotypes of DENV and can significantly increase the virus to host RNA ratio. The principle driver of the current dengue epidemic in Sri Lanka is the same DENV-1 genotype that has been in circulation since 2009.
Aedes albopictus is now established in at least 27 countries in Europe. It is a serious nuisance species in the Mediterranean region and is expanding rapidly northwards. A significant outbreak of Chikungunya in northern Italy in 2007 and sporadic cases of Dengue and Chikungunya in other regions have established it as a public health problem. Space sprays (ULV) dispensed from road vehicles are the principal strategy used for control. We used oviposition rate and adult capture to monitor the impact of ULV-deltamethrin on local Ae. albopictus populations in a suburb of Nice, France. Despite conditions that were considered ideal, we saw little evidence of any reduction of females. The numbers of males, however, appeared significantly reduced. We suggest that ULV pre-treatment could greatly increase the efficacy of control strategies that involve release of large numbers of males (e.g. genetically modified, radiation-sterilized or Wolbachia-infected) by boosting the ratio between the released males and wild insects that had survived the treatment.
Classifying Dengue Hemorrhagic Fever: My Journey in Time

Suchitra Nimmannitya

Prof. Suchitra Nimmannitya is Senior Consultant Paediatrician at Queen Sirikit National Institute of Child Health, Thailand. She had her Master of Public Health in Infectious Diseases and Epidemiology from Yale University, USA and the Certificate of Child Health/Teaching of Child Health from University of London.

She received the Prince Mahidol Award for her outstanding works on DHF in 1996 and APSSEAE Award in 2000 as the Outstanding Paediatrician in Asia. She worked as a WHO Consultant and Advisor on DHF in many South East Asian and Western Pacific Countries and South American countries including Columbia, Brazil, Venezuela from 1972 to 2000. Among her publications are chapters on Dengue/DHF in The Oxford Textbook of Medicine (1987 & 1996), Manson’s Tropical Infectious Diseases (1996, 2003 and 2009), WHO Monograph 1993 and over 100 papers on paediatric infectious diseases including 70 peer review papers on DHF.

ABSTRACT

Dengue hemorrhagic fever (DHF) that emerged in Asia around 1950 has become the global problem. DHF a severe form of dengue and dengue fever (DF) are now among the most important infectious diseases affecting tropical urban areas. Unlike DF, an old disease known for ages DHF is more common in children than adults and associated with high mortality.

Research studies at the Children’s Hospital since the early outbreaks in 1962-1964 revealed that DHF is a distinctive clinical entity, characterized by acute high continuous fever with hemorrhagic diathesis, and a tendency to develop shock as a consequence of critical plasma loss. The major pathophysiologic hallmarks that determine disease severity and distinguish DHF from DF are abnormal homeostasis together with plasma leakage due to increased vascular permeability selectively in pleural and abdominal cavities. Hypovolemic shock occurs as a consequence of critical plasma volume loss. Abnormal homeostasis including, increased capillary fragility (a positive tourniquet test), thrombocytopenia with impaired function and coagulopathy, in the most severe form as disseminated intravascular coagulating (DIC) contributing to varying dengue of hemorrhage and disease severity.

A unique natural history of DHF make it possible to make correct clinical diagnosis before the onset of shock. With early recognition of case and proper management CFR has been markedly reduced. The study on pathogenesis of DHF reveals that DHF/DSS occur in association with secondary infection and immunophagenesis including immune enhancement has been demonstrated. These findings lead to the qualification of ideal vaccine that must produce long lasting immunity to all 4 dengue serotypes.
Dr Lak Kumar Fernando is a Consultant Paediatrician with nearly 20 years of experience, attached to District General Hospital Gampaha and is the Clinical Head, Centre for Clinical Management of Dengue & Dengue Haemorrhagic Fever (CCMDDF), Negombo. CCMDDF is the first facility in Sri Lanka to treat Dengue patients that handles both children and adults by a common team of Physicians, Paediatricians, medical and nursing staff using common management principles. He has academic qualifications from both Sri Lanka and United Kingdom. He has received training on Dengue at Queen Sirikit Hospital in Bangkok, a WHO Collaborating Centre specialising in the management and training in Dengue. He contributed actively by co-authoring Sri Lanka’s National Guidelines for Dengue Case Management both Children and Adults. His special interests include infectious disease, epilepsy and paediatric Neurology. He has many international publications and presentations to his credit.

