APEC Conference on Severe Dengue Prevention and Strategies for Reducing Disease Burden

May 3-4, 2018 | Chinese Taipei

Table of CONTENT

Welcome Message

Welcome Message

Welcome to the “APEC Conference on Severe Dengue Prevention and Strategies for Reducing Disease Burden”.

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. More than 70% of the APEC member economies are at risk of dengue. It poses a significant health, economic and social burden on the populations of endemic areas, especially in terms of the medical care costs for severe dengue cases. Considering the urgent need for APEC members to take appropriate actions against the growing dengue epidemic, Chinese Taipei proposed this conference to provide APEC developing economies with a platform to share and discuss the latest information and technologies on dengue prevention and control, which will help improve the regional capacity to detect and respond to dengue outbreaks, and formulate effective prevention strategies against dengue.

This conference will include the following activities: (1) interactive sessions that promote sharing and exchange of prevention strategies and clinical management experience on dengue/severe dengue, (2) site visit to the Mosquito-Borne Diseases Control and Research Center and (3) poster presentation that showcases the results of the participating APEC economies’ dengue prevention and control.

On behalf of the conference organizer, we hope you will find this conference stimulating, enjoyable and productive. We thank you for your participation and contributions to this event, and wish you a wonderful time in Tainan.

Jih-Haw Chou, D.D.S., M.P.H.
Director-General
Centers for Disease Control, Chinese Taipei

Conference Information

● *Date*

May 3-4, 2018

● *Venue*

3F Regency, Evergreen Plaza Hotel (Tainan)

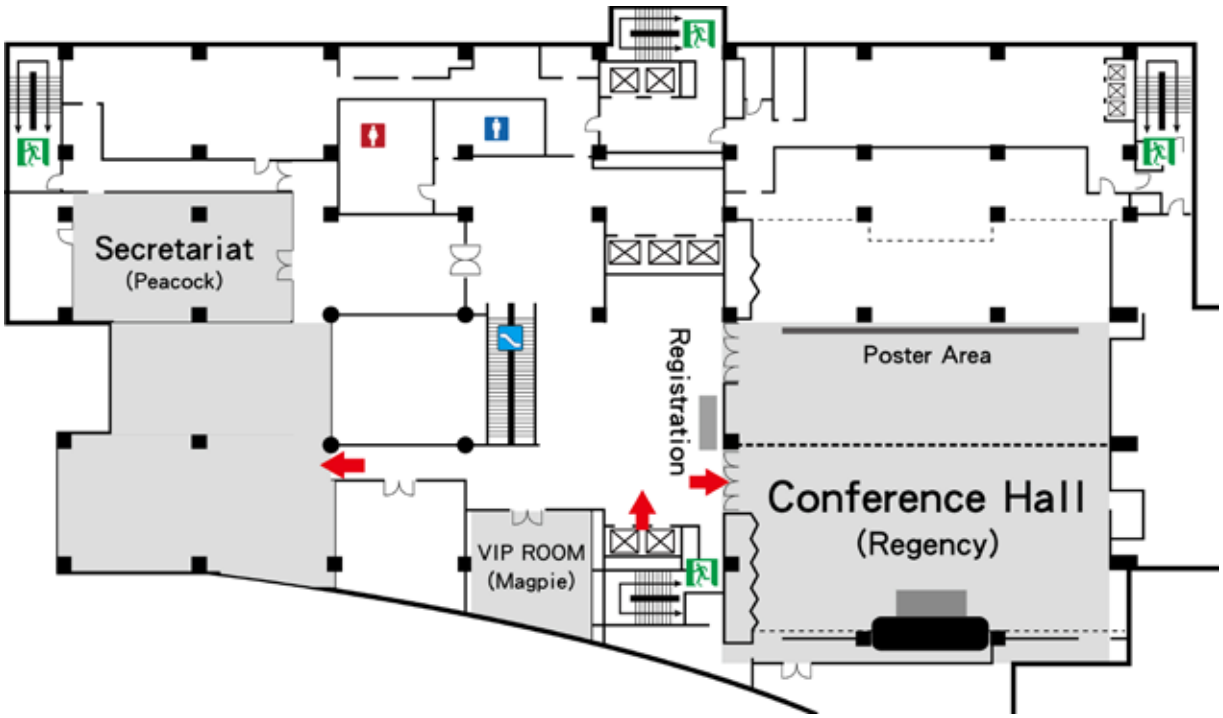
(Hotel Address: No.1, Ln. 336, Sec. 3, Chunghua E. Rd., East Dist., Tainan)

● *Organizer*

Centers for Disease Control, Chinese Taipei

● *Floor Plans*

3F Regency, Evergreen Plaza Hotel (Tainan)



Program Agenda

Thursday, May 3, 2018		
Time	**Subject**	**Moderator / Speaker**
08:20-09:00	Registration	
09:00-09:10	Cultural Performance	
09:10-09:20	Opening Remarks	***Dr. Chi-Kung Ho*** Deputy Minister, Ministry of Health and Welfare, Chinese Taipei
09:20-09:30	Group Photo (Invited Guests)	
09:30-10:10	**Keynote Speech** Aedes-Transmitted Diseases: A Global Public Health and Economic Threat	**Moderator** ***Dr. Jih-Haw Chou*** Director-General,Centers for Disease Control, Chinese Taipei **Speaker** ***Prof. Duane J Gubler*** Emeritus Professor, Emerging Infectious Diseases, Duke-NUS Medical School, Singapore / Adjunct Professor, International Health, Johns Hopkins School of Hygiene and Public Health / Adjunct Professor, Infectious Diseases, Duke University Medical School, The United States
10:10-10:30	**Coffee Break**	
Session I	***Early Diagnosis and Clinical Management***	**Moderator** ***Prof. Ih-Jen Su*** Distinguished Professor, Department of Biotechnology, Southern Taiwan University of Science and Technology, Chinese Taipei
10:30-11:00	Epidemiology and Strategies for Early Detection of Dengue Case in Chinese Taipei	***Dr. Chin-Hui Yang*** Division Director, Division of Acute Infectious Diseases, Centers for Disease Control, Chinese Taipei
11:00-11:30	Dengue Fever in Thailand	***Dr. Darin Areechokchai*** Deputy Director, Bureau of Vector-borne Diseases, Department of Disease Control, Ministry of Public Health, Thailand
11:30-12:00	Dengue Illness: Emphasizing Diverse Clinical Manifestations in Adults	***Dr. Jien-Wei Liu*** Medical Doctor, Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Chinese Taipei
12:00-12:30	Clinical Predictors and Case Management of Severe Dengue in Singapore	***Prof. Yee-Sin Leo*** Executive Director, National Centre for Infectious Diseases, Singapore
12:30-12:40	**Panel Discussion**	
12:40-14:00	**Lunch Break**	
Session II	***Dengue Vaccine***	**Moderator** ***Prof. Duane J Gubler*** Emeritus Professor, Emerging Infectious Diseases, Duke-NUS Medical School, Singapore / Adjunct Professor, International Health, Johns Hopkins School of Hygiene and Public Health / Adjunct Professor, Infectious Diseases, Duke University Medical School, The United States
14:00-14:30	Dengue Vaccine: Current Situation and Public Health Impact	***Dr. In-Kyu Yoon*** Director, Global Dengue & Aedes-Transmitted Diseases Consortium (GDAC), International Vaccine Institute, Republic of Korea
14:30-15:10	Update of Dengue Vaccine Development at the US NIH	***Dr. Stephen Whitehead*** Senior Associate Scientist, Laboratory of Infectious Diseases, NIAID, NIH, The United States ***Prof. Anna Durbin*** Professor, Johns Hopkins Bloomberg School of Public Health, The United States
15:10-15:30	**Coffee Break**	
15:30-15:50	Dengue Drivers, Restrainers, and the role of Biomedical Interventions	***Prof. Michael Malison*** Adjunct Professor, Department of International Health, Rollins School of Public Health, Emory University, The United States
15:50-16:20	Update of Dengue Vaccine Developed by Sanofi Pasteur	***Dr. Ta-Wen Yu*** Regional Medical Head, Regional Medical Affairs, Sanofi Pasteur, Singapore
16:20-16:50	**Panel Discussion**	
16:50-17:00	**Group Photo (All Participants)**	
18:00-20:00	**Welcome Party (Invited Only)**	

<table>
<tr><th colspan="3">Friday, May 4, 2018</th></tr>
<tr><th>Time</th><th>Subject</th><th>Moderator / Speaker</th></tr>
<tr><td>08:30-09:00</td><td>Registration</td><td></td></tr>
<tr><td>Session III</td><td>New Technology Development in Vector Surveillance and Control</td><td>Moderator
Dr. Ching-Len Liao
Investigator and Director, National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Chinese Taipei</td></tr>
<tr><td>09:00-09:30</td><td>Project Wolbachia Singapore -
Using Male Aedes to Fight Dengue Mosquitoes</td><td>Dr. Cheong-Huat Tan
Research Scientist, Environmental Health Institute, National Environment Agency, Singapore</td></tr>
<tr><td>09:30-10:00</td><td>Field Experience on Ecological Control of Dengue and Malaria Vectors</td><td>Dr. Kun-Hsien Tsai
Associate Professor, Institute of Environmental Health, National Taiwan University, Chinese Taipei</td></tr>
<tr><td>10:00-10:20</td><td colspan="2">Coffee Break</td></tr>
<tr><td>10:20-10:50</td><td>New Approach of Mosquito Vector Surveillance and the Application of Environment Management</td><td>Prof. Wu-Chun Tu
Professor, Medical Entomology Laboratory, Department of Entomology, National Chung Hsing University, Chinese Taipei</td></tr>
<tr><td>10:50-11:20</td><td colspan="2">Panel Discussion</td></tr>
<tr><td>11:20-11:30</td><td>Closing Remarks</td><td>Dr. Jih-Haw Chou
Director-General,Centers for Disease Control, Chinese Taipei</td></tr>
<tr><td>11:30-12:30</td><td colspan="2">Lunch Break</td></tr>
<tr><td>12:30-13:00</td><td colspan="2">Shuttle to the Mosquito-Borne Diseases Control Research Center (Invited Only)</td></tr>
<tr><td>Session IV</td><td>Site Visit to the Mosquito-Borne Diseases Control Research Center</td><td>Dr. Ching-Len Liao
Investigator and Director, National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Chinese Taipei</td></tr>
<tr><td>13:00-15:30</td><td>• Registration & Team Assignment
• Introduction of MDC
• Visit & Practice*
<table><tr><th>Team I</th><th>Team II</th><th>Team III</th></tr><tr><td>A</td><td>D</td><td>C</td></tr><tr><td>B</td><td>A</td><td>D</td></tr><tr><td>C</td><td>B</td><td>A</td></tr><tr><td>D</td><td>C</td><td>B</td></tr></table>• Discussion</td><td>★Visit & Practice area:
A Mosquito factory
B Mosquito rearing rooms
C Biological control measures
D Chemical control measures</td></tr>
</table>

Scan this QR code for the most updated version of the agenda and presentation information.

NOTE

Opening Remarks Speaker

Dr. Chi-Kung Ho

Position: Deputy Minister
Department / Organization: Ministry of Health and Welfare
Economy: Chinese Taipei

Educational Background

- Master of Science, Public Health, Graduate Institute of Public Health, National Taiwan University, Chinese Taipei (1986-1988)
- M.D. Kaohsiung Medical University, Kaohsiung, Chinese Taipei (1977-1984)

Professional Career

- Director-General, Department of Health, Kaohsiung City Government (2007-2016)
- Professor, Department of Public Health, Kaohsiung Medical University (2012-present)
- President, Taiwan Environmental and Occupational Medicine Association (2004-2008)
- Deputy Commander, Infectious Disease Prevention Network in Kaohsiung & Pingtung Area, Executive Yuan (2003-2007)
- Chief, SARS Taskforce of Southern Chinese Taipei, Executive Yuan (2003-2003)
- Director, Department of Community Medicine, Kaohsiung Medical University Hospital (2003-2007)
- Director, Graduate Institute of Occupational Safety and Health. Kaohsiung Medical University (2000-2007)
- Visiting Scholar, Occupational Health Program, Harvard School of Public Health, Boston, USA (1999-2000)
- Commissioner, Committee of Occupational Disease Identification, Kaohsiung City Government (1997-2007)
- Director, Office of Labor Safety and Health, Kaohsiung Medical University (1997-1999)
- Director, Department of Occupational and Environmental Medicine, Kaohsiung Medical University Hospital (1994-2007)
- Attending Physician, Department of Occupational Medicine, Kaohsiung Medical University Hospital (1992-1994)
- Director, Office of Labor Health and Safety, Kaohsiung Medical University Hospital (1992-1997)
- Chief Resident, Department of Occupational Medicine, Kaohsiung Medical University Hospital (1991-1992)
- Resident, Department of Internal Medicine, Kaohsiung Medical University Hospital(1988-1991)

Keynote Speech

Aedes-Transmitted Diseases: A Global Public Health and Economic Threat

Moderator

Jih-Haw Chou
Director-General, Centers for Disease Control, Chinese Taipei

Speaker

Duane J Gubler
Emeritus Professor, Emerging Infectious Diseases, Duke-NUS Medical School, Singapore / Adjunct Professor, International Health, Johns Hopkins School of Hygiene and Public Health / Adjunct Professor, Infectious Diseases, Duke University Medical School, The United States

Dr. Jih-Haw Chou

Position: Director-General

Department / Organization: Centers for Disease Control

Economy: Chinese Taipei

Educational Background

- MPH (Environmental Toxicology), University of California at Berkeley, U.S.A.
- MPH (Epidemiology), National Taiwan University, Chinese Taipei
- DDS, Taipei Medical College, Chinese Taipei
- LLB, Fu Jen Catholic University, Chinese Taipei

Professional Career

- Deputy Director-General, Centers for Disease Control, Chinese Taipei
- Health Commissioner, Taipei County Health Department
- Deputy Health Commissioner, Taipei County Health Department
- Director, Div. Research, Planning and Development, Taipei City Health Department
- Branch Chief, National Quarantine Service, Department of Health, Executive Yuan
- Specialist, Bureau of Communicable Disease Control, Department of Health, Executive Yuan

Publications

- Huang Angela SE, Chen WC, Huang WT, Huang ST, Lo YC, Wei SH, Kuo HW, Chan PC, Hung MN, Liu YL, Mu JJ, Yang JY, Liu DP, Chou JH, Chuang JH, Chang FY. Public Health Responses to Reemergence of Animal Rabies, Chinese Taipei July 16-December 28, 2013. PLoS ONE. 10(7):e0132160, 2015.
- Chiu HH, Hsieh JW, Wu YC, Chou JH, Chang FY. Building core capacities at the designated points of entry according to the International Health Regulations 2005: a review of the progress and prospects in Chinese Taipei Global Health Action. 7:24516, 2014.
- Chiu HH, Hsieh JW, Wu YC, Chou JH, Chang FY. Maintaining Human Health at the Border of Chinese Taipei Biosecurity and Bioterrorism.12(6):346-355,2014.
- Lo YC, Chuang JH, Kuo HW, Huang WT, Hsu YF, Liu MT, Chen CH, Huang HH, Chang CH, Chou JH, Chang FY, Lin TY, Chiu WT. Surveillance and vaccine effectiveness of an influenza epidemic predominated by vaccine-mismatched influen-za B/Yamagata-lineage viruses in Chinese Taipei 2011-12 season. PLoS ONE. 8(3):e58222, 2013.
- Chuang JH, Huang AS, Huang WT, Liu MT. Chou JH, Chang FY, Chiu WT. Nationwide vsurveillance of influenza during the pandemic (2009-10) and post-pandemic (2010-11) periods in Chinese Taipei PLoS ONE. 7(4):e36120, 2012.

