Joint Congress to 9th ICTP: 3rd Travel Medicine and Immunization "Travel Medicine in the Tropics" Scintific Program

JOINT CONGRESS TO 9th ICTP: 3rd TRAVEL MEDICINE AND IMMUNIZATION "TRAVEL MEDICINE IN THE TROPICS" PROGRAM: OCTOBER 18-19, 2011

Tuesday, 18 October 2011	Wednesday, 19 October 2011
8.00 – 8.30 **Registration** **Opening Remarks**	8.00 – 8.30 **Registration**
8.30 – 9.30 **The Challenges of Travel Medicine in the 21st Century: Priorities in Travel Vaccines-Influenza is the Leader** Robert Steffen	8.30 – 9.30 **Influenza and Avian Influenza: Hazard for Travel** Prasert Thongcharoen
9.30 – 10.00 **Travel Clinic in Different Countries** - Travel Health Practice in a Developed Non- Tropical Country Tony Gherardin - Travel Health Practice in a Tropical Country Suda Sibunruang	9.30 – 10.00 **Emerging and Re-Emerging Zoonosis in Asia** - Encephalitis- What We Know and What We Don't Know About Potential Emerging Threats from Animals and Wildlife Thiravat Hemachudha
10.00 – 10.30 **Coffee Break**	10.00 – 10.30 **Coffee Break**
10.30 – 11.00 **Adult and Pediatric Travelers: How to Prepare** Tony Gherardin	10.30 – 11.00 **Dengue and Chikungunya in Travelers to Asia** Usa Thisyakorn
11.00 – 12.00 **Animal Toxins** - Harzards of Animal Toxins Visith Sitprija - Animal Poisoning Suchai Suteparak	11.00 – 11.30 **Malaria: New Anti-Malarial Drugs for Treatment and Prophylaxis** Polrat Wilairatana 11.30 – 12.00 **Tropical Dermatologic Diseases** Chulabhorn Pruksachatkun
12.00 – 13.30 Lunch Symposium **Hazard from Travel: Up to the Height-Down to the Ocean** - Altitude Illness Navaporn Verayangkura - Decompression Illness and Marine Injuries Thanasawat Chaiyakul	12.00 – 13.30 Lunch Symposium (Sanofi Pasteur)
13.30 – 14.00 **Travelers' Diarrhea and Enteric Diseases in Asia: Prevention and Management** Robert Steffen	13.30 – 14.00 **New JE Vaccines for Travelers** Pornthep Chanthavanich
14.00 – 15.30 **Common Problems in Returning Travelers** Watcharapong Piyaphanee Sukhjit Takhar Kevin Lunney	14.00 – 15.00 **Rabies Prophylaxis in Travels: from Beginning to End** - Rabies Among Travelers Beatriz Quiambao - New Trends in Rabies Post-Exposure Treatment in Developing Countries Terapong Tantawichien
15.00 – 15.50 ICTP Poster Viewing Plenary Hall I	15.00 – 16.00 **Update on Meningococcal Disease and Yellow Fever** Annelies Wilder Smith
16.00 – 17.00 **Opening Ceremony 9th ICTP by Her Royal Highness Princess Maha Chakri Sirindhorn** Keynote Speech "Global Partnerships and Networking for Child Health" His Excellency Ambassador Kulkumut Singhara Na Ayudhaya	

JOINT CONGRESS TO 9th ICTP: 3rd TRAVEL MEDICINE AND IMMUNIZATION "TRAVEL MEDICINE IN THE TROPICS"

SPEAKER'S ABSTRACT

Challenges of Travel Medicine in the 21st Century: Priorities in Travel Vaccines- Influenza is the Leader

Robert Steffen
University of Zurich ISPM, Epidemiology and Prevention of Communicable Diseases, WHO Collaborating Centre for Travellers' Health, Zurich, Switzerland

Travel vaccines are an effective means to reduce the risk of infection, incapacitation, also of sequelae and death among travelers. In the past, priorities were mainly determined basing on incidence rates, but also severity must be taken into account. That can be defined by assessing permanent pathological conditions resulting from disease and case fatality rates. Influenza has been demonstrated to occur with an incidence rate per month of 1% in the tropics and subtropics; it is certainly a relevant travel health risk also among those originating there to visit destinations in temperate zones in winter. Outbreaks have been described particularly on cruise ships, where fatalities occurred.

There are other vaccine preventable diseases in travelers known to result in higher rates of sequelae, particularly Japanese encephalitis, meningococcal disease, tick-borne encephalitis or almost eradicated poliomyelitis. Others have a higher case-fatality rate, such as rabies, yellow fever, tetanus, diphtheria or hepatitis B. However, when taking into account also aspects of cost efficiency, influenza is the leader. Thus, influenza immunization in travelers should no longer be neglected. This vaccine ought not only to be recommended to traditional risk groups, such as older adults or persons with pre-existing conditions, but it must at least be considered in every future traveler.

Travel Clinic in Different Countries: Travel Health Practice in a Developed Non-tropical Country

Tony Gherardin
National Medical Adviser, Travel Doctor-TMVC, Australia

Travel medicine practice in Australia and New Zealand has been well established for many years, our specialised practice commenced in 1987. It evolved from the apparent need to manage risk for travellers to developing country destinations, and travel medicine now intersects public health, general practice, occupational health and infectious disease practice. Although overall the majority of pre-travel consultations occur in general practice (family medical practice is the basis of our health systems), specialised travel medicine clinics play an important role in the community and provide a focus for best clinical practice in travel medicine. The majority of work is pre-travel consultations, but post-travel ambulatory cases are seen, and in Australia our cases are registered into the GeoSentinel database.

The model in Australia and New Zealand is a doctor-nurse combination, where the risk assessment, vaccine and medication prescription is done by the doctor, and the nurse gives the vaccines, dispenses medications, and provides further information. Travel medicine clinics provide “one-stop-shop” service, where all vaccines, medications, traveller’s medical kits for self-management and travel health products are available. The risk assessment is individual, specialist clinics avoid the ‘cookbook” approach.