Dr Fernando received the Senior Ashok Fellowship from Ashok Foundation of the United States in 2012 for the change making role he played in case management of dengue both in and outside Sri Lanka. This year the Asia Pacific Paediatric Association awarded him the Outstanding Asian Paediatrician Award 2016 recognizing contributions made by him both nationally and internationally.

**ABSTRACT**

Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF) are the two main clinical entities that results from dengue virus infection. Though only a relative minority develop DHF compared to DF over 90% of the all dengue deaths are within DHF. Treatment of both DF and DHF are largely symptomatic and in the absence of specific drug therapy it is the fluid management in DHF that determine the final outcome of the patient whether it is death, complete recovery, admission to intensive care unit etc. Various guidelines or protocols have evolved guiding the clinician about the judicial use of crystalloids, colloids, blood and blood product etc. Commonly the manually and periodically checked blood pressure, pulse volume on palpation, heart rate, changes in haematocrit, changes in platelet counts, and urine output were the main criteria that determined the fluid types, rates and volumes. Clinical decisions on the severity and progression of fluid leaking in the critical phase of DHF were made on assumptions based the above parameters. At the Centre for Clinical Management of Dengue & Dengue Haemorrhagic Fever we introduced some improvements to the above to observe and learn about the process of fluid leaking more objectively and accurately to decide on fluid therapy. This was able to bring in near zero mortality to cases of DHF also with an extremely uneventful recovery phase that greatly reduced complications and almost eliminated the need for intensive care units to manage DHF patients.
ABSTRACT

Bleeding, a dreaded complication in Dengue, can range from positive Hess’s test to severe overt bleeding. Increasing bleeding tendency in Dengue is multifactorial and include vasculopathy, thrombocytopaenia, platelet dysfunction, clotting abnormalities and disseminated intravascular coagulation. Many patients get minor bleeds in the skin or gum bleeding which are not of any clinical significance. Some get severe bleeding, which can be often concealed. Therefore, high degree of clinical suspicion and regular monitoring of haematocrit and vital parameters of these patients are essential to detect this. Delay in treating bleeding may lead to further bleeding and shock.

Overt bleeding generally manifests as haematemesis, per rectal bleeding or per vaginal bleeding. Even normal menstrual bleeding may have clinical significance in a Dengue patient with fluid extravasation. In the early stage of the disease, commonest cause for bleeding is NSAID induced gastropathy or pre-existing gastric ulcers and in the latter stage the commonest reason is prolonged shock. Trauma including intramuscular injection is another possible reason.

In most instances, significant bleeding occurs when the platelet count is less than 100,000 per ml though bleeding has no direct relationship with the platelet count. Therefore, prophylactic platelet transfusions have no place in treatment except in very selective instances like pre-operatively in emergency surgery. Bleeding should be treated with blood transfusions if it is severe enough to cause instability in vital parameters. If bleeding continues in spite of blood transfusions, then, therapeutic platelet transfusions may be considered. Concentrated Factor VII has only a limited place in treating bleeding in Dengue in instances such as localized bleeding. If bleeding occurs as a result of prolonged shock, Factor VII has no effect. Thromboelastography is not useful in deciding treatment of bleeding in Dengue.
Dr. Paba Palihawadana is a Specialist in Public Health and presently the Chief Epidemiologist of the Epidemiology Unit, Ministry of Health, Sri Lanka since 2008. She has been a Post-Doctor Fellow/Visiting Scientist at the Surveillance Division of the Centre for Disease Control (CDC), Atlanta, USA. She was awarded a Doctorate in Community Medicine by the University of Colombo in 2000. She was the team leader in investigation of Dengue outbreak in Lahore, Pakistan, 2011-2014. She is a co-author of Immunization Hand Book, National Guideline for Acute Flaccid Paralysis and Vaccine Preventable Diseases Surveillance, Immunization Guidelines by SLMA and Guidelines on Communicable Diseases Prevention and Control. She has numerous publications in peer reviewed journals. She is a member of PIP (Pandemic Influenza Preparedness) Advisory Group/WHO, Member of Advisory Group for Peer Learning for Immunization in GAVI and also a Governing Council Member of IAIM.