Speaker

Prof. Duane J Gubler

Position: Emeritus Professor / Adjunct Professor
Department / Organization: Emerging Infectious Diseases, Duke-NUS Medical School, Singapore / International Health, Johns Hopkins School of Hygiene and Public Health / Infectious Diseases, Duke University Medical School
Economy: The United States

Biography

Dr Duane J Gubler, ScD, FAAAS, FIDSA, FASTMH, is Emeritus 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, the Duke University School of Medicine and Duke Global Health Institute. He has spent his entire career working on tropical infectious diseases with an emphasis on dengue and other Aedes transmitted diseases. He has extensive field experience in Asia, the Pacific, tropical America and Africa, and has published extensively on all aspects of dengue and other vector-borne infectious diseases, with over 350 publications and 2 books to his credit. 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, CDC in Fort Collins, Colorado for 15 years and Chair, Department of Tropical Medicine, Medical Microbiology and Pharmacology, University of Hawaii School of Medicine, in Honolulu for 5 years. He has and continues to serve on numerous WHO, national and international committees and study groups, and on the Scientific Advisory Boards of a number of companies and institutions. Prof Gubler was founding Chair, Board of Councillors, Pediatric Dengue Vaccine Initiative in Seoul, Korea, founding Chair, Partnership for Dengue Control in Lyon, France, and the Global Dengue and Aedes-transmitted Diseases Consortium in Seoul, Korea, for which he currently serves as Chairman. Prof Gubler is a Fellow, Infectious Disease Society of America, Fellow, American Association for the Advancement of Science, and Fellow and Past President of the American Society of Tropical Medicine and Hygiene.

Publications

- Pang, T, Gubler, DJ, Goh, DYT, Ismail, Z, on behalf of the Asia Dengue Vaccine Advocacy Group. 2018. Dengue vaccination: a more balanced approach is needed. The Lancet, vol. 391, February 17.
- Bodinayake CK, Tillekeratne LG, Nagahawatte A, Devasiri V, Kodikara Arachchi W, Strouse JJ, et al. (2018) Evaluation of the WHO 2009 classification for diagnosis of acute dengue in a large cohort of adults and children in Sri Lanka during a dengue-1 epidemic. PLoS Negl Trop Dis 12(2): e0006258. https://doi.org/10.1371/journal.pntd.0006258.
- Musso, D, Rodriguez-Morales, AJ, Levi, JE, Lormeau, VMC, Gubler, DJ. 2018. Recent Arboviral Black Swan Events: Lessons Learned from the Pacific and Tropical America, Lancet Infect. Dis, In Press.
- Kuno, G, Mackenzie, JS, Junglen, S, Hubálek, Z, Plyusnin, A, and Gubler, DJ. 2017. Vertebrate Reservoirs of Arboviruses: Myth, Synonym of Amplifier, or Reality? Viruses, 9, 185; doi:10.3390/v9070185
- Gubler, DJ, Vasilakis, N, and Musso, D. 2017.History and Emergence of Zika Virus, JID 2017:216 (Suppl 10).

Speech Abstract

Aedes-Transmitted Diseases: A Global Public Health and Economic Threat

The past 40 years has seen a dramatic emergence of epidemic arboviral diseases transmitted by the yellow fever mosquito, Aedes aegypti. The frequency and magnitude of the epidemics have progressively increased over time, accelerating in the past 10 years. Dengue was the first of these viruses to emerge, spreading from less than 10 known endemic countries and only a few thousand cases reported each year in the 1960s, to 124 endemic countries, an estimated 400 million infections and 100 million symptomatic cases annually.

Dengue has been followed by chikungunya and Zika fever, both of which have followed the same pattern of geographic spread and increasing epidemic frequency and magnitude. Waiting in the wings is yellow fever, which is at the highest risk for urban epidemic transmission in 60 years. If urban epidemics of yellow fever begin, it will threaten global economic security and create a global public health emergency that will make the SARS epidemic pale by comparison. This talk will briefly review the changing epidemiology of these and other potential epidemic diseases and the pos-sibility of prevention and control.

Aedes-Transmitted Diseases: A Global Public Health and Economic Threat

Duane J Gubler, ScD, FAAAS, FIDSA, FASTMH
Emeritus Professor
Program in Emerging Infectious Diseases,
Duke-NUS Medical School, Singapore,
Chairman, Global Dengue & Aedes-Transmitted Diseases Consortium

Disclosure

Provided consultation and advice on dengue to:

Sanofi Pasteur
Takeda
Inviragen
NIH
Merck
GSK
Janssen
Globavir
Novartis
Hawaii Biotech
Bayer

Patent holder of Takeda dengue vaccine

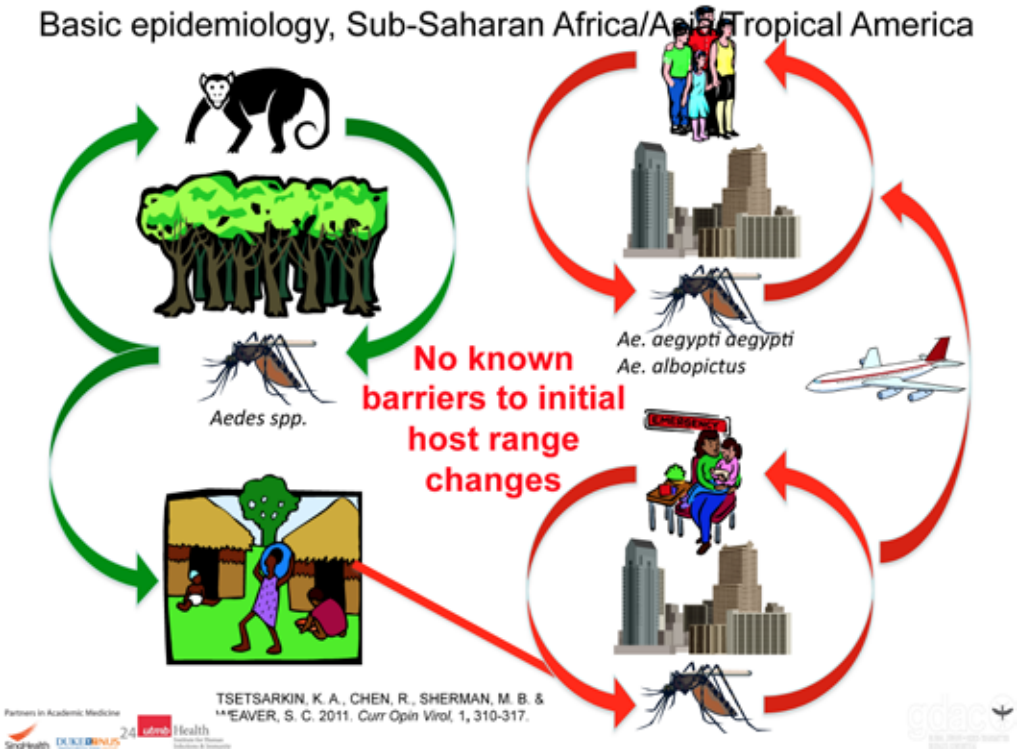
Emergence and Geographic Spread of *Aedes*-transmitted Viruses

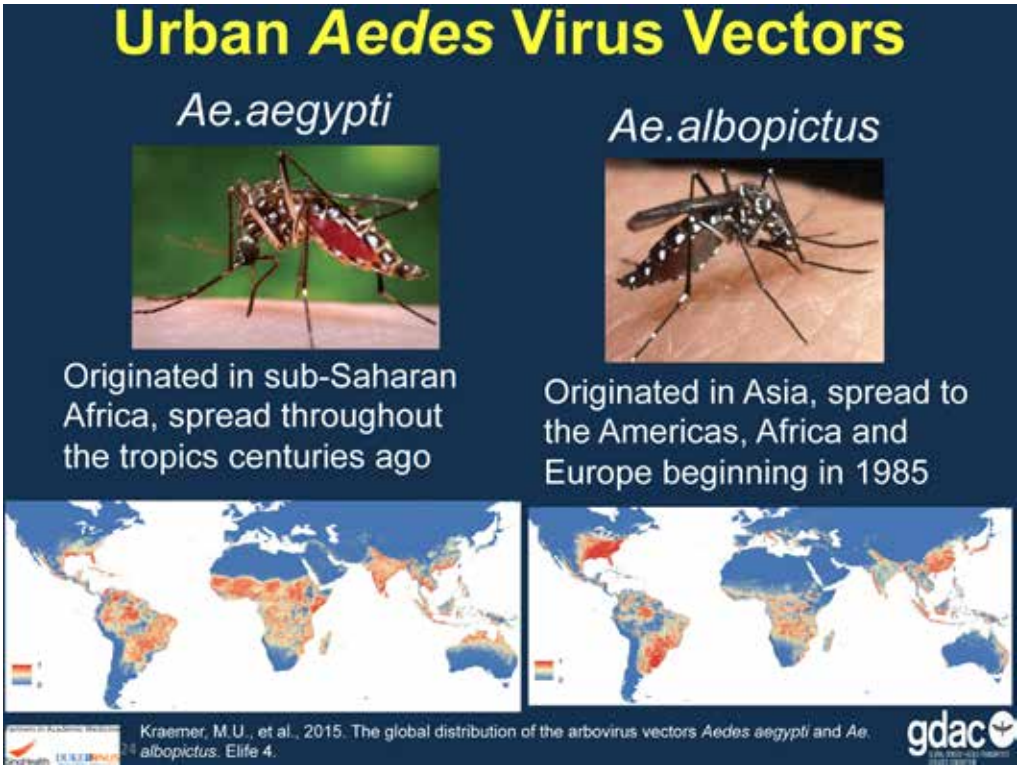
Talk Outline

- Viruses involved
- Basic epidemiology
- Changing epidemiology
- Drivers of emergence
- Other viruses/ yellow fever
- Preparedness and conclusions

Emergent Arboviruses Currently Causing Urban Epidemics Transmitted by Aedes (Stegomyia) Species Mosquitoes

- Flaviviruses
  - Dengue
  - Zika
  - Yellow fever
- Alphaviruses
  - Chikungunya


Basic epidemiology, Sub-Saharan Africa/Asia/Tropical America
Aedes spp.
No known barriers to initial host range changes
Ae. aegypti aegypti
Ae. albopictus
TSETSARKIN, K. A., CHEN, R., SHERMAN, M. B. &
WEAVER, S. C. 2011. Curr Opin Virol, 1, 310-317.


Urban Aedes Virus Vectors
Ae.aegypti
Ae.albopictus
Originated in sub-Saharan Africa, spread throughout the tropics centuries ago
Originated in Asia, spread to the Americas, Africa and Europe beginning in 1985
Kraemer, M.U., et al., 2015. The global distribution of the arbovirus vectors Aedes aegypti and Ae. albopictus. Elife 4.
gdac

Other Potential Urban/Peridomestic Mosquito Vectors

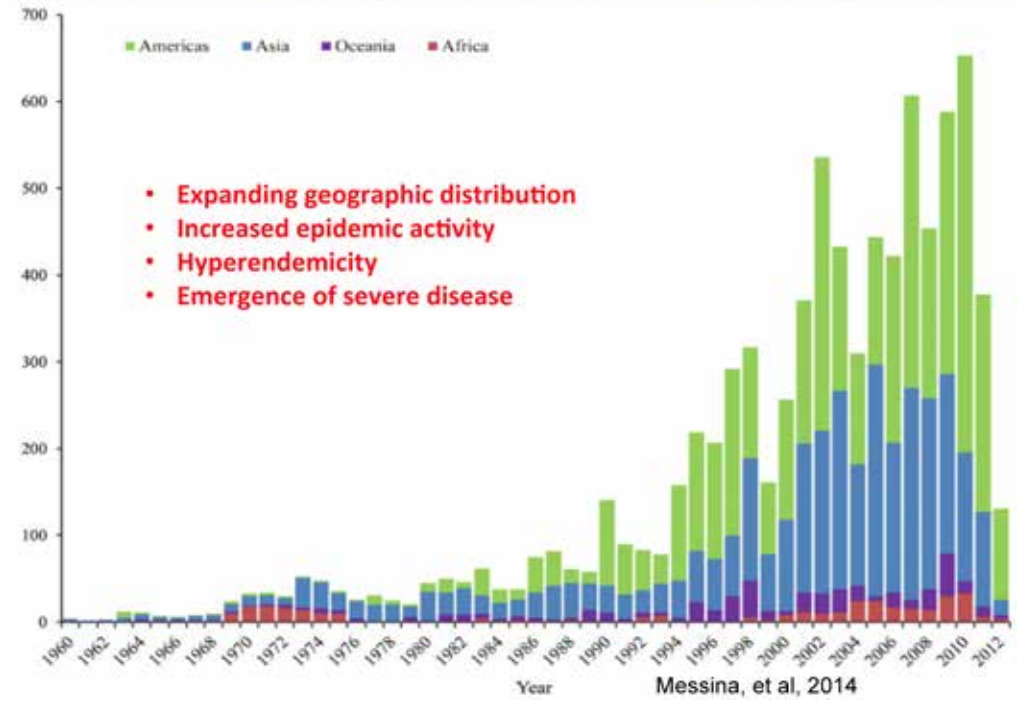
Pacific and Asia

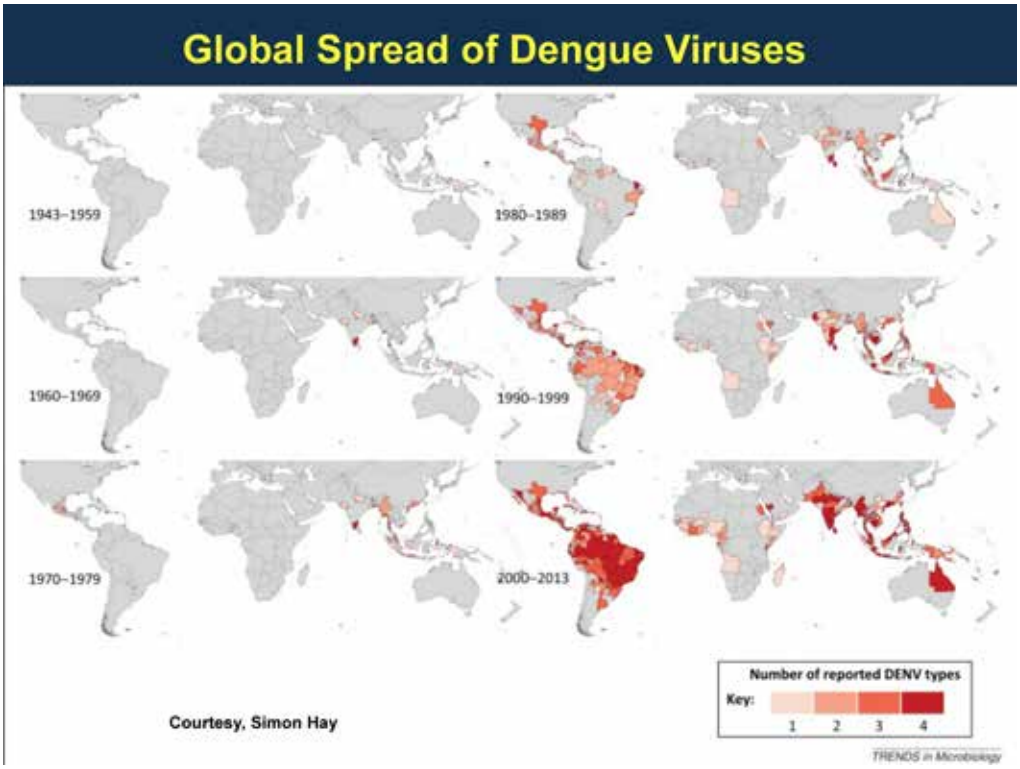
- *Aedes polynesiensis*
- *Aedes hensilii*
- *Aedes malayensis*
- Other *Aedes scutellaris* species