For individual patients, travel clinics handle complex itineraries, complicated travellers, exotic post-travel illness and provide expertise in a changing area of knowledge. In Australia, many GPs refer complex cases to travel clinics. For organisations, travel clinics provide a level of quality and assurance not found in general practice, as well as the ability to standardise services in more than one location.

Travel Health Practice in a Tropical Country

Suda Sibunruang
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Scarce information was available about travel health practices in tropical countries. Therefore, we report demographic profiles, itineraries, purposes of travel and pre-travel immunization of travelers visited travel clinic of Queen Saovabha Memorial Institute in Bangkok-Thailand during 2006-2010.

A total of 20,664 travelers (mean age 35.9 ±11 years, range 1-88 years, female:male 1: 2.6) attended. Of which 85.4% were Thai, 9.4% were European and American, 5.2% were Japanese and other Asians. Among our Thai visitors whose destinations were in Africa (66.8%), Asia (4.4%), North America (2.8%) and South America (1.8%), 53.8% of them embarked on mission works as labors and seamans, 14.7% went on business trips, 6.6% continued education abroad, 4.7% travel for leisure and 0.9% migrated overseas. The majority of travelers (53.3%) caught up routine immunizations such as tetanus/diphtheria vaccine while the rest of them needed obligatory vaccinations for their particular missions. Despite perceiving through the risk of different tropical disease infection in Africa, less than 1% of Thai carried malaria chemoprophylaxis. For foreigners, most of them planned to journey around in Thailand and Southeast Asia. 24.2% were imminently departed travelers who came to continue their immunized schedules while 75.8% just started seeking travel advice. Hepatitis A and B, typhoid, Japanese encephalitis and rabies were the most frequent vaccines being vaccinated.

Details of travel characteristics in distinct regions are diverse. Thoroughly recognize this fact would enable to provide appropriate recommendation and management to travelers who are going to or coming from the tropics.

Adult and Pediatric Travellers: How to prepare

Tony Gherardin
National Medical Adviser, Travel Doctor-TMVC, Australia

Preparing adults and children for international travel is the purpose and role of travel medicine, a specialised area of preventive medicine that has emerged in the last 25 years. Protecting traveller's health requires a systematic and detailed assessment of risks, and employing various strategies to mitigate those risks. Risks will be influenced by the particular detail of the itinerary and the medical status of the individual traveller. Risks may be different for adults and for children.

Factors of the itinerary that influence risk include the exact geography of the destination, the timing and duration of the stay, the traveller's activities during the trip, the type of accommodation, and access to healthcare during travel. Factors related to the traveller that influence risk include age, medical history including allergies and medications, immune status and previous vaccinations.

Strategies for managing risks involve providing information and education about potential risks to facilitate behavioural changes, providing specific vaccinations to alter immunity, providing selected prophylactic medications (such as anti-malarial drugs), and providing safe medications for self-management of selected common traveller's maladies.

Differences between adults and children need to be accommodated, as children have less-mature immune systems which can mean greater risk of certain diseases. Children need to have completed their basic routine vaccines as a priority. Vaccineand medication choice and doses may need to be varied. Awareness of different risk profile in children is important. Good preparation of travelling families involves ensuring a broad approach, and the provision of comprehensive and cost-effective preventive management.

Animal Toxins: Harzards of animal toxins

Visith Sitprija
Queen Saovabha Memorial Institute, The Thai Red Cross Society, Bangkok, Thailand

Basically, toxins are produced by animals for predation and protection. Predation is by way of induction of paralysis and death of the prey by tissue injury. Small animals protect themselves from the enemies by body structure, armour and production of substances to deter the other animals. Animal toxins are well recognized for their hazards to man. Genetic evolution of toxins through global environmental changes is fascinating. Consisting of peptides, enzymes, chemicals and proteins, animal toxins therefore can cause injury with a broad spectrum of clinical manifestations. Peptides acting on ion channels produce neurological and cardiovascular symptoms. Enzymes such as phospholipase A2 and proteases cause blood coagulopathy tissue destruction and induce the release of proinflammatory cytokines and vasoactive mediators which result in hemodynamic alteration. Chemicals such as terpen cause irritation and local symptoms including pain itching, swelling and redness. Most ion channel acting toxins are mostly produced by marine animals. Therefore neurological symptoms are common in poisoning by marine toxins such as ciguatoxin, tetrodotoxin and conotoxins. Arthropod and vertebrate toxins consisting of both peptides and enzymes produce more severe effects including neuromuscular symptoms, hemodynamic changes and organ injury. The extent of injury depends on the amount of toxin produced. In this respect, vertebrate venoms such as snake venoms with larger amount of toxins cause more symptoms with various organ involvement and mortality.

Animal Poisoning

Suchai Suteparuk
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Of all poisonous animals, poisonous snakes are the most recognized creatures. Due to the climate and ways of life, snakebites are health problems in most regions of Asia especially in Southeast region and Indian subcontinents. The medically important poisonous snakes are elapidae, such as cobras, king cobras and kraits which produce neurotoxin; viperidae such as vipers and pit-vipers which produce hematotoxin; sea snakes which produce myotoxin; and rear-fanged snakes. The clinical features of snakebites, which are determined by the toxins, are local manifestations such as swelling, tenderness, edema, blisters and hemorrhagic blisters; and systemic manifestations such as respiratory paralysis, bleeding tendency, rhabdomyolysis and hyperkalemia. Though many modalities of treatment including herbal and alternative medicine have been practiced, the most reliable treatment is the administration of antivenom.

The magnitude of bites and stings by hymenoptera, such as bees and wasps, and other arthropods, such as scorpions, spiders and centipedes; are much underestimated due to their self-limited and rather non-fatality clinical features. The usual manifestations are pain and local inflammation. Severe systemic or life-threatening manifestations result from anaphylaxis or massive attacks. Intoxication from marine creatures is sporadic or in small outbreaks. Deaths have been reported for the contact with box jellyfish, and consumption of puffer fish or horseshoe crabs. Symptomatic and supportive care is the key treatment.