Integrated vector management is defined as “a rational decision making process for the optimal use of resources for vector control”. Our focus on Dengue control and prevention mainly lies with national strategies like vector control and surveillance. Vector control activities carried out in the field is further empowered by the “Prevention of Mosquito Breeding Act 2007” which gives legislative powers to the field level staff to take legal action.

Vector control activities mainly include larval and pupae control and adult mosquito control measures. These activities continued throughout the year and are also useful in forecasting impending outbreaks, so early mitigating measures could be planned. To control the vector population, we initiated a door to door program aimed at environmental cleaning which is carried out through proper solid waste disposal, regular clean up campaigns and container removal programs which have found to be very effective. Chemical control is also been used as complementary to other vector control measures. The biological control of mosquito larvae are commonly used when water storage tanks/barrels have been identified as a major contributor to dengue vector breeding. The adulticidal control measures include residual spraying of chemicals like Malathion in the form of thermal fogs or ULV. In vector control, as in other areas of public health, staffing levels and capacity strengthening are important. In particularly, public health entomologists, vector control personnel, environmental specialists, social scientists and communication specialists play pivotal roles.

ABSTRACT

Integrated vector management is defined as “a rational decision making process for the optimal use of resources for vector control”. Our focus on Dengue control and prevention mainly lies with national strategies like vector control and surveillance. Vector control activities carried out in the field is further empowered by the “Prevention of Mosquito Breeding Act 2007” which gives legislative powers to the field level staff to take legal action.

Vector control activities mainly include larval and pupae control and adult mosquito control measures. These activities continued throughout the year and are also useful in forecasting impending outbreaks, so early mitigating measures could be planned. To control the vector population, we initiated a door to door program aimed at environmental cleaning which is carried out through proper solid waste disposal, regular clean up campaigns and container removal programs which have found to be very effective. Chemical control is also been used as complementary to other vector control measures. The biological control of mosquito larvae are commonly used when water storage tanks/barrels have been identified as a major contributor to dengue vector breeding. The adulticidal control measures include residual spraying of chemicals like Malathion in the form of thermal fogs or ULV. In vector control, as in other areas of public health, staffing levels and capacity strengthening are important. In particularly, public health entomologists, vector control personnel, environmental specialists, social scientists and communication specialists play pivotal roles.
Dr. Waseem Akram did his PhD from Pakistan and from 2002 to date has worked on vector borne issues. He has worked on dengue vector management since 2002. He produced five PhD students and around 24 MPhil students on different aspects of Aedes mosquitoes beside his work on agriculture entomology at both PhD and masters level. He has presented papers in American Mosquito Control Association (AMCA) besides attending and presenting papers in many other International Conferences in the world. He is an author of 62 scripts including articles in PLOS-1 and other high impact factor journals and 7 books of both national and international levels. He is a [2012] member of UNITED Dengue with the head office in National Environment Agency Singapore.

Dr. Waseem Akram is main focal person of the Chief Minister’s Punjab dengue prevention and technical team. He has extended his expertise to all departments and has designed SOPs and trained people throughout the Punjab. He is also on the list of WHO, UNICEF, WASH PAKISTAN Dengue experts of Pakistan. He has completed projects on the management of Aedes mosquitoes funded by HEC, EFS and International Organization. He is also on board with PITB as technical expert and member of DEAG. His total teaching, research and administrative experience is over 22 years.

ABSTRACT

Pakistan in particular Punjab faced an outbreak of dengue that resulted in exponential increase in the number of cases and causalities in a period of 72 days. The combined efforts with international experiences helped to manage the disease at 22000 cases out of the total suspected 0.6 million and deaths to around 375 in 2011. The hard hit areas included Lahore, Rawalpindi and Faisalabad.

Various tools, interventions and strategies have been designed immediately during the 2011 outbreak and these have been polished during the years to minimize the overall disease burden, cost on the program and involvement of the people for a collaborative program that ultimately brings long term prospects in managing the disease. Furthermore the entire dengue control program is bridged up through a technological sound dengue portal system that counts each and every breeding spot, patient, hospital, indoor and outdoor surveillance data and the case response done against each of the confirmed case during the low disease season and suspected to confirmed patients during the high disease times so as to minimize the infection chances and puts it on the dengue tracking dash board for analysis and monitoring at all forums.