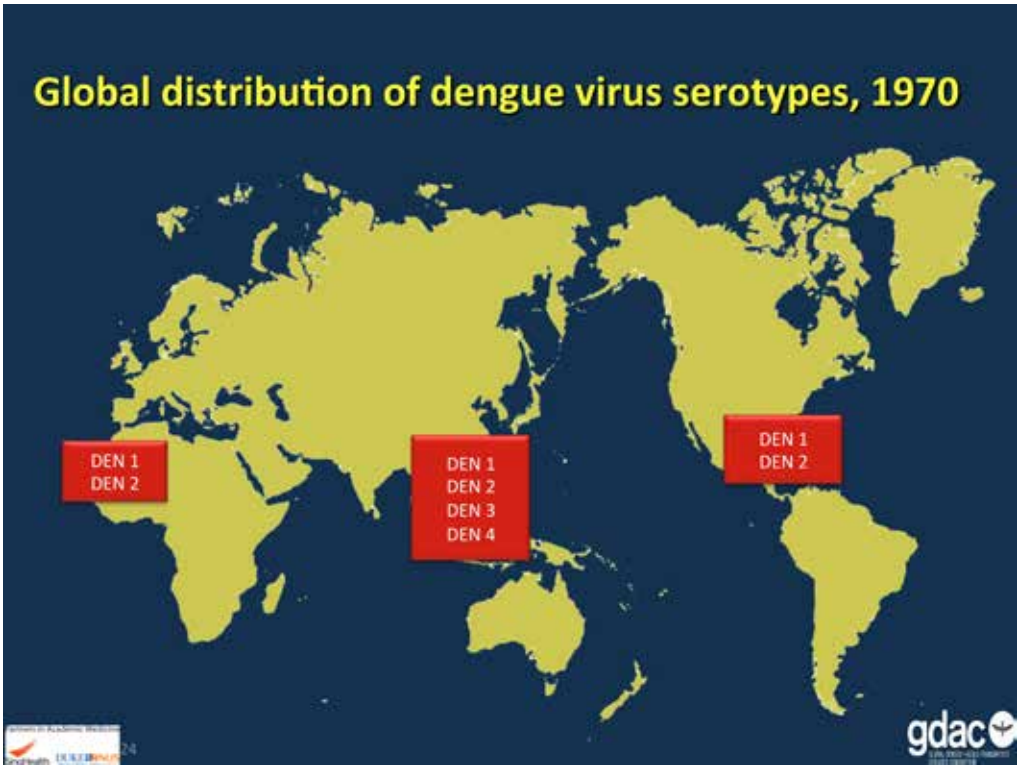
Other *potential vectors*

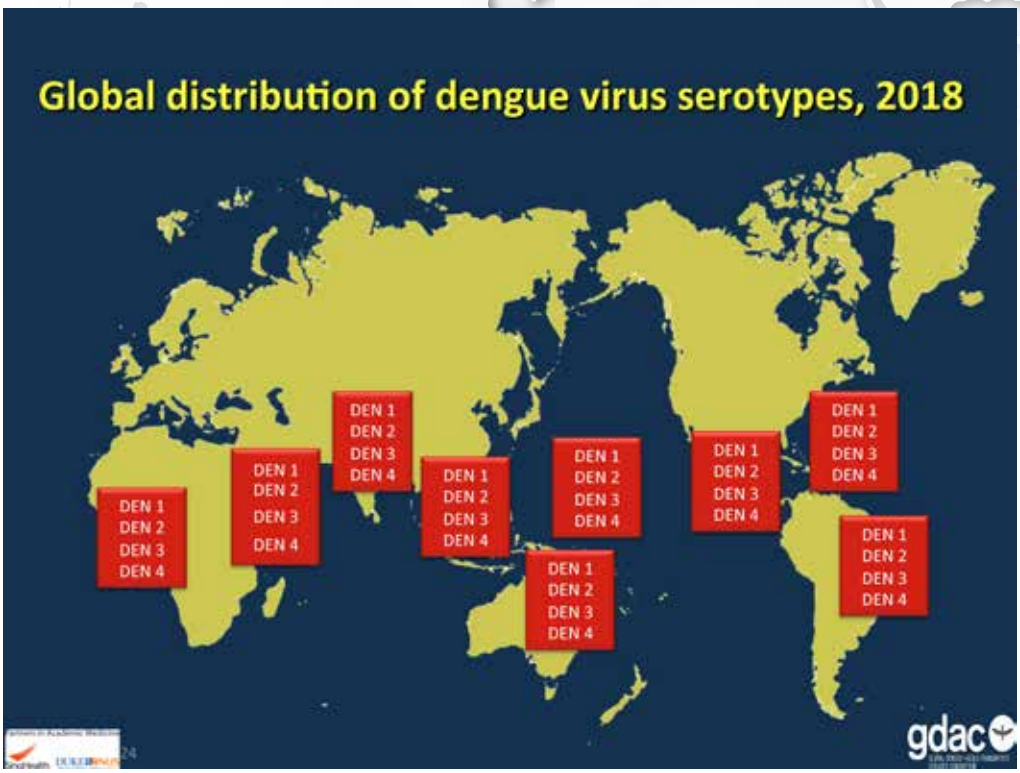
- Aedes triseriatus
- Aedes spp

Pandemic dengue spread to 128 countries in 40 years

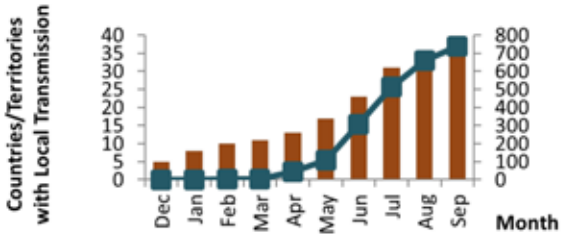


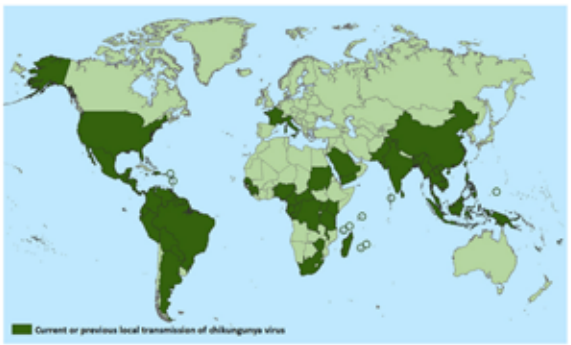

Global Spread of Dengue Viruses
1943–1959
1960–1969
1970–1979
1980–1989
1990–1999
2000–2013
Courtesy, Simon Hay
Number of reported DENV types
Key:
1
2
3
4
TRENDS in Microbiology


Global distribution of dengue virus serotypes, 1970
DEN 1
DEN 2
DEN 1
DEN 2
DEN 3
DEN 4
DEN 1
DEN 2
gdac

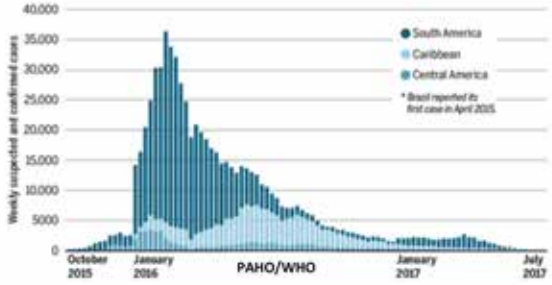


Pandemic chikungunya spread to 37 countries in 10 years

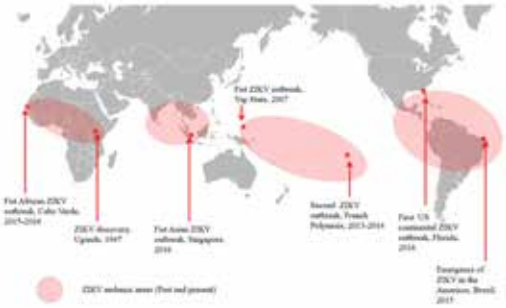




Pandemic Zika spread to 79 countries in 7 years



ZIKV endemic areas (past and present)



Why have we seen such a dramatic increase in epidemic arboviral diseases?

- Complacency, Lack of Political Will
- Policy Changes
- Changes in Public Health
- Changing Life Styles/Behavior
- Microbial Adaptation
- Technology
- Intent to Harm
- Climate Change?

Why Have we Seen Such a Dramatic Geographic Expansion in Epidemic *Aedes*-Transmitted Diseases?

Major Drivers

- Demographic changes (Pop Growth)
  - Environmental change
    - Unprecedented urban growth
    - Changing lifestyles
- Increased transmission and emergence of viruses with greater epidemic potential
- Modern transportation (Globalization)
  - Increased movement of people, animals, commodities & pathogens
- Lack of effective vector control

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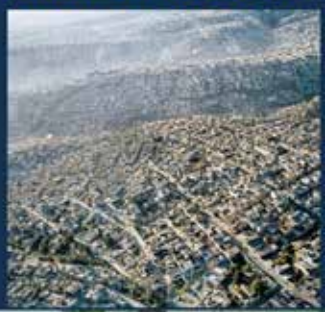
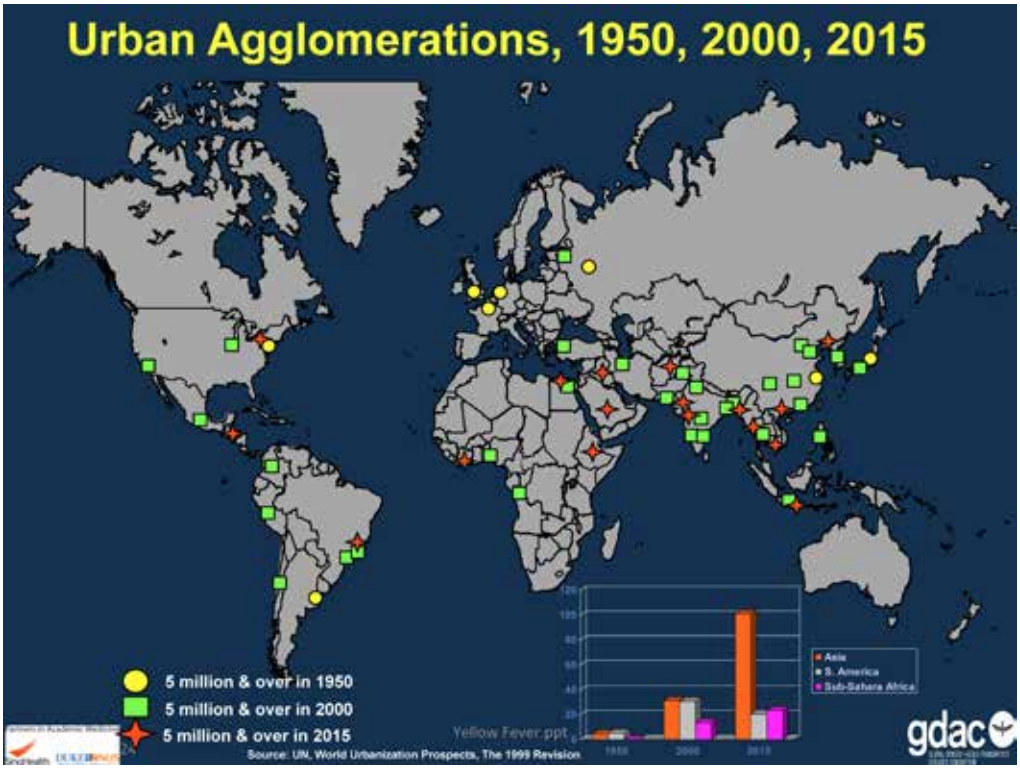
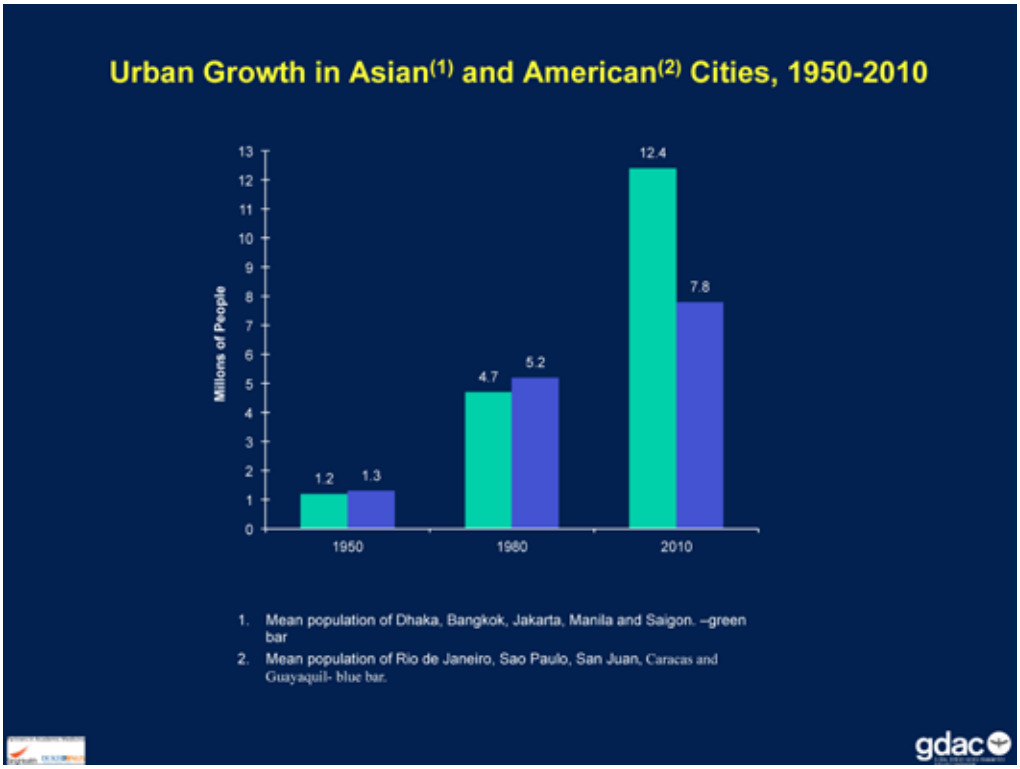
The Global Threat of Urban Epidemics of Arboviral Diseases