Travelers' Diarrhea and Enteric Diseases in Asia: Prevention and management

Robert Steffen
University of Zurich ISPM, Epidemiology and Prevention of Communicable Diseases, WHO Collaborating Centre for Travellers' Health, Zurich, Switzerland

Travelers' diarrhea (TD) has become are rare risk in Asia, particularly when travelers originate in this region. Although the impact of TD is limited, incapacitation may result in major frustration. Also, mainly post-infectious irritable bowel syndrome may persist. For prevention, avoidance of 'dangerous' food and beverages would be biologically plausible, but compliance with such recommendations is minimal and evidence of benefit is limited. Among the drugs suggested for chemoprophylaxis, probiotics showed at best a low protective efficacy rate. Bismuth subsalicylate is modestly effective. Among antimicrobial agents, trimethoprim-sulfamethoxazole, doxycycline and others are considered obsolete because of antimicrobial resistance by prevalent enteric bacterial pathogens. Although fluoroquinolones have been demonstrated to be effective in the prophylaxis of TD, there is concern with widespread use over a prolonged period of time because of fear of systemic reactions and resistance. Poorly absorbed antibiotics, mainly rifaximin, are far more attractive for this indication. There is no highly effective vaccine marketed against TD. As current prophylactic measures are unsatisfactory, (self)-therapy of TD remains an important strategic option against TD. While oral rehydration solutions are the first line strategy in pediatric and geriatric patients, they do not offer relief in the usual adult TD cases, unless dehydration is severe. Fluroquinolones seem still to be effective in most parts of the world, but there are indications that azithromycin or rifaximin are the drugs of choice in

SE-Asia. Often a single antimicrobial dose will be sufficient to cure TD, this may be accompanied by an antimotility agent.

Common Problems in Returning Travelers

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The number of international travelers has increased rapidly worldwide over the past few decades. In 2010, over 900 million people traveled outside their home countries. Tropical countries are among the most popular destinations for tourists, and have experienced the greatest increases in traveler numbers. Health problems are common; some studies have shown that 23-64% of travelers have reported various health problems, either during or after their trip. Although most illnesses are mild-such as diarrhea, upper respiratory tract infections and skin problems-there have been occurrences of severe, or even fatal, problems.

Clinicians should familiarize themselves with, and be able to manage, common and severe problems among travelers in tropical regions. Fevers are the most important symptoms, since they may indicate potentially life-threatening diseases, like malaria. Although the risk of contracting malaria while traveling in Southeast Asia is low, its existence in travelers has been confirmed, including from the Bangkok Hospital for Tropical Diseases. More commonly, dengue also causes fever, which is another dangerous disease that travelers can contract in Southeast Asia.

Emerging and Re-emerging Zoonosis in Asia: Encephalitis- What we know and what we don't know about potential emerging threats from animals and wildlife

Thiravat Hemachudha[1], Supaporn Wacharapluesadee[1], Pornpun Supavonwong[1], Henry Wilde[1], Witaya Sungkarat[2], Abhinbhen Saraya[1], Kanitta Suwansrinon[1], Aekkapol Mahavihakanont[1], Henry Cheng[1], Jiraporn Laothamatas[2]
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Background: Encephalitis remains an enigma. By applying an algorithmic approach on encephalitis patients using clinical features, imaging, rapidity of deterioration of consciousness and interval between the times of onset to peak, etiologies that have been identified were mainly DNA viruses and Japanese encephalitis and rabies viruses. A substantial number of patients did not have causative agents identified. A paradigm shift in approaching encephalitis is urgently needed. These include identification of cases

with unusual presentations, surveillance for new encephalitic viruses in bats and other wildlife reservoirs. Development of newer methods in imaging and molecular techniques that encompass hundred of pathogens is also warranted.

Materials and Methods: A comprehensive assessment of encephalitis patients was conducted to determine whether there were specific characteristic patterns in differentiating between those with and without identified causes. Pathogens reported to have caused outbreaks in neighboring regions were included in the screening. Surveys in Thai bats were done to determine whether they were infected. Diffusion tensor imaging technique was developed using dogs as a model. Economical diagnostic platforms were developed to achieve higher sensitivity with broader coverage of viral families.

Results: From 2002 to 2010, 486 patients with encephalitis were admitted to King Chulalongkorn Memorial Hospital. Two hundred and thirty one patients (47.5 %) had etiologies identified (herpes viruses 72%, JE 17%, dengue 8%). Different patterns of imaging could be identified between groups with known and unknown causes. Fourteen parameters were utilized in categorizing patterns [vascular origin, symmetrical or asymmetrical, brainstem only, brainstem and other midline thalamus-basal ganglia (+/- medial temporal), thalamus only, basal ganglia only, thalamus and basal ganglia, cerebellum only, lobe structure – single or multiple, cortical structure only, subcortical or deep white matter, meninges, splenium, combination]. The search for Nipah virus revealed evidence of infection either by serology or RNA detection in bat biological samples. Three fruit bat species were found to be reservoirs. One insectivorous species may be the result of spillage. Viral transmission was most active in April, May and June. Preliminary results from deep sequencing and a real-time PCR array platform for simultaneous examination of 108 viruses suggest that prior whole transcriptome amplification is needed to compensate its compromised sensitivity. A newer brain mapping technique was successfully developed in dogs. It showed higher sensitivity than conventional magnetic resonance imaging.

Conclusion: The management of encephalitis demands prediction and preemptive measures before outbreak as well as tools to identify "unusual" cases which may potentially be associated with zoonotic pathogens and appropriate utilization of diagnostic platforms.

Dengue and Chikungunya in Travelers to Asia

Usa Thisyakorn
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Dengue, one of the most devastating mosquito-borne viral diseases in humans, is now a significant problem in many countries. The disease, caused by the four dengue virus serotypes, ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF) and severe dengue hemorrhagic fever (DHF) with or without shock. DF is characterized by the triad of high fever, pain in various parts of the body, and a maculopapular rash. DF is rarely fatal while DHF is considered a distinct disease characterized by high fever, bleeding diathesis and increased vascular permeability with a tendency to develop a potentially fatal shock syndrome. Chikungunya is a silent worldwide health threat with the characteristics of high fever, rash and severe arthralgia. Both dengue and chikungunya are arboviruses that have caused major outbreaks and infected travelers. Dengue virus and chikungunya virus also possess

the potential to cause autochthonous transmission in temperate regions of developed countries due to the presence of the vector mosquito. No specific drugs are available for both dengue and chikungunya. Treatment of both dengue and chikungunya are symptomatic and supportive care. Prevention of both viruses depends primarily on control of the mosquito vector. The feasibility of a dengue vaccine is high.