Thus the success in the dengue control program reflects a commitment based strategy that is geared up by a strong political monitoring system, bureaucratic bridging and the technocratic involvement in Punjab that has ultimately brought the disease toll to 258 in 2012, 2661 in 2013, 1440 in 2014 and 4323 in 2015 with very few deaths.
New Discoveries on the Human B-cell Response to Dengue Infection

Aravinda de Silva

Professor de Silva is a member of the Department of Microbiology and Immunology at the UNC School of Medicine. He has studied dengue for the past 20 years. His current work focuses on dengue pathogenesis and human immunology. He is collaborating with several companies to support the development of dengue vaccines. He also works closely with colleagues and students to support basic and applied research on dengue in Sri Lanka. Professor de Silva received his PhD in Cell Biology (1993) and MPH in Infectious Disease Epidemiology (1997) from Yale University, USA.

ABSTRACT

Joint studies conducted by the University of North Carolina School of Medicine, Genetech Research Institute and the Sri Lanka Ministry of Health to understand the natural history and human immunology of dengue led to precise estimates of DENV infection and disease among children living in Colombo. A strong relationship between the levels of neutralizing antibodies and the possibility of developing clinically apparent dengue infections was also observed.

In separate studies our group and others have mapped sites on DENV targeted by neutralizing and protective human antibodies. Novel tertiary and quaternary structure epitopes on the surface of DENV targeted by human antibodies and a model developed to explain the origin of these protective antibodies will be discussed in detail and the implications of our work for developing safe and effective DENV vaccines.
The Human T-Cell Response to Dengue: Impact of HLA Protein Variation on T-Cell Responses and Disease

Alessandro Sette

ABSTRACT

Studies aimed at addressing the old controversy, whether T cell responses were a correlate of protection or susceptibility to severe DENV disease were conducted with samples from normal blood donors from Colombo. Samples that were associated with multiple infections revealed that magnitude of allele specific Class-I T cell responses negatively correlates with reported disease susceptibility. This suggested that Class-I restricted CD8 T cells are a correlate of protection. Since most CD8 responses are focused on the NS proteins, which are absent in the Sanofi vaccine, these results might also provide a possible explanation for the incomplete protection afforded by this vaccine.

More recent experiments focused on HLA Class-II responses showed that Dengue virus infection elicits highly polarized CX3CR1+ cytotoxic CD4+ T-cells associated with protective immunity. Marked expansion of effector memory subsets is associated with DENV infection history and the DRB1 *0401 protective allele. The majority of the responding cells are TEM/TEMRA and not associated with usual T helper subsets (CXCR3-, CCR4- and CCR6- and CXCR5). These DENV CD4+ T-cells are directly cytotoxic, and also express granzyme, perforin, CD107 and Tbet/Eomes. A broad panel of HLA DRB1 variants for high coverage was selected from the Sri Lanka population. We identified a total of 365 epitopes recognized in at least two or more were identified. 60% of the CD4 epitopes were derived from NS proteins, and 40% of them were derived from structural proteins. This is in contrast with the case of CD8 responses where NS3, NS4B and NS5 are dominant. Only 19% of the response is against structural proteins. As in the case of CD8 T cells, we observed wide variation in responses as a function of restricting HLA. We next examined whether HLA class II variation can predict disease susceptibility. To address this issue we performed HLA typing in approximately 800 donors categorized as normal blood donors, hospitalized DF cases, and hemorrhagic fever cases. In the case of the DR4 antigens, we are able to confirm that the dominant T cell DRB1 *0401 allele is protective, while the less dominant allele (DRB1 *0403) is neutral and the rare DRB1 *0405 allele is a risk factor.