- Unplanned urban growth unprecedented
- Crowded tropical urban centers provide ideal ecological conditions to maintain viruses and mosquito vectors
- At risk population exceeds 3.6 billion people

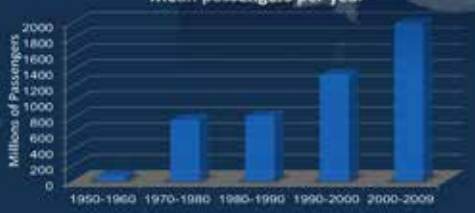



Urban Agglomerations, 1950, 2000, 2015
5 million & over in 1950
5 million & over in 2000
5 million & over in 2015
Source: UN, World Urbanization Prospects, The 1999 Revision
Yellow Fever.ppt
Asia
S. America
Sub-Sahara Africa
gdac


Urban Growth in Asian(1) and American(2) Cities, 1950-2010
Millions of People
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.2
1.3
4.7
5.2
12.4
7.8
1950
1980
2010
1. Mean population of Dhaka, Bangkok, Jakarta, Manila and Saigon. –green bar
2. Mean population of Rio de Janeiro, Sao Paulo, San Juan, Caracas and Guayaquil- blue bar.
gdac

The Global Threat of Urban Epidemics of Arboviral Diseases

- Globalization and modern transportation provides ideal mechanism to move viruses and vectors among population centers
- In 2017, estimated 3+ billion passengers will travel by air



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Global Threat of Epidemic Arboviral Diseases

- Disease and Trade-interwoven History
  - 14th century, Europe discovers exotic goods from Asia
- Global Trade Flourishes
  - 18th, 19, 20th centuries
- New Millennium
  - Integrated global economic system with a transnational flow of capital, products, people, animals, knowledge, and pathogens
  - Rapid spread of epidemic infectious disease from point of origin

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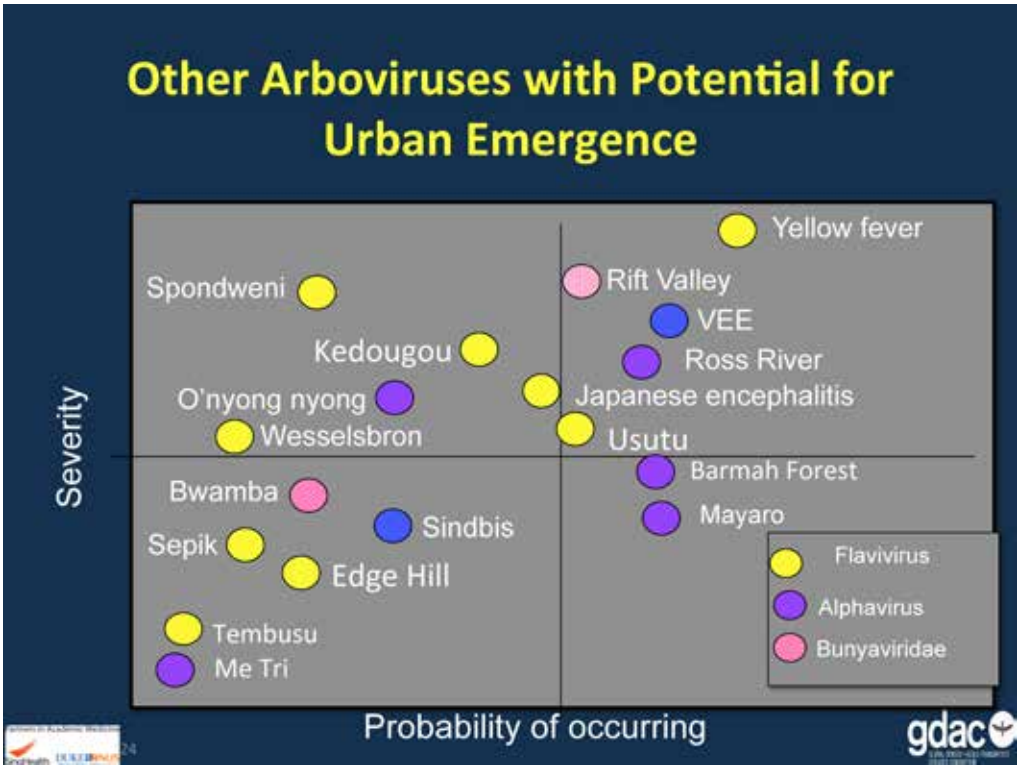
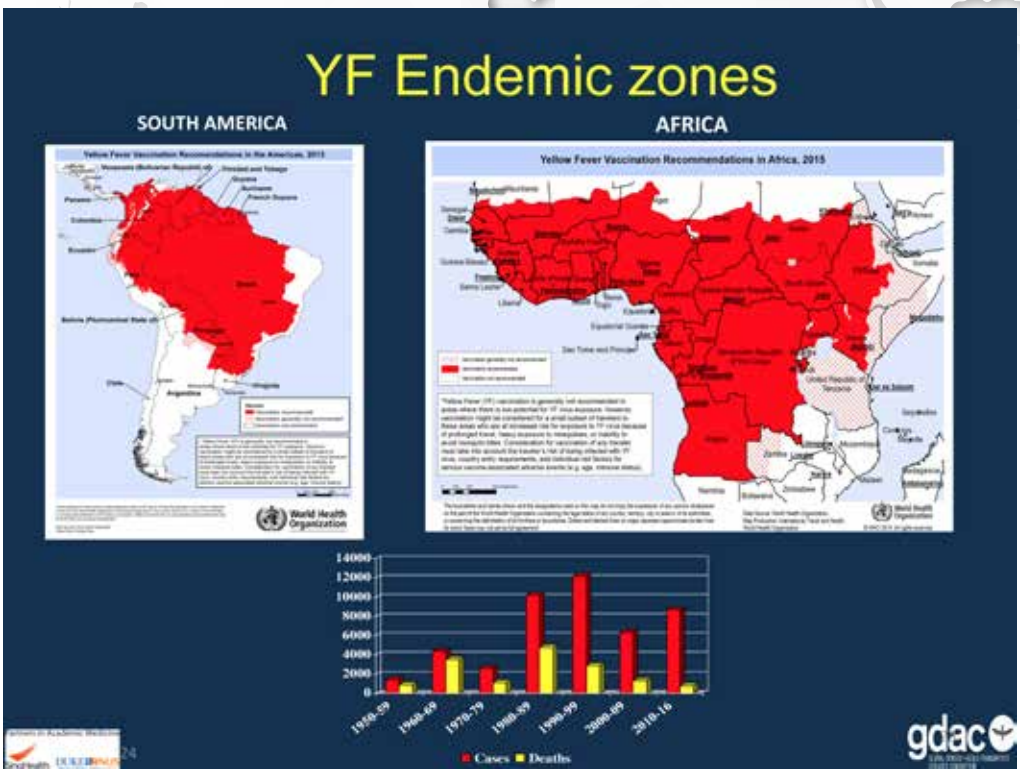

Other Arboviruses with Potential for Urban Emergence
Yellow fever
Spondweni
Rift Valley
VEE
Kedougou
Ross River
O'nyong nyong
Japanese encephalitis
Wesselsbron
Usutu
Barmah Forest
Bwamba
Mayaro
Sindbis
Sepik
Edge Hill
Flavivirus
Alphavirus
Bunyaviridae
Tembusu
Me Tri
Severity
Probability of occurring
gdac


Pandemic yellow fever: the next global threat?
ASIA
YELLOW JACK
gdac


YF Endemic zones
SOUTH AMERICA
AFRICA
Yellow Fever Vaccination Recommendations in Africa, 2015
World Health Organization
14000
12000
10000
8000
6000
4000
2000
0
1950-59
1960-69
1970-79
1980-89
1990-99
2000-09
2010-16
Cases
Deaths
gdac


Search for a destination
Brazil
South Atlantic Ocean
© EarthEnv © Mapbox © OpenStreetMap
Vaccine recommended
Vaccine recommended
Vaccine recommended due to current outbreak
Vaccine not recommended
gdac

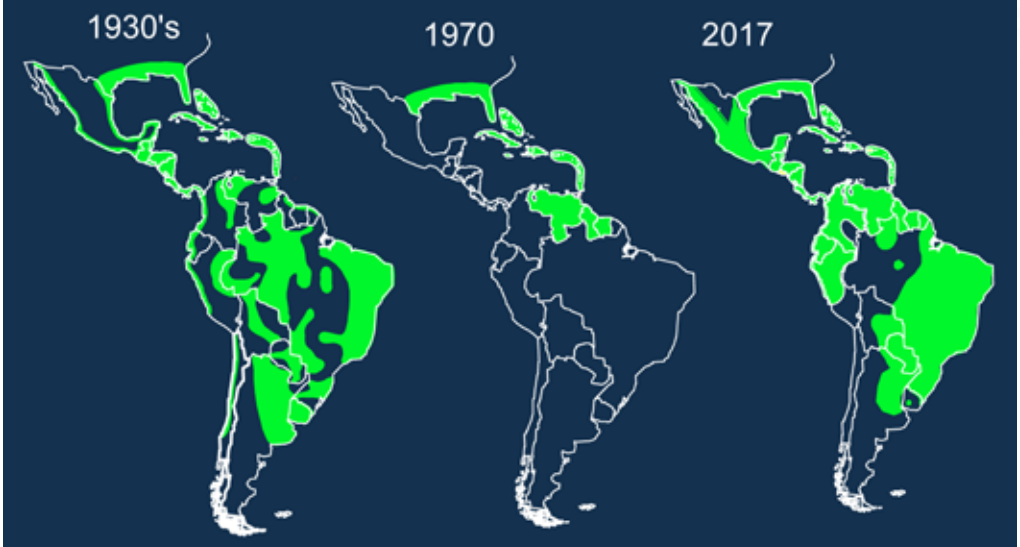
What is the Risk of Urban Epidemics of Yellow Fever Today?

Risk Factors

- Unplanned urban growth unprecedented
- Crowded tropical urban centers provide ideal ecological conditions to maintain viruses and mosquito vectors
- Globalization provides ideal mechanism to move viruses and vectors among population centers
- At risk susceptible population exceeds 3.6 billion people
- Low herd immunity in humans
- Increased encroachment of humans on sylvatic cycle
- *Aedes aegypti* and *Ae. albopictus* have global distribution
- Vector control has been unable to prevent epidemic dengue, chikungunya and Zika
- Vaccine unavailable or inadequate supply

gdac

Aedes aegypti Distribution in the Americas



Adapted from Gubler, 1998

Why hasn't epidemic Yellow Fever in occurred in Urban Centers of South America and Asia?

Most Probable Reasons

- Barriers of YF immunity in endemic countries
- Cross protective flavivirus immunity
- No YFV lineage adapted to Ae aegypti and human cycle

Table 10. Comparative susceptibility of Asian, Caribbean and African strains of *Aedes aegypti* to oral infection with yellow fever virus.*

Mosquito Strain	Number†	% Infected	Transmission Rates
Gambia, West Africa	9/17	52.9	0
Koro, West Africa	21/30	70.0	18.2
Shimba Hills, East Africa	8/19	42.1	0
Colombo, Sri Lanka	26/30	86.7	50.0
Jakarta, Indonesia	16/27	59.3	0
San Juan, Puerto Rico	27/28	96.4	33.3
Port au Prince, Haiti	15/20	75.0	28.6

* Dakar strain – 5 mouse brain passages. Virus titer in monkey at time of feeding was $10^{8.3}$ MID_{50}/ml.
† Number Infected/number tested
§ Percentage of infected female mosquitoes transmitting after 20 days extrinsic incubation.

POTENTIAL GLOBAL SPREAD OF URBAN YELLOW FEVER

Pandemic Yellow Fever

Are we Prepared?

NO!

Vaccine situation

- Stocks: existing world stocks are insufficient
- to counter major epidemics
- Supply: surge production of vaccine
- cannot be ramped up fast enough to provide protection to all at risk areas
- Distribution: vaccine requires a cold chain -- these exist in many at risk countries but are only adequate to handle enough for the childhood cohort

Vaccine situation

- Application: a crash program of mass training and mobilization of vaccinators is beyond the capacity of many low resource countries
- Adverse effects: 1or 2 deaths due to the vaccine (inevitable during mass campaigns) are sufficient to shut down a vaccination program
- Cultural resistance: some at risk countries may resist vaccination (as happened recently with polio vaccination in Nigeria, measles in USA & Europe).
- Fractional dilution of vaccine could help in an emergency
- WHO/GAVI program to increase supply

Vector control situation

Existing vector control programs in at risk countries are failing to control dengue

- Introduction of new tools could help
- But a crash program of training & deployment of spray workers would take time
- Many people find spray obnoxious,
  - close up their houses when sprayers pass
  - protecting the mosquitoes inside!

gdac

Hospital situation

In cities, if a major epidemic occurred:

- Inadequate numbers of beds
- Stocks of intravenous fluids would soon be exhausted
- Stocks of syringes, needles, etc., would run out and be re-used, risking other infections
- A potential infection rate of 20% & CFR of 50% would create chaos
- Air transport system shut down

gdac

Containment

- Populace may flee-
  When plague broke out in Surat, India in 1994
  - 500 000 people (one-fourth of population) fled the city
  - including doctors, nurses and other health workers
- Some reached New Delhi, Bombay, Calcutta & even Pakistan- potential spread

Urban Yellow Fever Epidemics

CONCLUSIONS

- Risk is highest in history of the disease due to global trends of urbanization and globalization
- Global vaccine supply is inadequate
- Egg-based production makes it difficult to scale up vaccine supply quickly for emergency response
- Vector control has been unable to prevent epidemic dengue, chikungunya and Zika
- We should expect more emergent epidemic viruses transmitted by *Aedes Stegomyia* mosquitoes

Urban Yellow Fever Epidemics

CONCLUSIONS

- The most cost effective strategy to prevent a global yellow fever public health emergency will be to include yellow fever vaccine in the EPI in every at risk country in Africa, Central and South America
- Vaccine alone will not be enough

GDAC Paradigm to Rollback Dengue and Other *Aedes*-Transmitted Diseases Using New Tools in the Control Pipeline

Integration and Synergy

International mobilization of resources

- Build public health capacity
- Fund program implementation
- Fund research

Global Dengue and *Aedes*-transmitted Diseases Consortium (GDAC)

Session I

Early Diagnosis and Clinical Management

Moderator

Ih-Jen Su
Distinguished Professor, Department of Biotechnology,
Southern Taiwan University of Science and Technology,
Chinese Taipei

Moderator

Prof. Ih-Jen Su

Position: Distinguished Professor
Department / Organization: Department of Biotechnology, Southern Taiwan University of Science and Technology
Economy: Chinese Taipei

Educational Background

- Doctor of Philosophy. MD, Ph.D., Department of Pathology and Graduate Institute of Pathology of National Taiwan University

Professional Career

- Professor & Chair, Department of Pathology, National Cheng Kung University Medical School and Hospital, Tainan, 1995~2010 Chinese Taipei; Director, NIID, National Health Research Institutes (2002~2013)
- Director General of Centers for Disease Control, Chinese Taipei 2003-2004 (SARS period)

Publications

- Su IJ, Lily HC Wang, Hsieh WC, Wu HC, Teng CF, Tsai HW, Huang W (review article): The emerging role of HBV pre-S2 deletion mutants in HBV tumorigenesis. J Biomed Science (2014)
- Deng CF, Hsieh WC, Yang CW, Su HM, Tsai TF, Sung WC, Huang WY, Su IJ: A bi-phasic response pattern of lipid metabolomics in the stage progression of hepatitis B virus X tumorigenesis. Molecular Carcinogenesis (2015)
- Dou HY, Chen YY, Kou SC, and Su IJ (review article): Prevalence of Mycobacterium tuberculosis strain genotype in Taiwan reveals a close link to ethnic and population migration. Journal of Formosan Medical Association 2015;114:484-488.
- Tsai HW, Lin YJ, Wu HJ, Chang TC, Wu IC, Cheng PN, Yeh CJ, Huang W, Su IJ: Resistance of ground glass hepatocytes to oral antivirals in chronic hepatitis B patients and implication for the development of hepatocellular carcinoma. Onco-target 2016.
- Teng CF, Wu HC, Shyu WC, Jeng LP, Su IJ: Pre-S2 mutan-induced mammalian target of rapamycin signal pathways as potential targets for hepatitis B virus-associated hepatocellular carcinoma. Cell Transplantation 2017.