Malaria: new anti-malarial drugs for treatment and prophylaxis

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Malaria is the world most important parasitic infection in many endemic countries and is also risk of infections in travelers. Emergence and spreading of drug resistance are the important issues today. Prompt parasitological confirmed diagnosis by microscopy or alternatively by rapid diagnostic test is recommended in all suspected patients of malaria before treatment is started. Treatment based only on clinical suspicion may be considered when parasitological diagnosis is not available. Delayed diagnosis and treatment may cause uncomplicated falciparum malaria patients (UM) turning to severe falciparum malaria (SM). Artemisinin-based combination therapies are preferably recommended to treatment of UM. Since 2010, WHO has approved dihydroatemisinin plus piperaquine as a new option for the first-line treatment of UM. In treatment of SM, intravenous artesunate is better than intravenous quinine in reducing mortality in both adults and children. Before prescribing chemoprophylaxis, risk of malaria infection and risk of adverse events from chemoprophylaxis should be weighted. Chemoprophylaxis is not advised for travelers who will go to the area where annual incidence of malaria in the indigenous population below 10 cases per 1,000 individuals but they should rely on mosquito-bite prevention and stand-by emergency treatment. Atovaquone-proguanil, mefloquine, doxycycline, chloroquine combined with proguanil are antimalarial drugs for today prophylaxis and tafenoquine may be future alternative. However recommendations on drug of choice differ among countries due to lacks of precise and update data in many areas. Travelers should be advised to seek medical attention when they have fever, whether or not they have been taking chemoprophylaxis.

Tropical Dermatologic Diseases

Chulabhorn Pruksachatkun
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Infections and infestations of skin are common problems of dermatologic diseases among children. They could be either primary or secondary diseases. The prevalence of those diseases has been underestimated. The neglected diseases could result in reemergence by spreading from person to person directly or through clothing, towels or mattresses.

New Japanese Encephalitis Vaccines for Travelers

Pornthep Chanthavanich
Department of Tropical Pediatrics, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Japanese encephalitis (JE) is a serious mosquito-borne arboviral infection. It is one of the most common causes of encephalitis in Asia. It occurs throughout most of Asia and its annual incidence is estimated at 30,000 to 50,000 cases which results in 10,000 to 15,000 deaths. The case fatality rate is 25-30 % and 30-50 % of survivors have neurologic or psychiatric sequelae. For most travelers to Asia, the risk of JE is very low, but varies based on destination, season, duration of stay, and activities. Behavioral risk factors include dawn, dusk or night visits to rice growing areas, and living in villages near rice fields and farm animals during the transmission season. The risk of JE among tourists traveling to endemic areas is < 1:1,000,000. The risk for rural travelers in the JE season is higher, at about 1:5,000 to 1:20,000 per week, or 1:5,000-10,000 per month.

The older inactivated mouse brain-derived vaccine has been associated with localized injection- site reactions in about 20% of vaccinees, and mild systemic side effects in about 10% of vaccinees. Allergic hypersensitivity reactions (e.g. urticaria or angioedema) range from 10-260:100,000 vaccinees. Moderate to severe neurologic adverse events (e.g. seizure or encephalitis) have been reported at a rate of 0.1-2:100,000 vaccinees.

New cell culture-derived JE vaccines with improved safety profile are available. The benefits of the vaccine are likely to outweigh the risks for a greater number of travelers. The new JE vaccines include IXIARO^{TM} (inactivated vero cell-derived vaccine based on SA 14-14-2 strain) is registered for use in the USA, Europe, and Australia. CD-JEVAX ^{TM} (live attenuated vaccine based on SA 14-14-2 strain) is registered for use in India, Nepal, Sri Lanka, Thailand, China, and Korea. IMOJEV^{TM} (live attenuated, chimeric vaccine based on SA 14-14-2 strain) is registered for use in Australia and Thailand. JEVAC^{TM} (inactivated vero cell derived vaccine based on Beijing P-3 strain) is registered for use in China. All these new vaccines produce high seroconversion rates and high GMTs of JE neutralizing antibodies.

Rabies Prophylaxis in Travels: From Beginning to End
Rabies among travelers

Beatriz P Quiambao
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Annually, approximately 55,000 human rabies deaths occur worldwide, majority of these in developing countries where dog rabies has not been successfully controlled. There have been many reports of travelers being bitten in rabies endemic areas and developing the disease upon return. Even tourist destinations have not been spared of rabies outbreaks. It is difficult to estimate the rate of rabies exposure among travelers since many exposures go unreported. Street dogs and monkeys living near temples represent the most frequent risk for bites and contact with these animals should be avoided. Appropriate advice should be given to travelers regarding prevention of animal bites. Any dog bite should be

considered as a potential rabies exposure and appropriate post-exposure prophylaxis (PEP) instituted immediately. Unfortunately, PEP using modern tissue culture vaccines and rabies immuneglobulin may not always be readily available. Rabies vaccination before exposure, called pre-exposure prophylaxis (PrEP), is routinely recommended for individuals, whose occupation puts them at high risk of exposure, including veterinarians, animal handlers, cavers, missionaries, hospital staff caring for rabies patients and rabies research and diagnostic laboratory staff. In the Philippines, PrEP is also recommended for children aged 5 to 14 years. Depending on the incidence of rabies in an area, the duration of stay and activities to be conducted, PrEP may be recommended to travelers. Completion of PrEP will entail only booster doses without the need for rabies immune globulin in the event of an exposure.