In conclusion, HLA genes dramatically influence DENV responses and disease susceptibility. In the case of DR4 subtypes Class II responses actually predicts protection from severe disease. Detailed binding studies are in progress to address the mechanism of this effect and to address whether breadth of repertoire of responses is connected to these observations.
Dr. Shibadas Biswal, MD is currently working as associate medical director at Takeda Vaccines in Singapore involved in the clinical development of Takeda’s dengue vaccine candidate. He has nearly 10 years of experience in clinical development of new and generic drugs in the pharmaceutical industry. He is a medical doctor by training with specialization in clinical pharmacology.

## ABSTRACT

Takeda’s live attenuated tetravalent dengue vaccine candidate (TDV) contains a molecularly characterized dengue serotype 2 virus and three recombinant viruses expressing the pre-membrane (prM) and envelope (E) structural genes for serotypes 1, 3, and 4 in the dengue serotype 2 virus genetic backbone. The safety and immunogenicity of TDV were previously demonstrated in Phase 1 clinical trials in healthy, flavivirus-naïve adults aged 18–45 years, and in a previously reported phase II study in children and adults living in dengue endemic countries.

In a phase II placebo-controlled, multi-center trial (DEN-204; NCT 02302066) we assessed the safety, reactogenicity and immunogenicity of different vaccination schedules of TDV in 1800 subjects 2 to <18 years of age, living in dengue endemic areas of the Dominican Republic, Panama and the Philippines. Here we present six month safety and one month immunogenicity results for this trial.

The safety profile of the vaccine was consistent with previous results. Vaccinations were well tolerated and no safety signals were seen. Satisfactory antibody responses were elicited against the four DENV serotypes in initially dengue seropositive and seronegative subjects.

These results support the continued development of Takeda’s vaccine candidate.
Muruga Vadivale is a Senior Director, Dengue Medical Affairs Asia Pacific, Sanofi Pasteur at Singapore since Jan 2014. Muruga has more than 23 years industry experience having managed Malaysia, Singapore, Brunei, Indonesia, Sri Lanka, Nepal, India, and South Korea in Medical Affairs, Regulatory and Clinical Trials.

He started his career in Ministry of Health Malaysia, managing a district Hospital (Chief Medical Officer) and later as a District Health Officer (Public Health Officer) before embarking his career in Pharma. He did his medical in University of Mysore, India and his Master's in Occupational Medicine in National University of Singapore. He joined the industry in 1992 and sanofi (Aventis) in 2000. Muruga has been one of the contributors to the first and second Malaysian GCP guidelines. He is currently also a member of the advisory board to Jeffrey Cheah School of Medicine and Health Sciences, Monash University Sunway Campus, Malaysia.

**ABSTRACT**

Dengue vaccine is urgently needed as part of integrated Dengue prevention and control strategies in dengue endemic countries including Sri Lanka. The most advanced candidate is a tetravalent, live-attenuated recombinant dengue vaccine (CYD-TDV) from Sanofi Pasteur. Results from the phase 3 efficacy studies of CYD-TDV, across ten endemic countries in more than 30,000 children and adolescents in Asia (CYD14, 2-14 years) and in Latin America and the Caribbean (CYD15, 9-16 yrs) were reported.

Pooled analysis of efficacy for symptomatic dengue during the first 25 months was 65.6% (95% CI, 60.7 to 69.9) for those 9 years of age or older in CYD14 and CYD15 with significant reduction of hospitalized dengue cases and severe dengue cases of over 80% and over 93%, respectively. An acceptable safety profile was observed for the first 25 months. Furthermore, efficacy trials results also showed that vaccine efficacy varied by age, baseline dengue sero-status, and sero-types circulation.

The interim combined analysis of the long-term follow-up of CYD14, CYD15, and CYD57 (Ph2b) trials during year 3 showed continued reduction in risk of hospitalization for dengue among participants who were 9 years of age or older in the vaccine group as compared to those in the control group. Long-term follow-up of individuals aged <9 years will provide additional clinical information to draw conclusion on benefit risk in this age group (Hadinegoro et al. 2015).