Session I

Early Diagnosis and Clinical Management

Speaker

Chin-Hui Yang
Division Director, Division of Acute Infectious Diseases, Centers for Disease Control, Chinese Taipei

Darin Areechokchai
Deputy Director, Bureau of Vector-borne Diseases, Department of Disease Control, Ministry of Public Health, Thailand

Jien-Wei Liu
Medical Doctor, Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Chinese Taipei

Yee-Sin Leo
Executive Director, National Centre for Infectious Diseases, Singapore

Speaker

Dr. Chin-Hui Yang
Position: Division Director
Department / Organization: Division of Acute Infectious Diseases, Centers for Disease Control
Economy: Chinese Taipei

Educational Background

- PhD, School of Public Health, Taipei Medical University
- MD, School of Medicine,Chung Shan Medical University

Professional Career

- Division Director, Division of Acute Infectious Diseases, Centers for Disease Control, Chinese Taipei
- Adjunct Assistant Professor, School of Medicine, Taipei Medical University

Publications

- Huang AS, Shu PY, Yang CH. A new reportable disease is born: Taiwan Centers for Disease Control's response to emerging Zika virus infection. J Formos Med Assoc. 2016 Apr;115(4):223-5. doi: 10.1016/j.jfma.2016.03.002.
- Huang SY, Yang JR, Lin YJ, Yang CH, Cheng MC, Liu MT, Wu HS, Chang FY. Serological comparison of antibodies to avian influenza viruses, subtypes H5N2, H6N1, H7N3 and H7N9 between poultry workers and non-poultry workers in Taiwan in 2012. Epidemiol Infect. 2015;143(14):2965-74. doi: 10.1017/ S0950268815000394.
- Yang CH, Chen KJ, Tsai JJ, Lin YH, Cheng SH, Wang KF, et al. The impact of HAART initiation timing on HIV-TB co-infected patients, a retrospective cohort study. BMC Infectious Diseases 2014, 14:304.
- Yang CH, Chan PC, Liao ST, Cheng SH, Wong WW, Huang LM et al. Strategy to better select HIV-infected individuals for latent TB treatment in BCG-vaccinated population. PLoS One 2013; 8(8):e73069.
- Wu HS, Yang JR, Liu MT, Yang CH, Cheng MC, Chang FY. Influenza A(H5N2) virus antibodies in humans after contact with infected poultry, Taiwan, 2012. Emerg Infect Dis. 2014;20(5):857-60. doi: 10.3201/eid2005.131393.

Speech Abstract

Epidemiology and Strategies for Early Detection of Dengue Case in Chinese Taipei

Chinese Taipei is located in the Pacific Ocean and overlying the tropical and subtropical zones. The island remains humid throughout the year and the temperature is very hot in summer. It is ideal for the growth of dengue vectors. Aedes aegypti and Aedes albopictus are the main vectors in Chinese Taipei. Aedes aegypti is geographically limited to southern part of the island, and the “nervous feeder” leading to higher transmission rates.

In 2014, Chinese Taipei experienced a serious DEN-1 outbreak with 15,492 locally-acquired cases. However, a more serious DEN-2 outbreak occurred with 43,419 locally-acquired cases in 2015. The epidemic occurred mainly in Tainan City (22,760 cases) and Kaohsiung City (19,723 cases), located in the south. Mainly adults were affected by the disease. There were 228 deaths due to dengue infection, and the case fatality rate was 5.3 ‰. The average age of those who died 73.66 years (range 29–96) and 90% of them were older than 60 years. Most of those who died had comorbidities.

The dengue outbreak in 2015 not only affect human health, but also caused widespread social disruption and economic losses. We reviewed and improved our strategies for dengue control, and dengue epidemic dropped significantly in 2016–2017. Only 10 locally-acquired cases occurred in 2017. We found that taking actions earlier is very important. The strategies include fever-screening at international airports, using NS1 rapid test at international airports and primary care clinics, and optimizing dengue surveillance system to detect the suspected cases earlier; to urge local public health authorities to start multi-pronged control earlier, and encourage people to eliminate mosquito-breeding containers in the communities; to held training courses of clinical case management for doctors and remind them to be aware and notify suspected cases. We also have established the Mosquito-Borne Diseases Control Research Center to develop novel tools, and use scientific empirical data to do a good job of dengue prevention and control.

EPIDEMIOLOGY AND STRATEGIES FOR EARLY DETECTION OF DENGUE CASE IN CHINESE TAIPEI

Chin-Hui Yang, MD, PhD
Division of Acute Infectious Disease
Centers for Disease Control, Chinese Taipei

2018-5-3

DENGUE

IN TROPICAL AND SUB-TROPICAL CLIMATES WORLDWIDE

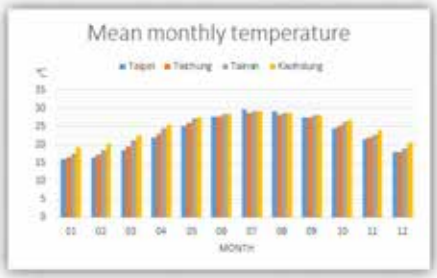
Dengue, countries or areas at risk, 2013

2

CHINESE TAIPEI

Located in the Pacific Ocean and overlying the tropical and subtropical zones

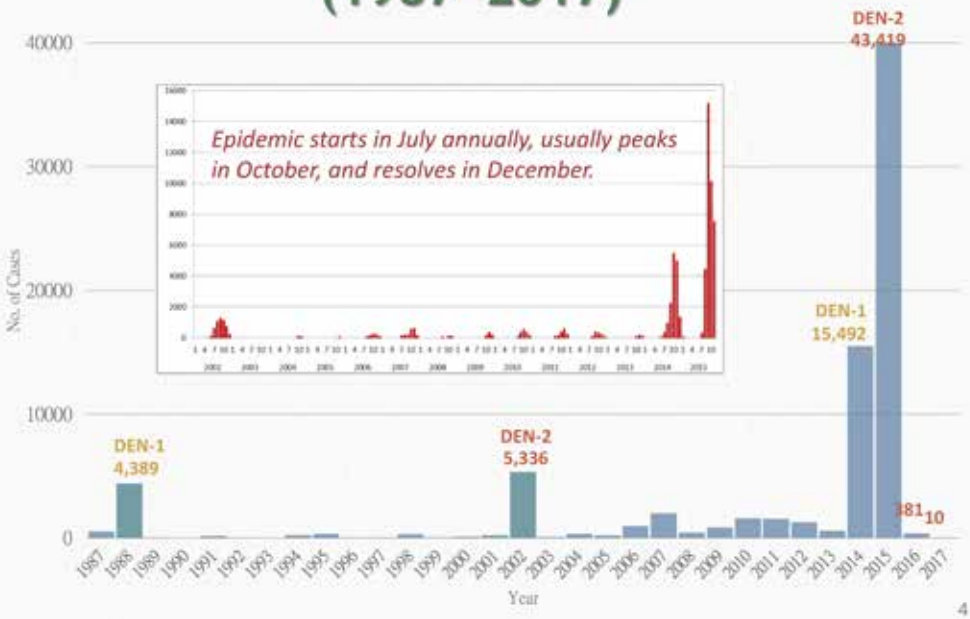
- Landmass : 35,882.6 km²
- Population/Density: 23 million/649.7 per km²
- Humid throughout the year and receives abundant rainfall
- Mean monthly temp. in summer: 28~29 ℃



Source: Central Weather Bureau, Chinese Taipei

3

ANNUAL REPORTED INDIGENOUS DENGUE CASES (1987–2017)



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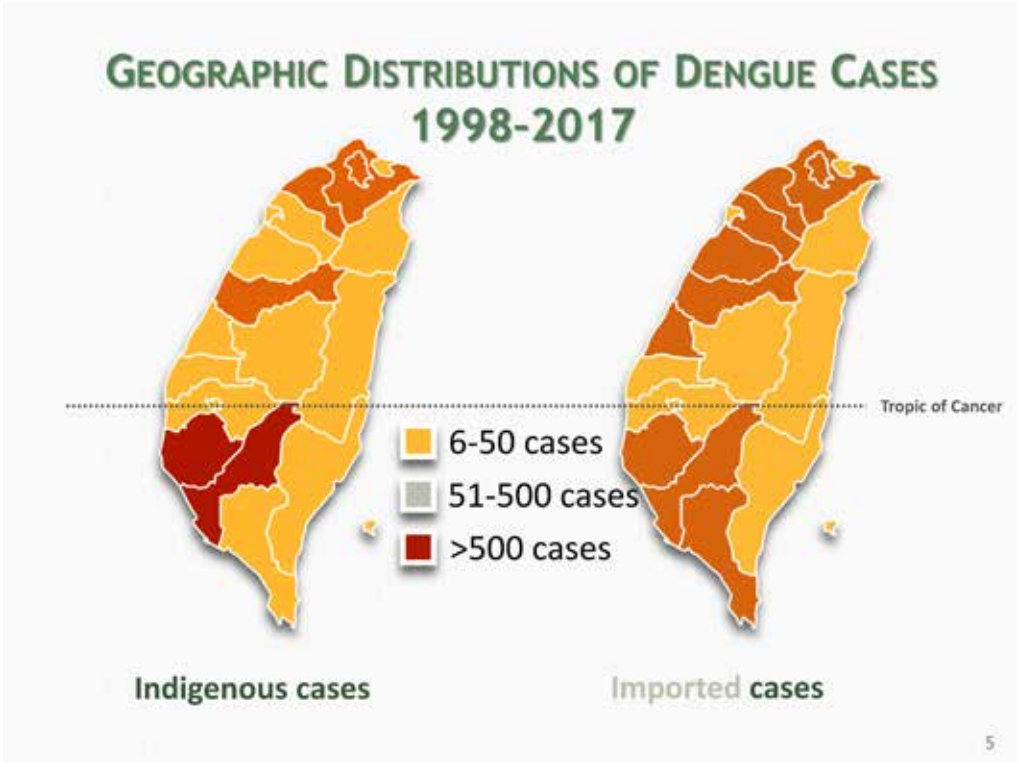
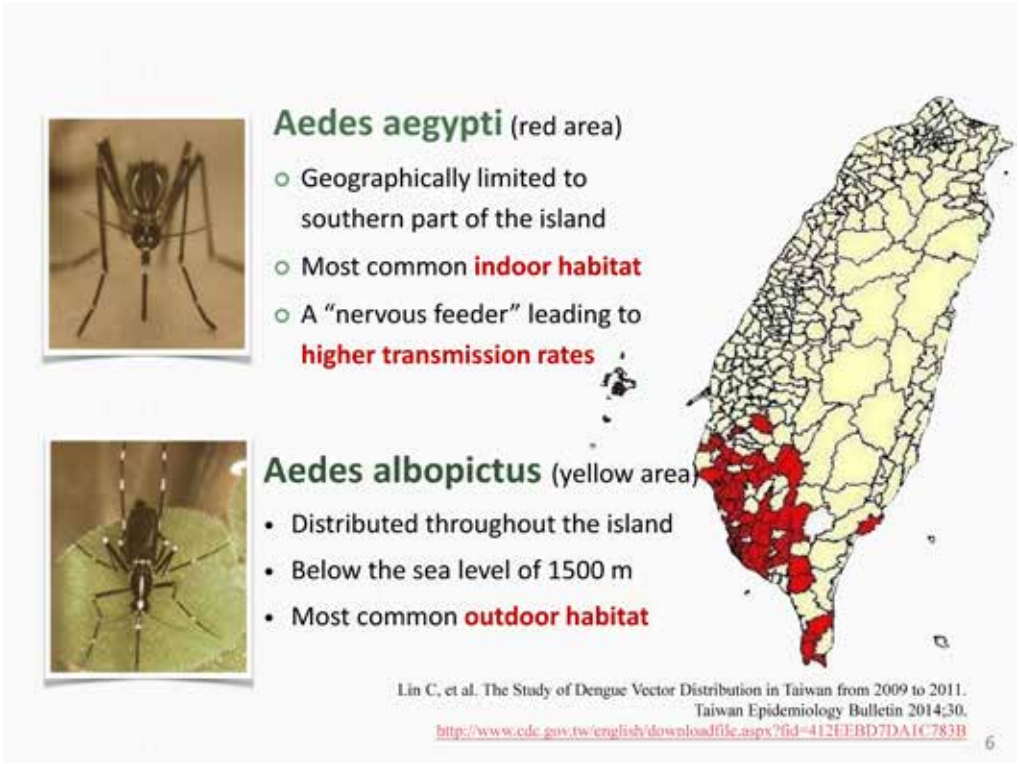
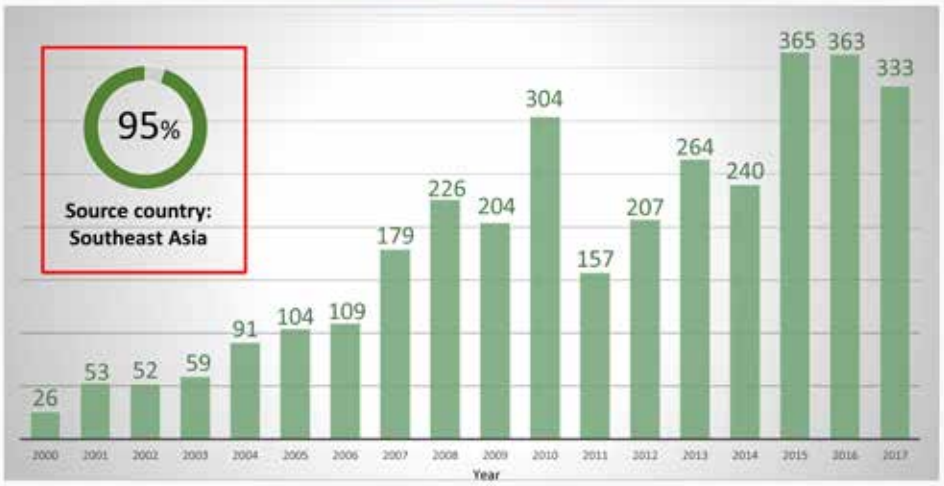