New Trends in Rabies Post-exposure Treatment in Developing Countries

Terapong Tantawichien
Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Chulalongkorn University and Queen Saovabha Memorial Institute, Bangkok, Thailand

The majority of human rabies occur in Africa and Asia after exposure to dog transmitted rabies virus. Visitors to countries where canine rabies is endemic must assume that most local dogs have not been vaccinated. It has been shown that the risk of exposure to rabid animals for backpackers travelling in Thailand where is rabies endemic area was significant with an incidence of being bitten or liked of 6.9 and 36 per 1,000 individuals, in an average stay of 30 days. Although, pre-exposure rabies prophylaxis (PrEP) for the international travellers is not routinely recommended, we recommend that travelers who visiting a rabies-infected country should receive pre-exposure prophylaxis (PrEP) when the travel involves a significant risk of exposure to rabies or when it is to a rabies-infected area where modern rabies vaccine and rabies immunoglobulin may not be available. PrEP should be particularly considered for children at high risk of being exposed to rabies, who are leaving for a long stay (more than one year) and who will not have rapid access to medical services and rabies immunobiologics. PrEP for travelers are not designed to provide long-term protection but to better induce protective immune response that can be boosted after exposure to a potentially rabid animal, so PrEP is a medical decision that must be individualized for every traveler and is made through personal travel destination, itinerary, behavior, duration of trip, and vaccine cost. PrEP does simplify post-exposure treatment, although it does not abrogate the need for booster vaccination after rabies exposure.

Update on Meningococcal Disease and Yellow Fever

Annelies Wilder-Smith
Institute of Public Health, University of Heidelberg, Heidelberg, Germany

Neisseria meningitidis causes an estimated 500,000 cases of invasive meningococcal disease (including meningitis, meningococcemia and other forms of invasive disease) and 50,000 deaths annually. Meningococcal disease can be rapidly progressive and fatal in previously healthy individuals. Among survivors, permanent sequelae, such as limb loss, hearing loss and cognitive deficits are common.

Meningococcal disease epidemiology is highly region specific. The highest incidence of disease occurs in the meningitis belt of sub-Saharan Africa, a huge area that extends from Senegal to Ethiopia, where attack rates during epidemics can be as high as 1%. In countries where the disease is primarily endemic, including much of the Americas and Europe, rates of disease are much lower, ranging from 0.30–8.90 cases per 100,000 population. In travellers, the highest risk has been associated with the Hajj pilgrimage. Over the past decade, substantial advances in meningococcal vaccine development have occurred and much has been learned about prevention from countries that have incorporated meningococcal vaccines into their immunization programs. The burden of meningococcal disease is unknown for many parts of the world because of inadequate surveillance, which severely hampers evidence-based immunization policy. As the field of meningococcal vaccine development advances, global surveillance for meningococcal disease needs to be strengthened in many regions of the world. For countries with meningococcal vaccination policies, research on vaccine effectiveness and impact, including indirect effects, is crucial for informing policy decisions. Each country needs to tailor meningococcal vaccination policy according to individual country needs and knowledge of disease burden. Innovative approaches are needed to introduce and sustain meningococcal vaccination programs in resource-poor settings with a high incidence of meningococcal disease.

Yellow fever (YF) is an acute viral haemorrhagic disease transmitted by infected mosquitoes, mainly Aedes and Haemagogus species. Up to 50% of severely affected persons without treatment will die from yellow fever. There are an estimated 200,000 cases of yellow fever, causing 30,000 deaths, worldwide each year. The virus is endemic in tropical areas of Africa and Latin America, with a combined population of over 900 million people. The number of yellow fever cases has increased over the past two decades due to declining population immunity to infection, deforestation, urbanization, population movements and climate change. YF 17D is a live, attenuated vaccine that has been in use for over 70 years, with hundreds of millions of doses administered. Recent events, such as the changing epidemiology of YF and continued reports of rare but serious adverse events associated with YF vaccine, have highlighted the need to revisit criteria for designating areas with risk for YF virus (YFV) activity and to revise the vaccine recommendations for international travel. The World Health Organization convened a working group of international experts to systematically review factors important for the transmission of YFV and country-specific YF information, establish criteria for additions to or removals from the list of countries with risk for YFV transmission, update YF risk maps, and revise the recommendations for YF vaccination for international travel. This talk details the recommendations made by the working group regarding criteria for designating risk and specific changes to the classification of areas with risk for YFV transmission.

9th ICTP: SYMPOSIUM ON DENGUE INFECTION

SYMPOSIUM ON DENGUE INFECTION PROGRAM: OCTOBER 20, 2011
(SUPPORTED BY WHO)

08.30-10.00	**Dengue Epidemiology** **Chairperson:** *Suchitra Nimmannitaya*	
08.30-08.55	Controversies in Dengue Pathogenesis	*Scott B. Halstead*
08.55-09.20	Global Dengue Situation	*Robert Gibbons*
09.20-09.40	Dengue in Latin America	*Roberto Tapia –Conyer*
09.40-10.00	Dengue Situation in Africa	*Fred N Were*
10.00-10.15	**Coffee Break**	
10.15-11.00	**Dengue Infection in Special Circumstances** **Chairperson:** *Scott B Halstead*	
10.15-10.30	Dengue Fever and Dengue Hemorrhagic Fever in Adolescent and Adult	*Terapong Tantawichien*
10.30-10.45	Dengue Infection in Pregnancy	*Suvit Bunyavejchevin*
10.45-11.00	Dengue in International Travelers	*Annelies Wilder-Smith*
11.00-12.00	**Dengue: A New Paradigm** **Chairperson:** *Krisana Pengsaa*	
11.00-11.20	Novel Issues on Dengue Virology	*Nopporn Sittisombut*
11.20-12.00	WHO New Dengue Case Classification: is need to be implemented?	*Sri Rezeki HADINEGORO*
12.00- 13.00	**Lunch Break**	
13.00-14.30	**Management and Control of Dengue** **Chairperson:** *Tawee Chotpitayasunondh*	
13.00-13.20	Fluid Management in Dengue	*Thanh Hung NGUYN*
13.20-13.45	Experience in Latin America: Community Participation in the Prevention and Control of the Spread of Dengue	*Roberto Tapia -Conyer*
13.45-14.10	WHO Strategy and policy on dengue for SEARO	Aditya Prasad Dash
14.10-14.30	NRA Strengthening and Impact on Vaccine Production in Developing Countries	*Lahouri BELGHARBI*
14.30-15.00	**Closing Ceremony of 9th ICTP**	