The CYD-TDV candidate vaccine has recently been approved for the prevention of Dengue in individuals 9 through 45 years of age living in endemic areas in Mexico, the Philippines, Brazil and El Salvador; while two other candidates are close to enter into phase 3 efficacy trials.
Professor Asita de Silva has held many positions in academic medicine over the last 23 years. He is a Clinical Pharmacologist, and is currently Professor in Pharmacology at the Faculty of Medicine, University of Kelaniya, Sri Lanka. He is also Director of the Clinical Trials Unit in the same institution, which he founded in collaboration with the University of Oxford in 2005. Graduated with MBBS in 1991 from the North Colombo Medical College, he had his postgraduate training in clinical pharmacology at the Radcliffe Infirmary in Oxford. He holds a doctorate in Clinical Pharmacology from the University of Oxford (Exeter College) and is a Fellow of the Royal College of Physicians, London.

Prof de Silva’s research interests have focused on the epidemiology of Alzheimer dementia, and clinical trials in neglected tropical diseases and major non-communicable diseases. He has published his research widely in peer-reviewed international medical journals and has delivered many orations and invited lectures on these subjects. He has received Presidential awards for medical research on numerous occasions. Prof de Silva holds senior positions in both national and international academic organizations, and is a recipient of many research grants from international organizations such as the Wellcome Trust, Medical Research Council, UK, and the National Health and Medical Research Council, Australia.

**ABSTRACT**

5.9 million children under the age of 5 died in 2015; out of this about 50% die of vaccine preventable diseases. The problem is compounded by the absence of effective therapies for many infectious diseases. Although the number of under-five deaths worldwide has declined from 12.7 million in 1990 to 5.9 million in 2015, the rate of decline failed to achieve one of Millennium Development Goals.

More than half of under-five child deaths are due to diseases that are preventable and treatable through simple, affordable interventions. For some of the most deadly childhood diseases, such as Measles, Polio, Diphtheria, Tetanus, Pertussis, Pneumonia due to Haemophilus influenzae type B and Streptococcus pneumoniae and diarrhoea due to Rotavirus, vaccines are available and can protect children from illness and death. However, other infectious diseases such as Dengue, for which there is at present no specific treatment, continue to cause significant childhood morbidity and mortality.

Since vaccines have a preventive role, the target population for vaccines is primarily healthy children and infants. As a result, most of the vaccine studies are conducted in children. Focus on important research ethics associated with large clinical trials, particularly those involving vaccines, will be discussed.
Professor Scott O’Neill (PhD, FAA, FAAAS) heads the Eliminate Dengue Research Program. His team is developing and testing a Wolbachia biological control method that reduces the ability of Aedes aegypti mosquitoes to transmit dengue, Chikungunya and Zika viruses. The program – currently field testing in five countries - is expanding and gearing up for efficacy trials over the next few years.

Professor O’Neill has published over 150 high-impact research papers with some 8500 ISI citations. He has received many awards including the Australian Centenary Medal, the Mackerras Medal and is a Fellow of the Australian Academy of Science, the American Association for the Advancement of Science and the American Academy of Microbiology. He has spent his academic career at Yale University, The University of Queensland and Monash University where he has been Dean of Science since mid 2011.

**ABSTRACT**

Examining the potential use of inherited bacterial symbionts of insects known as *Wolbachia* is a novel method to interfere with arbovirus transmission. This work has now progressed from basic bench studies into open field trials in five countries.

An overview of Wolbachia-mosquito-pathogen interactions as well as the current status of the global eliminate dengue program that aims to deploy Wolbachia infections as a cost effective and sustainable approach to disease control will be discussed.
Dr. Rushika Perera is an Assistant Professor of RNA Virology in the Arthropod-borne and Infectious disease Laboratory (AIDL) in the Department of Microbiology, Immunology and Pathology at Colorado State University (CSU), Fort Collins, Colorado, USA. She received her bachelor’s degree at Goshen College and her doctorate at Purdue University, in Indiana, USA and joined CSU in 2013.

The research in her laboratory is focused on understanding how biochemical networks (cellular metabolism) in the human host or mosquito vector change upon infection with flaviviruses such as Dengue, Chikungunya and Zika. She aims to use this information to identify novel ‘transmission blocking’ vaccines to prevent arbovirus transmission. Specifically, she uses a systems biology approach including metabolomics and proteomics combined with molecular virology, cell biology, and structural biology to study flavivirus-host interactions.

Successful transmission of Dengue virus and other arboviruses such as Chikungunya and Zika by Aedes aegypti requires effective entry, replication and dissemination within mosquito tissues. Given that these viruses are enveloped viruses, membranes and lipids play a significant role in the life cycle of the virus in the human host and mosquito.