GEOGRAPHIC DISTRIBUTIONS OF DENGUE CASES
1998-2017
Tropic of Cancer
6-50 cases
51-500 cases
>500 cases
Indigenous cases
Imported cases
5

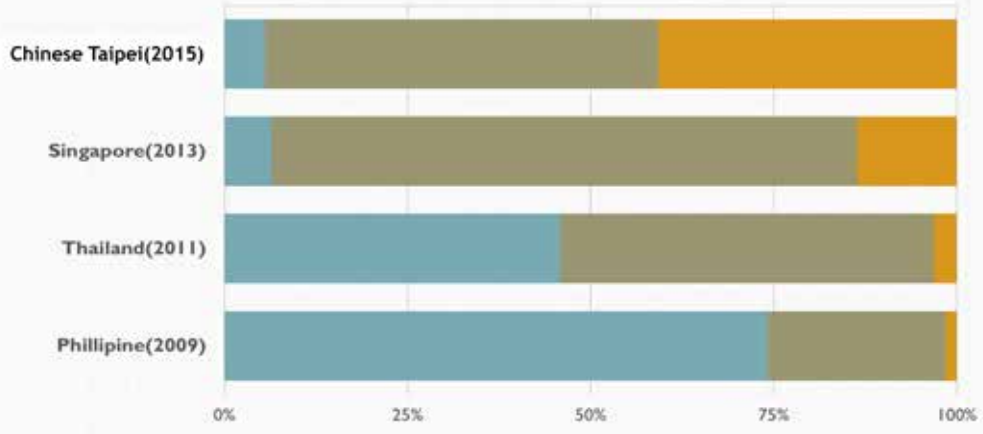

Aedes aegypti (red area)
Geographically limited to southern part of the island
Most common indoor habitat
A "nervous feeder" leading to higher transmission rates
Aedes albopictus (yellow area)
Distributed throughout the island
Below the sea level of 1500 m
Most common outdoor habitat
Lin C, et al. The Study of Dengue Vector Distribution in Taiwan from 2009 to 2011. Taiwan Epidemiology Bulletin 2014;30.
http://www.cdc.gov.tw/english/downloadfile.aspx?fid=412EEBD7DA1C783B
6

IMPORTED DENGUE CASES 2000-2017, CHINESE TAIPEI



According to the molecular analysis of the virus, most indigenous acquired dengue cases were connected to the imported cases preceding the local transmission.

7

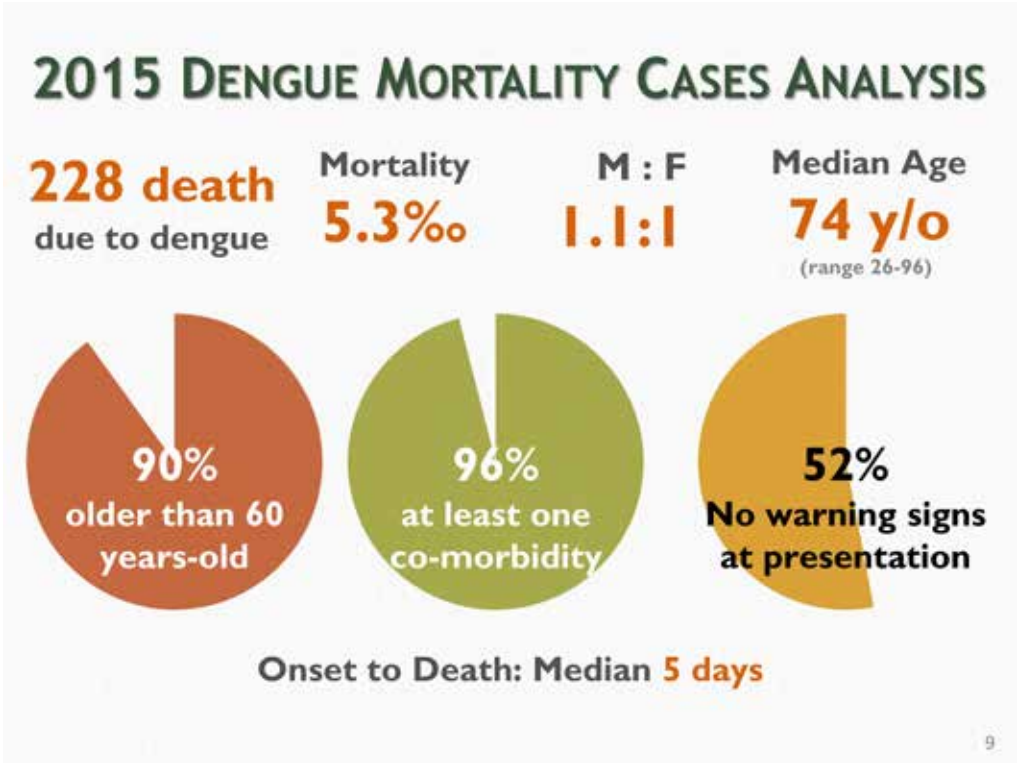


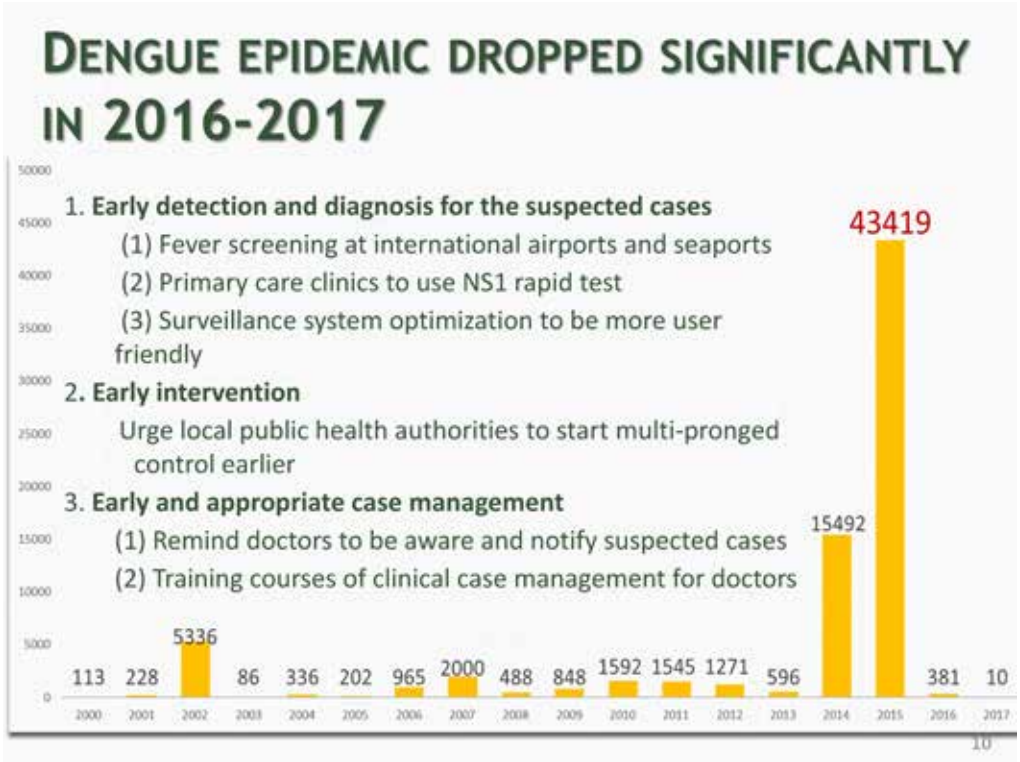
AGE DISTRIBUTION OF REPORTED DENGUE CASES

0-14
15-54
55+

https://goo.gl/8e270F
Epidemiology of Dengue Disease in the Philippines (2000–2011): A Systematic Literature Review. PLoS Negl Trop Dis. 2014 Nov; 8(11): e3027.
Epidemiology of Dengue Disease in the Philippines (2000–2011): A Systematic Literature Review. PLoS Negl Trop Dis. 2014 Nov; 8(11): e3241

8

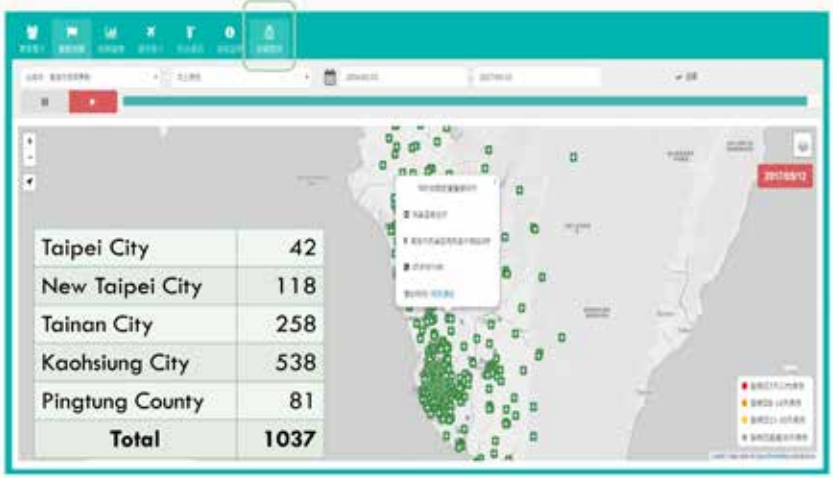

2015 DENGUE MORTALITY CASES ANALYSIS
228 death
due to dengue
Mortality
5.3‰
M : F
1.1:1
Median Age
74 y/o
(range 26-96)
90%
older than 60
years-old
96%
at least one
co-morbidity
52%
No warning signs
at presentation
Onset to Death: Median 5 days
9


DENGUE EPIDEMIC DROPPED SIGNIFICANTLY IN 2016-2017
1. Early detection and diagnosis for the suspected cases
(1) Fever screening at international airports and seaports
(2) Primary care clinics to use NS1 rapid test
(3) Surveillance system optimization to be more user friendly
2. Early intervention
Urge local public health authorities to start multi-pronged control earlier
3. Early and appropriate case management
(1) Remind doctors to be aware and notify suspected cases
(2) Training courses of clinical case management for doctors
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
113
228
5336
86
336
202
965
2000
488
848
1592
1545
1271
596
15492
43419
381
10
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
10

BORDER FEVER SCREENING

11

HOSPITAL AND CLINICS OFFERING PUBLIC-FUNDED DENGUE NS1 RAPID TESTS



Taipei City	42
New Taipei City	118
Tainan City	258
Kaohsiung City	538
Pingtung County	81
Total	**1037**

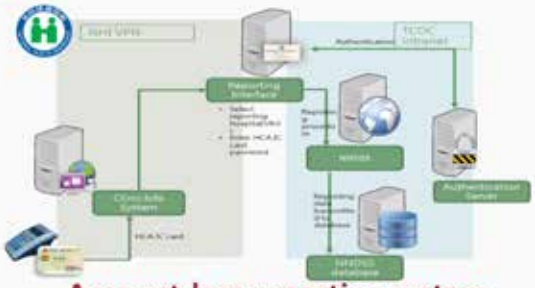
http://cdcdengue.azurewebsites.net/

12

DISEASE SURVEILLANCE

Notifiable disease surveillance system

- Reporting a suspected case to health authority within 24 hours (by internet)
- Awarding NTD 2,500 to doctor for reporting a confirmed imported case



Account-less reporting system

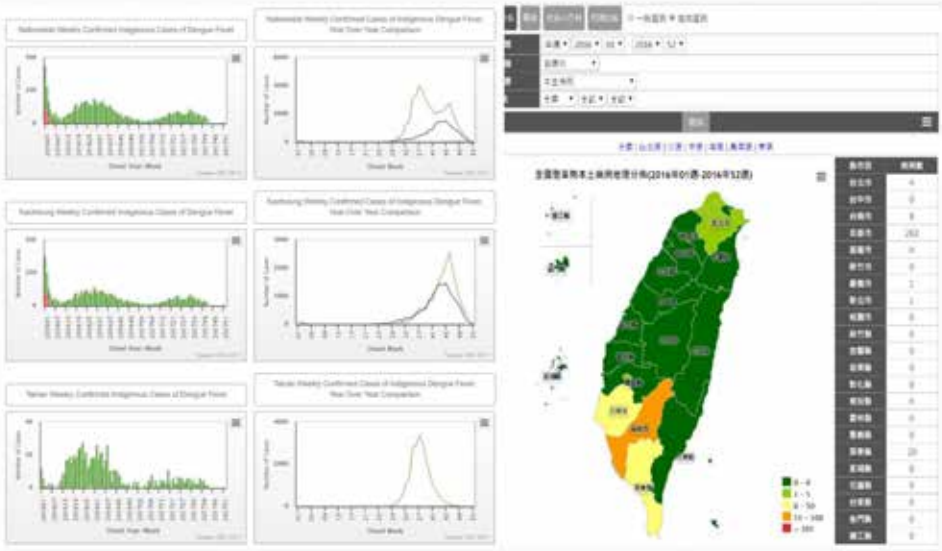
13

PUBLIC ACCESSIBLE NATIONAL INFECTIOUS DISEASES STATISTICS WEBSITE

http://nidss.cdc.gov.tw/

14

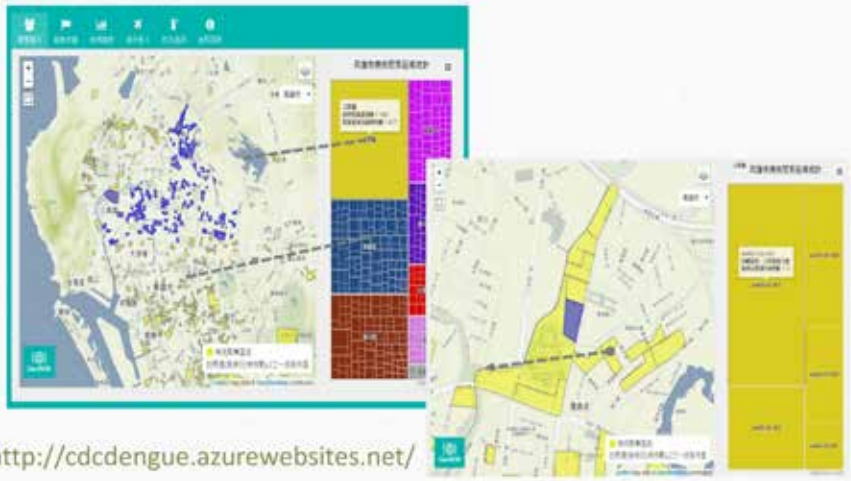
DENGUE FEVER DASHBOARD



15

DENGUE CASE CLUSTERS MAP

登革熱 病例群聚地圖



http://cdcdengue.azurewebsites.net/

16

DENGUE EPIDEMIC IN TAINAN CITY, 2015

http://cdcdengue.azurewebsites.net/

17

RELATIONSHIP BETWEEN INTERVENTIONS AND DENGUE CASES

http://cdcdengue.azurewebsites.net/

18

NEW APPROACH OF VECTOR MOSQUITO SURVEILLANCE IN 2016~2017

To remind local public health authorities to eliminate the breeding sites as soon as possible