9th ICTP: SYMPOSIUM ON DENGUE INFECTION SPEAKER'S ABSTRACT

Dengue Epidemiology: Controversies in Dengue Pathogenesis

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Four dengue viruses (DENV) cause syndromes in human beings that are self-limited or severe. The severe syndrome, dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), characterized by sudden vascular permeability has consistently been observed to accompany dengue infections in individuals circulating heterotypic dengue antibodies at infection-enhancing concentrations, passively or actively acquired**.** In humans, dengue infections target monocytes/macrophages where, absent neutralization, heterotypic antibodies, perhaps directed at prM or domain I-II of the envelope protein form immune complexes, attach to Fc receptors resulting in enhanced productive infection. In dengue illness virus-infected cell mass correlates directly with disease severity. DENV, as do many other macrophagotropic micro-organisms, enters cells as non-neutralizing IgG antibody complexes. Paradoxically, the ligation of monocyte/macrophage Fcγ receptors by immune complexes suppresses innate immunity, liberates IL-10, biases Th 1 to Th 2 responses and results in increased productive infection per cell. Thus idiosyncratic Fcγ-receptor signaling induces intrinsic antibody-dependent enhancement of infection (iADE) that modulate the severity of disease. Evidence for iADE infections, insight into target cells for dengue infections in humans, mechanisms of neutralization and enhancement by antibodies and implications for enhanced disease severity following ligation of macrophage Fcγ receptors by infectious immune complexes will be presented. The following dengue pathogenesis controversies will be presented and discussed: 1.) The 1997 WHO case definition is inadequate and needs to be changed; 2.) DHF is not significantly associated with second dengue infections; 3.) DHF is caused by virulent viruses; 4.) DHF results from an abnormal T cell response; 5.) DHF results from dengue infection-induced autoimmunity; 6.) DHF results from DENV-infected endothelial cells.

Global Dengue Situation

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Dengue virus is the most common arboviral infection of humans in the tropical and subtropical regions of the world. This review briefly describes some of the challenges dengue presents. As an emerging disease, dengue is increasing in geographical distribution and severity despite being significantly underreported. In considering the epidemiology of dengue it is important to examine the role of the four closely related dengue virus serotypes- which can greatly affect dengue disease severity, the mosquito vectors- Aedes species, and perhaps most important- human behavior. These factors will be discussed in light of the evolving dengue picture in Asia and the Americas. In light of these difficulties, a safe and effective vaccine it the greatest prospect for stemming the tide of dengue.

Dengue in Latin America

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The Latin America region is undergoing a period for intensive dengue transmission, with half a million cases of dengue fever and almost 15,000 cases of severe dengue occurring on average per year. During the 1980´s an average of 91,000 cases were reported annually by 25 countries. Dengue statistics should be considered a proxy of real incidence. The upward trend and cyclical nature of dengue epidemics every 3 to 5 years, occurs at different moments in every country. The last major outbreaks occurred in both 2002 and 2007 with over 850,000 cases reported each year. From 2000 to 2008, more than 30 countries in the Americas have reported a total of 5,587,811 cases of dengue. A total of 151,060 cases of dengue hemorrhagic fever (DHF) and 1,976 deaths were reported in the same period resulting in a Case Fatality Rate (CFR) of 1.5%. Central America and the Caribbean sub-regions have countries that have presented high incidence rates and all four serotypes of dengue are currently circulating in the region (DEN-1, 2, 3, and 4).

The magnitude of transmission is modulated by several factors linked to the surveillance system and laboratory capabilities in each country. Dengue is a mandatory reportable disease, which means that every case should be systematically reported to the nearest epidemiology unit. The clinical spectrum of the infection, however, undermines surveillance activities, for several reasons. First, the majority of cases are asymptomatic and this proportion goes undetected by the surveillance system. These cases could be an important source of infection for vectors, and for risk of developing severe dengue, if a secondary infection occurs.

Secondly, a large proportion of infected individuals have the mild form of the disease, which is perceived as not serious enough to warrant health care. Dengue cases are misdiagnosed by medical personnel as a febrile syndrome, and therefore go unreported. When dengue fever is identified, regulatory guidelines required paired blood samples to confirm diagnosis, promoting that only a small proportion of cases are diagnosed, confirmed and reported. Dengue statistics in the region under-report mild and classic cases, and are not designed to recognize the more common forms. Confirmed cases face the technical caveats required to comply with the strict WHO classification criteria. Besides there are no regional laboratory capabilities to assess dengue infection because, for example, during 2006, only 4% of the total number of dengue cases was confirmed by laboratory tests. Mexico is the only country in the region that exclusively reported laboratory confirmed cases, and far from representing a solid laboratory-based infrastructure, it points out the underreporting of the real incidence in the country.

Dengue Situation in Africa

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It is estimated that globally, 3.6 billion people live at risk of dengue infection of whom 70-500 million get infected every year. Most of these are thought to be in Africa and Asia though the specific figures for Africa are not specifically known. Up to 36 million actual clinical cases are projected with 2.1 million being of the more severe dengue hemorrhagic fever variety. Some estimates project 21,000 deaths/year. The most important impact of this disease comes from its burden on medical facilities where its cost is colossal.

Dengue fever virus (DENV) is an RNA virus of the family *Flaviviridae*; genus *Flavivirus*. Other common members of the same family include yellow fever virus, West Nile virus, St. Louis encephalitis virus and Japanese encephalitis virus. Most are transmitted by arthropods (mosquitoes or ticks), and are therefore also referred to as arboviruses (arthropod-borne viruses).

Dengue fever has been sporadically documented in Africa since the 20th century though it is thought to have been around much longer. The first reported epidemic was in Durban, South Africa, in the mid 1920s. Despite poor surveillance for the disease, outbreaks caused by all the 4 subtypes have increased dramatically since the 1980s predominantly is Eastern Africa. Lesser epidemics continue to be reported in Western and even smaller ones in Southern Africa.