It is observed that the biochemical environment in the Aedes aegypti midgut is significantly changed upon virus infection and our studies have shown that these changes are required for the virus to replicate and disseminate from the midgut. Given the adaptability of these vectors to various ecological conditions and their vectorial capacity for several arboviruses, it is hypothesised that vector metabolism has a significant impact on disease transmission, vector competence and insecticide resistance, and presents a novel avenue that should be explored for intervention. Results of studies on Aedes aegypti metabolism and their relevance to dengue virus transmission and mosquito biology will be discussed.
Dr Anavaj Sakuntabhai, who heads an internationally recognized research laboratory at the Institut Pasteur, has significant experience in the coordination of international projects. He is a medical doctor with 10-years experience in clinical medicine before starting his career in basic sciences research. He obtained the diploma of doctor of philosophy (D. Phil.) in human molecular genetics from University of Oxford, United Kingdom in 1999. In 2007, he led his own laboratory Genetics of Human Response to Infections. He became Head of Laboratory in 2010 and succeeded in creating a research unit of Functional Genetics of Infectious Diseases at the Institut Pasteur.

He coordinated a global network for dengue research for the Institut Pasteur International Network. He is a principle investigator of one of the four consortial projects of the Bill and Melinda Gates financed MalariaGEN consortium. He is a co-partner of a Wellcome Trust financed project on the human genetics of dengue. He is a coordinator of European FP7 project on Dengue Framework for Resisting Epidemics in Europe (DENFREE) which aims at finding key factors determining dengue transmission and dengue epidemics in order to develop new tools and strategies for controlling dengue transmission.

The main objective of the DENFREE project is to focus on finding key factors determining dengue transmission and dynamics in order to develop new tools and strategies for controlling dengue transmission. Inherent in our program is the belief that improved surveillance and diagnosis of the asymptomatic dengue carriers will contribute to effective intervention, especially during early stages of pathogen invasion into a naïve region.

The hospital-based surveillance is inadequate – too little and too late. Implementation of such a surveillance strategy requires, however, a much improved understanding of what characterizes asymptomatic infections and what epidemiological role they may play. Can they infect mosquitoes? Is the duration of infection different from symptomatic episodes?

The resulting mass of well-characterized biological samples will enable development of the more fundamental aspects of dengue research that are necessary for advances in vaccine and anti-viral drug development, the generation of descriptive and advanced warning epidemiological models and novel diagnostic tools.
Prof. Neelika Malavige is the Director at the Centre for Dengue Research, University of Sri Jayawardenapura and a visiting academic at the MRC Human Immunology Unit, University of Oxford. She is a medically qualified immunologist and obtained her DPhil from University of Oxford. She is also a fellow of the Royal College of Physicians, London and the Royal College of Pathologists, UK.

Her main research interests are pathogenesis of dengue and vascular leak. She has also done numerous studies on T-cell responses in Dengue and other viral infections and has over 50 publications in peer review journals. She has won many research awards including the TWAS Young Scientist Award in Biology in 2012, the Zonta Woman of Achievement Award in 2014, CVCD Award for Best Young Researcher in 2008, and the TOYP award in 2011.

**ABSTRACT**

Endothelial dysfunction, which leads to increased vascular permeability is the hallmark of severe dengue (SD). SD is commoner in secondary dengue infections and it is thought that both cross reactive T-cells and antibodies could be contributing to SD due to an aberrant immune response to the Dengue virus (DENV).

Previous studies have shown that platelet activating factor (PAF) is an important mediator of vascular leak. PAF is produced by mast cells, monocytes and endothelial cells. We found that although primary monocytes were the cells most frequently infected by the DENV, they did not produce PAF following DENV infection alone, or in the presence of dengue immune sera. Instead, it was found that mediators such as tryptase and secretory phospholipase, which are produced exclusively by mast cells, are significantly elevated in patients with DHF, during early infection. Both tryptase and secretory phospholipase followed the same pattern of production as PAF and therefore, mast cells are likely to play an important role in the pathogenesis of dengue.