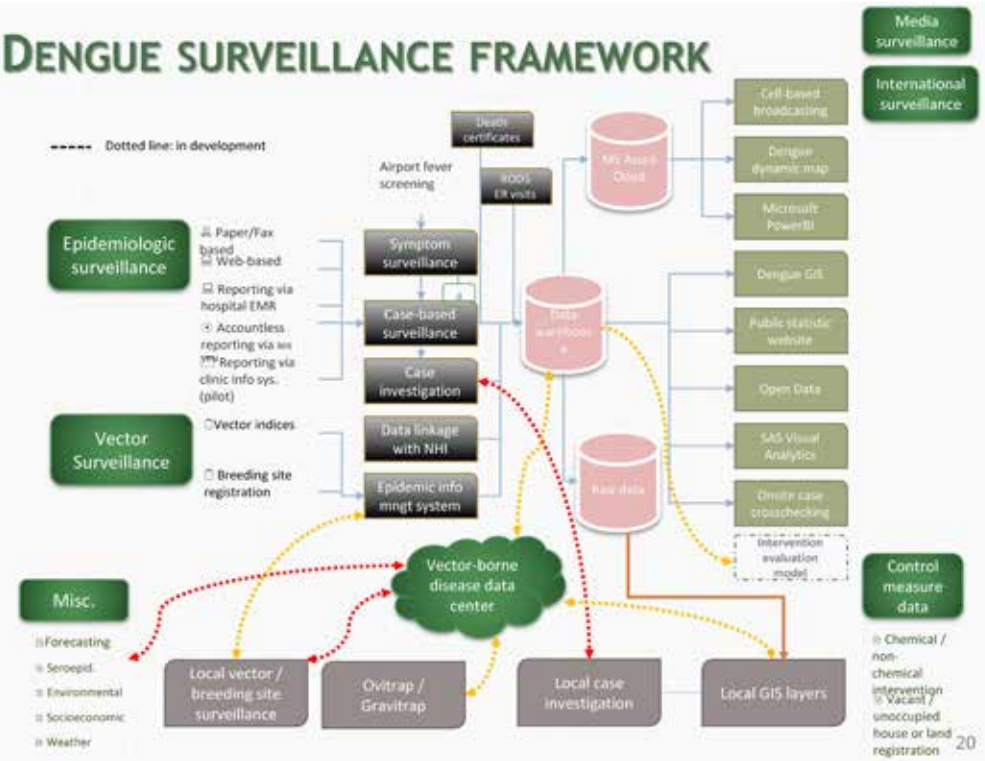
Ovitraps

	Ovitrap (+) 60%~100%	Ovitrap (+) 30%~59%	Ovitrap (+) 0%~29%
eggs≥ 500	Alert	Watch	
Eggs 251~499	Watch		
Eggs 0~250	Watch		

Source: National Mosquito-Borne Diseases Control Research Center

19

DENGUE SURVEILLANCE FRAMEWORK



20

HEALTH EDUCATION

- **Environment Management**
  - Container management
  - Elimination of breeding sites
- **Personal Protection**
  - Apply repellents (DEET) to exposed skin
  - Wear long-sleeved tops and pants
- **Doctor Encouragement**
  - Remind doctors to aware and notify suspected cases

Emptying and cleaning containers

Insect repellent (DEET)

Long-sleeved clothes and pants

21

COMMUNITY MOBILIZATION

- Encourage communities to organize volunteers to eliminate mosquito-breeding containers

22

Laboratory Diagnosis

Laboratory

- 2 central reference labs
- 3 authorized laboratory testing institutions for dengue

Method

- Virus Culture
- Real-Time RT-PCR
- DENV NS1 Ag Test
- Capture IgM and IgG ELISA

Clinical case management

Education and training for clinical diagnosis, treatment and case management.

Multiple materials to remind doctors to aware and notify suspected cases.

23

Dengue vaccine development for the elderly in collaboration with US NIH

- Developing the world's first dengue vaccine for people **older than 50** years
- Phase II clinical study of the vaccine will begin this year
- Plans on having locally produced vaccines for possible Phase III trial

24


Thank you for your attention
25

Speaker

Dr. Darin Areechokchai

Position: Deputy Director

Department / Organization: Bureau of Vector borne diseases, Department of Disease Control, Ministry of Public Health

Economy: Thailand

Educational Background

- 2000: Bachelor degree of Medicine, Mahidol University, Thailand
- 2007: Master of Clinical Tropical Medicine (MCTM) Mahidol University, Thailand
- 2015:Certification in Public Health Emergency Management Fellowship, Centers for Disease Control and Prevention, United State

Professional Career

- Aedes borne disease surveillance, prevention and control
- Emergency management during Zika epidemics in Thailand

Publications

- Areechokchai D, Vijitsoonthornkul K, Pongpan S, Maeakhian S. Population attributable fraction of stroke risk factors in Thailand: utilization of non-communicable disease surveillance systems. OSIR. 2017 Mar;10(1):1-6.
- Areechokchai D, Bowonwatanuwong C, Phonrat B, Pitisuttithum P, Maek-a-Nantawat W. Pregnancy Outcomes Among HIV-Infected Women Undergoing Antiretroviral Therapy. The Open AIDS Journal. 2009;3:8-13.
- Areechokchai D, Jiraphongsa C, Laosiritaworn Y, Hanshaoworakul W, O'Reilly M. Investigation of avian influenza (H5N1) outbreak in humans -- Thailand, 2004. MMWR Morb Mortal Wkly Rep2006;55:Suppl 1:3-6

Speech Abstract

Dengue Fever in Thailand

Background:

Thailand is located in the tropical area. The climate is under the influence of monsoon winds causing warm-moist air and abundant rain over the country. The rainy season usually extends almost six months a year. Therefore, mosquito, especially Aedes, borne diseases i.e. Dengue, Zika, and Chikungunya are important communicable diseases in Thailand.

Dengue epidemiology:

Dengue is an endemic disease in Thailand. The annual incidence has slightly increased over the past ten years with strong seasonal pattern. The number of case reports is approximately 1,000 – 5,000 cases per month in non-rainy season, however it can reach over 20,000 cases a month in rainy season. The average annual morbidity is 100 – 120 per 100,000 popu-lation with 80 – 100 deaths. In the past, the disease was common among children under 15 years old. However, during the past 5 years, adult cases have been reported in higher proportion. Most of fatal cases has underlying chronic diseases e.g. obesity, cardiovascular diseases, diabetes. All dengue serotypes, DEN1 – DEN4, have been circulated in Thailand every year.

Control measures:

To prepare and respond to the epidemic, risk assessment will be carried out before rainy season each year to identify high risk areas of dengue outbreak. Social mobilization is usually conducted to address environmental management in key places e.g. school, temple, and hospital. Larva survey is regularly performed by village health volunteers every month to evaluate the control measures. Community engagement is a major challenge for dengue control as publics still believe that vector control is a responsibility of health sector.

Dengue Epidemiology in Thailand

Asia-Pacific
Economic Cooperation

Darin Areechokchai M.D., M.C.T.M.
Deputy director, Bureau of Vector Borne Diseases
Department of Disease Control, MOPH Thailand

Contents

- Background
- Dengue surveillance and epidemiology
- Characteristics of dengue deaths
- Dengue control

Background

Climate of Thailand

Three seasons

- Cool season (Nov-Jan)
- Hot season (Feb-May)
- Rainy season (Jun-Oct)

Average annual Temp.

- high of 38 °C (100.4 °F)
- low of 19 °C (66.2 °F)

Background

- *Aedes aegypti* and *Aedes albopictus* are the main vectors of mosquito-borne viruses
  - Epidemics of dengue for >50 years
  - Zika outbreaks since 2016
  - Sporadic cases of chikungunya with occasional outbreaks

Surveillance and Epidemiology

5

Aedes-borne disease surveillance

Community risk factors
- HI, CI, BI
- key containers

Other factors
- temperature, rainfall
- Density of population

Environment

Viruses → **Infective vector** → **Trans-ovarian**

Agent

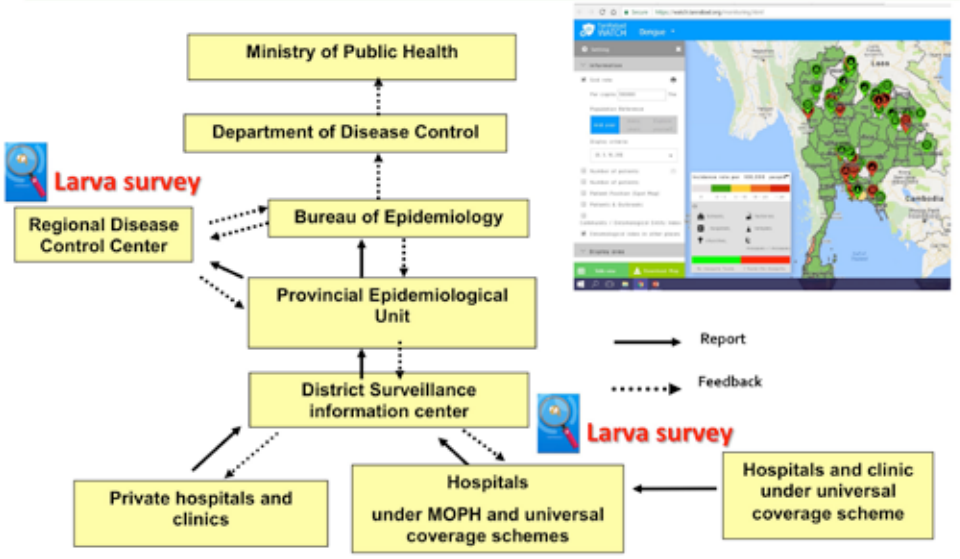
Host factors
- Age, underlying conditions, delayed diagnosis and treatment, etc.

Host

Cases → **Deaths**

6

Dengue Surveillance System in Thailand

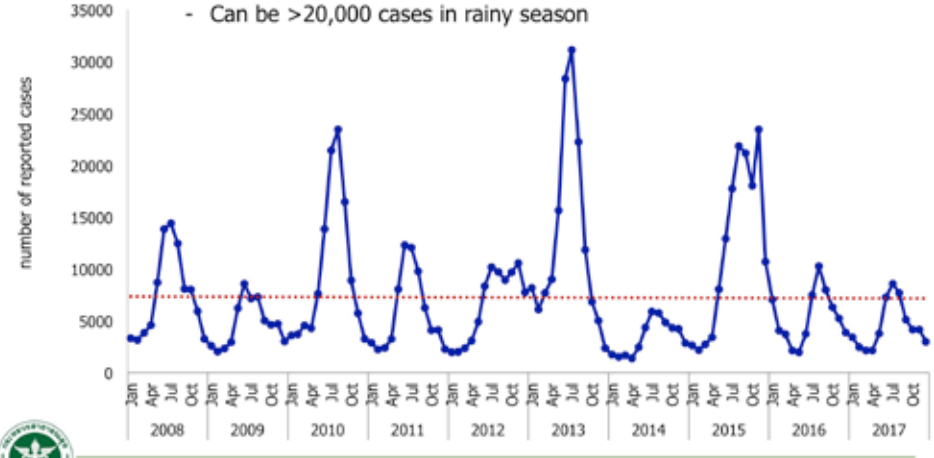


7

Ref: Bureau of Epidemiology, DDC, MOPH, Thailand

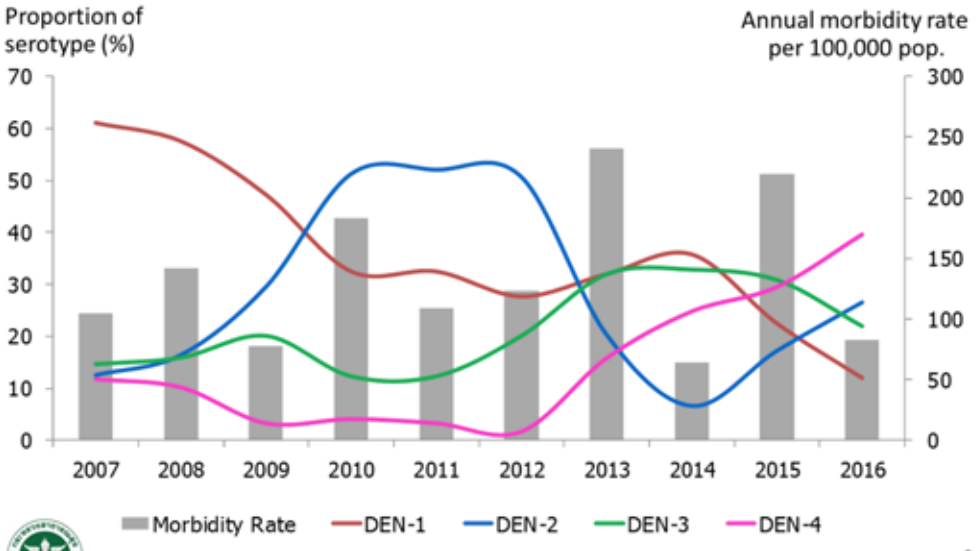
Monthly dengue cases, Thailand, 2008 - 2017

- Epidemic every other years or once every 2 – 3 years
- Strong seasonal pattern
  - 1000 – 3000 cases / month in non-rainy season
  - Can be >20,000 cases in rainy season