One of the larger outbreaks in Eastern Africa was reported in 1982 with more than 56,000 individuals affected. This outbreak started in the Indian Ocean Islands of Seychelles and Comoros but rapidly spread to the Kenyan coast. Between 1982 and 2008 many countries in the region, Tanzania, Djibouti, Kenya, Somalia, Eritrea and Mozambique have reported sizable epidemics.

The West African states of Nigeria, Senegal, Cape Verge, Ivory Coast and Burkina Faso have experienced repeated epidemics between 1975 and 2008. Though of lesser magnitude than the Eastern African region, the consistent occurrence of these epidemics remains evident. Some recent West African epidemics have even spilled into the Mediterranean Europe.

In addition to travelling to or living in tropical areas other risk factors to acquisition of dengue fever include previous infection, reduced host immunity and where only one sub-type circulates, younger age groups including infants.

Dengue Infection in Special Circumstances: Dengue Fever and Dengue Hemorrhagic Fever in Adolescent and Adult

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Dengue fever and dengue haemorrhagic fever are re-emerging diseases that are endemic in the tropical world. The global prevalence of dengue cases has increased in South-East Asia, the Western Pacific and the Americas. The increasingly widespread distribution and the rising incidence of dengue infections are related to increased distribution of *A. aegypti*, urban population and air travel. Several Southeast Asian countries show that age of the reported dengue cases has increased from 5-9 years to adolescent and adults. Dengue infection in adult has also been recognized as a potential hazard to travelers returning from endemic areas especially Southeast Asia. Dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome. Bleeding manifestations in adult patients including petechiae, menorrhagia were also frequently found, however, massive haematemesis may occurs in adult patients because of peptic ulcer disease and be not associated with profound shock as previous reports in children. Although shock and plasma leakage seem to be more prevalent as age decreases, the frequency of internal haemorrhage augments as age increases. Increase in liver enzymes found in adults indicated liver involvement during dengue infections. Pre-existing liver diseases in adults such as chronic hepatitis, alcoholic cirrhosis and hemoglobinopathies, may aggravate the liver impairment of dengue infection. Fulminant hepatitis is a rare but well described problem in adult patients. Currently no therapeutic agent exists for dengue. The early recognition of dengue infection, bleeding tendency, and signs of circulatory collapse would reduce mortality in adult patients with dengue infection.

Dengue Infection in Pregnancy

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Dengue infection (DI) is a common tropical disease in Thailand that nowadays has an increasing incidence during adulthood. DI is assocoicated with preterm birth or delivery, low birth weight, small-for-gestational age, spontaneous abortion, pre-eclampsia, eclampsia, or fetal death as search terms. Vertical transmission may occur, the fetal effects may be minimal due to the passive protective immune response from mother. But in near-term pregnancy, severe fetal or neonatal illness and death may occur. And the newborn can subsequently develop dengue hemorrhagic fever. Physicians should be aware of the atypical presentation in mothers or neonates. Travel in the endemic area should be avoided in pregnant women especially in late pregnancy. If travel is unavoidable, mosquito repellant or other protection measures are obligatory. The review literature was reviewed. From the literatures review showed high rates of cesarean deliveries and pre-eclampsia among women with dengue infection during pregnancy. Management during pregnancy is complicated especially in case with dengue hemorrhagic fever and low platelet due to bleeding tendency. Conservative medical and obstetrical management are the first line of treatments to avoid the complicated surgical outcome.

Dengue in International Travelers

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Many of the countries where dengue is endemic are popular tourist destinations. It does not come as a surprise then that in tandem with the increase in endemic countries, there has been an exponential increase of dengue reported in travellers.

In some case series of returning travellers, dengue is now the second most common diagnosis. The seroconversion in Israeli travellers to Thailand was reported to be 3.4 per 1,000 travellers. GeoSentinel is a worldwide network of travel medicine providers that see ill returning travellers. In an analysis of 17,353 ill returning travellers, 3,907 travellers presented with a febrile illness. Dengue was the most common cause of febrile illness in those returning from SE Asia, about 3 times more common than malaria. The main risk destinations are indeed SE Asia, followed by Latin America and the Caribbean. The risk for travellers seems to have a cyclical pattern. The peaks correspond with the national cyclical pattern of epidemics, a phenomenon that is still poorly understood.

Despite the fact that dengue is frequently reported in travellers, death remains a rare event. Nevertheless, dengue is often not a mild disease, leads to disruption of travel plans, and even to evacuations in 30% in some case series. Data have showed that pre-travel advice on personal protection does not seem to protect against dengue, a disease transmitted by day biting Aedes mosquitoes. The increasing incidence of dengue in travellers warrants a dengue vaccine for travellers.

Dengue: A new Paradigm
Novel Issues on Dengue Virology

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Recent progresses provide new insights into the structure and function of dengue virus particles, including a) the heterogeneity of virus particles, b) the localization of epitopes on the envelope proteins, E and prM, involved in neutralization and antibody-dependent enhancement of infection, and c) the nature of specific antibody responses in human after infection. Dengue virus particles are assembled in the ER lumen as non-infectious immature particles. During transport, particles are exposed to the acidic Golgi environment and changes in protein conformation allow cleavage of prM by furin, resulting in mature particles with high infectivity. Cleavage of prM occurs in the progressive manner and is often incomplete. Extracellular particles are a mixture of particles at different maturation levels. In the presence of anti-prM antibody, prM-containing particles can be internalized via specific IgG-FcγR interaction into leukocytes and

became infectious upon further prM cleavage. Antibodies specific for various epitopes in the three E domains vary in the neutralizing and infection-enhancing activities with those recognizing the receptor-binding EDIII domain exert strong neutralization. Anti-prM antibodies poorly neutralize virus infectivity, but can augment virus infection of leukocytes. Following dengue virus infection, anti-EDIII antibodies constitute a small fraction of the total particle-binding antibody and play a minor role in the neutralization by immune sera. Instead, B lymphocytes capable of producing cross-reactive, anti-prM and EDI-II-recognizing anti-E antibodies are common. Induction of cross-reactive, poorly neutralizing antibodies may represent a strategy to ensure the propagation of dengue serotypes in nature. These insights may influence the design of new generations of dengue vaccine.