There has been much debate on the role of DENV specific T-cells in the pathogenesis of dengue. Although pro-inflammatory cytokines produced by cross reactive T cells have been implicated in causing vascular leak in dengue, DENV specific T-cells have been observed in very low frequency in acute infection, especially in those with SD.
Yie Hou Lee is the Principal Scientist at KK Women’s and Children’s Hospital and Adjunct Assistant Professor at Duke-NUS, Singapore. He completed his Ph.D in National University of Singapore where he studied the toxic effects on the Sod2+/- mouse mitochondrial proteome with the aim of unravelling the mechanisms underpinning idiosyncratic hepatotoxicity. Further, he worked in the labs of MIT Professor Steven Tannenbaum for his post-doctoral training and applied biological mass spectrometry to discover biomarkers of dengue severity. At KKH and Duke-NUS, his research focuses on ‘omics, notably metabolomics, lipidomics and multiplex immunoassays of small proteins to understand host responses in dengue and influenza infections.

ABSTRACT

Prognosis of dengue remains a challenge in allowing the early, objective triage of patients with dengue fever of differing severity. Profiles of circulating cytokines, chemokines and growth factors (collectively known as immuno-modulators) change with the clinical course of dengue and are believed to have direct impacts on the manifestations of increased vascular permeability, plasma leakage and thrombocytopenia in dengue. Because molecular signaling seemingly precedes gross morphological or observable clinical symptoms, the potential use of biochemical signals such as immuno-modulators for early prognosis of severe dengue is especially welcoming.

Systematic reviews suggest patients with severe dengue have higher frequencies of significantly increased interleukin-10 (IL-10) level. Interferon-gamma (IFNγ) was another probable prognostic marker but its levels varied between studies. In an effort to uncover other early prognosis bio-markers that may be more consistent, we employed liquid-chromatography mass spectrometry (LC-MS/MS) to globally probe the serum metabolites from patients with dengue fever (DF) and dengue hemorrhagic fever (DHF) in the febrile phase (<96 h).
Prof Dr. Shamala Devi Sekaran began her career in immunology which then expanded to the field of virology, bacteriology, diagnostic microbiology, anticancer as well as anti-microbial drug/ peptide discovery and to endothelium dysfunctions in infectious diseases. Dengue was her primary focus during her Ph.D. programme and up to today, dengue has remained close to Prof Shamala’s heart.

Her stronghold in dengue would particularly lie in the field of diagnostics. The Dengue IgM capture ELISA which was developed by her is still used as an in-house method for the detection of Dengue IgM in suspected patients. She and her team have also developed various molecular diagnostic kits and have been actively involved in evaluation projects of Dengue diagnostic kits conducted by the WHO and collaborating partners around the world as well as with companies that are commercializing these kits.

ABSTRACT

Due to the absence of pathognomonic clinical features that can distinguish Dengue from other febrile illnesses, laboratory confirmation is an essential part in the diagnosing process. Dengue diagnostics have come a long way, with many researchers around the world attempting for a more efficient and reliable diagnostic method. Diagnosis today in many countries is still based on serology though the detection of NS1 has slowly become incorporated. Dengue diagnosis is not only important for clinical management of patients, but also for epidemiological surveillance, outbreak intervention and vaccine development and monitoring.

The main hurdle in developing an ideal diagnostic assay for Dengue would lie in the complicated pathogenesis of Dengue and the fact that multiple sequential infections can occur in Dengue endemic areas. Understanding the clinical conditions of Dengue patients is essential for appropriate usage of current Dengue diagnostics which are mostly serological-based, nucleic acid-based and antigen based.

Newer technologies are being applied to fine-tune available diagnostic arrays and also to design new assays that fit the ideal test concept like the application of biosensors in detecting Dengue.
This conference is supported by unrestricted educational grants from following groups:

European Community DengueTools Project through the Centre for Global Health Research at the University of Umea, Sweden

Partnership for Dengue Control (PDC) of the Fondation Merieux, France

World Health Organization through WHO Country Office, Sri Lanka

Takeda Vaccine through Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Sanofi Pasteur, France

Oxitec Ltd. Oxford, UK

George Steuart (Pvt) Ltd

National Health Development Fund (NHDF) Ministry of Health, Sri Lanka