WHO New Dengue Case Classification: is need to be implemented?

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Why does need new dengue case classification? Are there any problems with the dengue case classification that we have been used for more than forty years? We realized as a clinical syndrome, dengue infection has no pathognomonic signs. So, WHO in 1997 established the diagnosis criteria and dengue case classification by clinical manifestation and laboratory findings.

Some experts evaluated the WHO'97 either for diagnosis, classification, and management. Problems have been raised; dengue is just one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome. The current classification (DF, DHF, DSS) is not clearly correlated with disease severity, therefore it is recommended to establish a validated dengue classification using levels of severity. Other problems such as DF/DHF without bleeding, severe dengue did not associated with plasma leakage, usefulness of tourniquet test, etc. needs to be solved.

The DENCO (DENgue and COntrol) study collected data on dengue patients to categorise dengue patients according to disease severity, and this could potentially defined case classification. A classification using categories according to disease severity should not be intending to guide medical therapy and case management, therefore it is recommended to further develop treatment guidelines taking into account warning signs of severity of disease. Denco study, a multicentre clinical prospective study in seven countries enrolled in 2005-2007 described the clinical picture of dengue across different group/ countries and collected evidence for further refined dengue case classification. This study was also help refined existing guidelines for triage and management by the identification of key warning signs of severe disease. Denco study concluded more than 40% of the patients could not be classified without using population haematocrit data, and after including population reference data 18% still remains unclassifiable.

Other multicentre study on validated of new dengue case classification has been done in 18 countries of Asia and Latina America regions. The objectives of the study were to compare the two classification systems regarding applicability in clinical practice and for surveillance, usefulness for triage and clinical management, and user friendliness and acceptance by health staff. Conclusions from this study were the experts accepted revised the classification particularly in accordance to the ease and simple of this system to triage and management for primary health care. The revised dengue classification has a high potential for facilitating dengue case management and surveillance. It was shown and perceived to be more sensitive than the DF/DHF/DSS classification for timely recognition of severe disease. Both acceptance and perceived user-friendliness of the revised system were high, particularly in relation to triage and case management.

As a clinician and key person in dengue management in each country need to discuss further seriously among peer group, want to implementor not implement or implement with modified, still open for discussion.

Management and Control of Dengue:

Fluid Management in Dengue

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Dengue is a serious public health problem worldwide. Dengue shock syndrome (DSS) is severe form of Dengue. The patient in shock may die within 12-24 hours if appropriate treatment is not promptly administered. Early detection of shock, proper treatment and careful monitoring are vitally important. Prompt and adequate fluid resuscitation is the basic treatment for DSS. The recommended regimen for the treatment of DSS patients is as follows: a) Immediate and rapid replacement of the plasma loss with electrolyte or, in case of profound shock, colloid solutions; b) Continued replacement of further plasma losses to maintain effective circulation for 24-48 hours; c) Correction of metabolic and electrolyte disturbances; and blood transfusion- only to cases with severe bleeding. The majority of children with DSS can be treated successfully with isotonic crystalloid solutions. If a colloid is judged to be necessary a medium molecular weight preparation which combines good initial plasma volume support with good intravascular persistence and an acceptable side effect profile is probably the preparation of choice. With the improvement of case management of DSS patients, the case fatality rate of dengue has been reduced significantly during the last 20 years. However, there are some questions related to dengue management which need to be clarified: whether early fluid therapy will reduce severity of shock; which colloid solution is most effective for resuscitation in DSS patients?

Experience in Latin America: Community Participation in the Prevention and Control of the Spread of Dengue

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According to the strategies to prevent and control the spread of dengue, the household enables the adequate microclimate to ensure the survival of vector-borne diseases and therefore there is the need to modify it. Thus, the strategy "Patio Limpio y Cuidado del Agua Almacenada" (Clean Backyard and Suitable Care of Stored Water) was integrated taking the cumulated evidence of the Mexican experience into account.

The strategy consisted in organizing and training the community in the identification and further elimination of mosquito breeding sites. So as to achieve an adequate implementation, in each block an Activator was identified and selected by their peer neighbors and they had the responsibility of visiting the families at their homes to train them. In addition, the community established municipal health committees (Comités Municipales de Salud) demonstrating their value as health managers to limit the negative impact of the spread of dengue as well as supporting Activators work.

The results of the evaluation show that the households that did not receive a visit from the Activator had 2.4 greater risks of breeding mosquitoes compared to those who did receive a visit from the Activator. On the other hand, nearly 80% of the population is capable of identifying the best way to prevent the spread of dengue; yet only 30% of the population performs this action.

One of the findings of the strategy is that Activators perform better during dengue spreads if this is combined with the application of intensive mechanisms to control de spread of vectors such as aerosolizations, the application of larvicides and the elimination of mosquito breeding sites. The participation of the Activators impacts the effects of these actions by prolonging their effect several months after their initial implementation.

Although the participation of the community has not achieved to be the axis in the global control of the vector-borne diseases such as dengue, it must be maintained after the introduction of a dengue vaccine.

WHO/ SEA Regional Strategy and Policy on Dengue

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Over the past three decades, there has been a dramatic increase in the frequency of dengue fever. An estimated 50 million dengue infections occur annually in the world. Although dengue has a global distribution, the WHO South-East Asia (SEA) Region together with Western Pacific Region bears nearly

75% of the current global disease burden. A bi-regional Asia-Pacific Dengue Strategic Plan (2008–2015) was jointly developed between the two WHO Regional Offices and Member States to reverse the rising trend of dengue in the Member countries of these Regions. This has been endorsed by the Regional Committees of both the Regions. The strategy has six components viz., surveillance, integrated vector management, case management, social mobilization, outbreak response communication and research. Member countries have developed their national strategic plan based on the Asia –Pacific strategic plan and it has been implemented in many member countries. Recently a comprehensive guideline for prevention and control of dengue (2011) has been published and distributed, which will help member countries of the Region to scale up the implementation of the dengue control strategies.

NRA Strengthening and Impact on Vaccine Production in Developing Countries

Abstract is not available