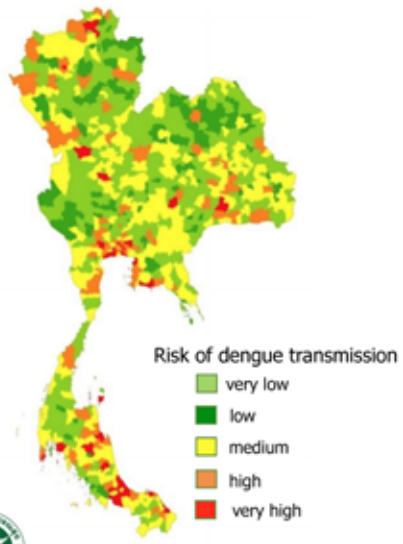


8

Proportion of dengue serotypes and morbidity rate, 2007 – 2016, Thailand

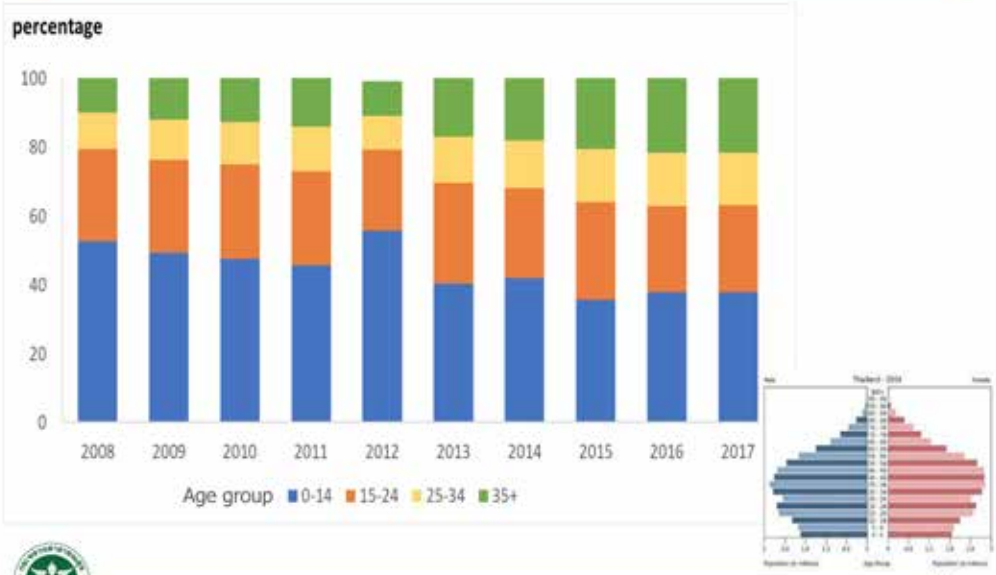


Risk of dengue transmission by district, 2013 - 2017



- Dengue spreads throughout Thailand
- 237 of 983 districts are high risk
- High dengue transmission presents in urban areas
- Bangkok and perimeter, and municipalities in the south are hyperendemic

Age distribution of dengue cases, 2008-2017



Dengue morbidity and mortality by age group, 2017

Age group (yrs)	Cases	Morbidity rate / 100,000 pop	Deaths	CFR (%)
0 – 14	20332	170.6	19	0.09
15 – 24	13140	137.5	12	0.09
25 – 34	6332	65.1	7	0.11
35 – 54	11449	54.6	27	0.24
55+	2708	18.6	6	0.22
รวม	**53961**	**97.7**	**64**	**0.13**

Characteristics of Dengue deaths in 2018

13

Dengue deaths in Thailand, 2018

- Total 18 deaths during January – April 2018
  - Serotype 1 (3 deaths)
  - Serotype 2 (3 deaths)
  - Serotype 4 (2 deaths)
  - Other 10 deaths had dengue IgM – positive or NS1 Antigen – positive without dengue PCR
- 14 deaths (78%) had underlying diseases or risky conditions
  - 4 Obesity
  - 3 DM, HT, cardiovascular diseases
  - 2 Thalassemia
  - 2 Epilepsy
  - 1 Alcoholism
  - 1 baby (5 months old)
  - 1 having menstruation

Data from dead case investigation

Dengue deaths in Thailand, 2018

- Admission diagnosis
  - 11 deaths were diagnosed dengue infection
  - 7 deaths had other disease diagnoses
    - Gastrointestinal bleeding, gastroenteritis, pneumonia, sepsis, anemia
- Causes of death
  - 10 Prolong shock and multiple organ failure
  - 6 massive bleeding with shock
  - 2 pulmonary edema

Data from dead case investigation

Dengue control

Surveillance data for disease control

Feedback to communities to raise awareness and community participation

Inform local government to accelerate outbreak response and resource mobilization

Report to executives for decision making
Alert the disease control network

Inform public about disease situations and personal protection

Community engagement

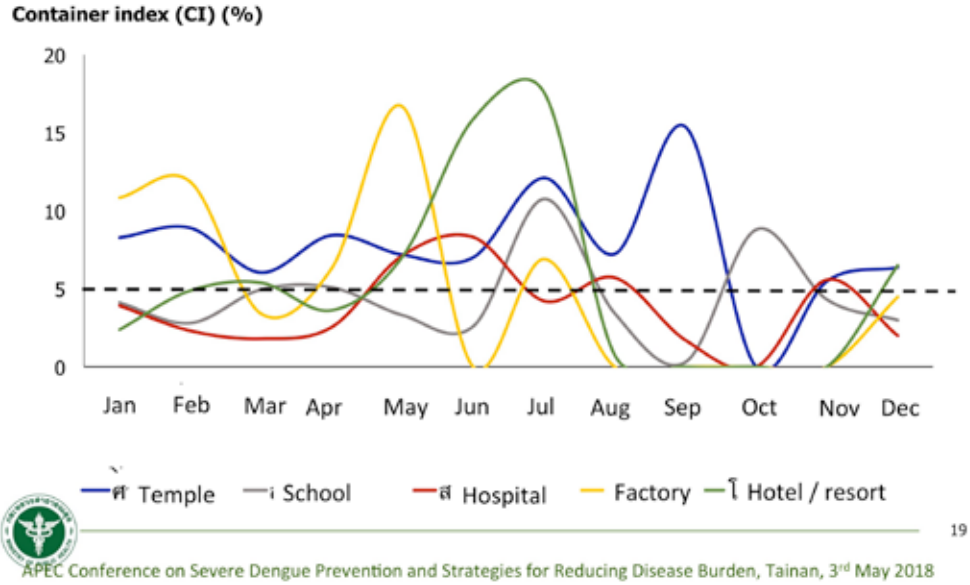
Schools: opening term

Tourist areas: resorts & hotels

Temples: Songkran & Buddhist lent day

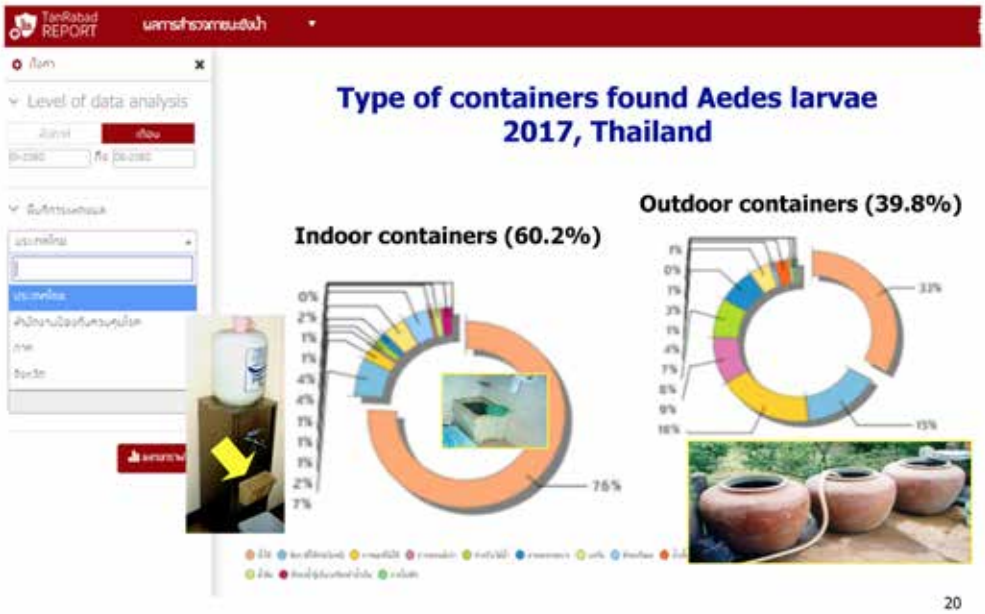
Work places

Vector control: Larva Index in public settings, 2017



19

Key containers of Aedes breeding sites



20

Conclusion and Challenges

- Dengue is an endemic disease in Thailand
- All serotypes have been circulating
- More adult dengue cases and deaths
- Vector control is ineffective in urban areas due to limitation of community engagement
- Several regulations have been developed but not seriously enforced

Speaker

Dr. Jien-Wei Liu
Position: Medical Doctor
Department / Organization: Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung
Economy: Chinese Taipei

Educational Background

- M. D., Chung Shan Medical University, Taichung, Chinese Taipei

Professional Career

- Chairman, Department of Internal Medicine (1 July, 2009–30 September, 2013), Kaohsiung Chang Gung Memorial Hospital, Chinese Taipei
- Professor (1 August, 2014–), Chang Gung University Medical College, Taoyuan, Chinese Taipei
- Chief, Division of Infectious Diseases (1 July, 1999–30 June, 2009), Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chinese Taipei

Publications

- WS Li, CH Lee, JW Liu*. Antifungal therapy did not improve outcomes including 30-day all-cause mortality in patients suffering community-acquired perforated peptic ulcer-associated peritonitis with Candida species isolated from their peritoneal fluid. Journal of Microbiology, Immunology and Infection 2017; 50: 370-376. (*Corresponding author)
- SW Ting, CH Lee, JW Liu*. Risk factors and outcomes for the acquisition of carbapenem-resistant Gram-negative bacillus bacteremia: a retrospective propensity-matched case control study. Journal of Microbiology, Immunology & Infection 2016. (In press)
- HJ Kuo, IK Lee, JW Liu*. Analyses of clinical and laboratory characteristics of dengue adults at their hospital presentations based on the World Health Organization clinical-phase framework: Emphasizing risk of severe dengue in the elderly. Journal of Microbiology, Immunology & Infection 2016. (In press).
- SY Huang, IK Lee, JW Liu, CT Kung, L Wang. Clinical features of and risk factors for rhabdomyolysis among adult patients. American Journal of Tropical Medicine & Hygiene 2015; 92: 75-81.
- CH Lee, CY Tsai, CC Li, CC Chien, JW Liu*. Teicoplanin therapy for MRSA bacteraemia: A retrospective study emphasizing the importance of maintenance dosing in improving clinical outcomes. Journal of Antimicrobial Therapy 2015; 70: 257–263. (*Corresponding author)

Speaker

Prof. Yee-Sin Leo

Position: Executive Director

Department / Organization: National Centre for Infectious Diseases

Economy: Singapore

Educational Background

- Master of Public Health, Saw Swee Hock School of Public Health, Singapore, 2013
- ISTM Certificate in Travel Health, The International Society of Travel Medicine, USA, 2012
- Fellow, Royal College of Physicians (UK), 2003
- Member, Royal College of Physicians (UK), 1989
- M.Med (Int Med), National University of Singapore, Singapore, 1989
- MBBS, National University of Singapore, Singapore, 1983

Professional Career

- **Clinical**
  - Inpatient and outpatient clinical duties at CDC-TTSH
  - Infectious Disease consultation to TTSH and other hospitals
  - Visiting Consultant to Blood Transfusion Services, Health Science Authority
  - Visiting Consultant to CIDER, NUS

- **Administrative**
  - Executive Director, National Centre for Infectious Diseases since July 2017
  - Director, Institute of Infectious Disease and Epidemiology since Nov 2012
  - Clinical Director, Communicable Disease Centre from 2003
  - Program Manager, Funding of National Disease Control Program
  - Principal Investigator for Centre Grant, Communicable Disease Centre since 2013
  - Serving multiple committees at hospital and national level
  - Serving as Expert Panel in regional / International bodies
  - Head of ID Department from 2003 to 2012 October (3 terms of 9 years)

● **Training / Teaching**

- Adjunct Professor SSH School of Public Health since 2013
- Clinical Professor Yong Loo Lin School of Medicine since 2013
- Adjunct Professor Lee Kong Chian School of Medicine since 2013
- Teaching post-graduate and under-graduate medical and nursing students, inclusive of local students
- i. Clinical Teacher in Lee Kong Chian School of Medicine 1 Dec 2016-30 June 2019
- Part-time lecturer in the Faculty of Medicine (Department of Microbiology)
- Invited speaker for talks and lectures at international conferences, workshops, etc.
- Examiner for Year 5 MBBS Summative Objective Structure Clinical Examination (OSCE) for Academic Year 2017/2018

Publications

● Antibody-mediated enhancement aggravates chikungunya virus infection and disease severity. Lum FM, Couderc T, Chia BS, Ong RY, Her Z, Chow A, Leo YS, Kam YW, Rénia L, Lecuit M, Ng LFP.

● Serum metabolome changes in adult patients with severe dengue in the critical and recovery phases of dengue infection. Cui L, Pang J, Lee YH, Ooi EE, Ong CN, Leo YS, Tannenbaum SR.

● Viral and Antibody Kinetics, and Mosquito Infectivity of an Imported Case of Zika Fever Due to Asian Genotype (American Strain) in Singapore. Tan CH, Tan LK, Hapuarachchi HC, Lai YL, Wong PSJ, Yap G, Mak KW, Wong WY, Leo YS, Wong MC, Ng LC.

● Diagnostic Accuracy of Parameters for Zika and Dengue Virus Infections, Singapore Ho HJ, Wong JGX, Mar Kyaw W, Lye DC, Leo YS, Chow A

● Progress and Challenges Towards Point-of-Care Diagnostic Development for Dengue Pang J, Chia PY, Lye DC, Leo YS

Speech Abstract

Clinical Predictors and Case Management of Severe Dengue in Singapore

Singapore, a highly developed island state situated in the tropics, has been experiencing dengue epidemic since the 60s. Although the vector index in the environment stays at very low level over past several decades because of aggressive vector control programs, the clinical cases notified to the national registry have shown a steady increase. Notably, the disease has shifted from a childhood illness to mainly an adult illness, with an increasing incidence in older adults.

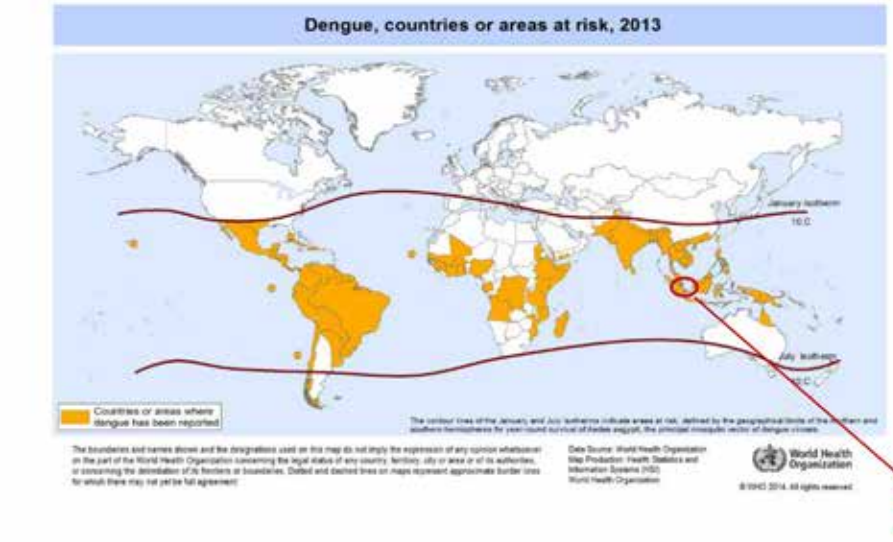
Assessing the utility of warning signs in predicting severe outcomes were done on 2 cohorts. First the retrospective study included more than 1000 records of adult cases yielded a high negative predictive value of disease progression in cases absence of any warning signs. This findings was further supported by a prospective study conducted at the Communicable Disease Centre, CDC. Older adults with dengue presented itself different set of challenges; majority of them had concomitant pre-existing medical illnesses, mortality was higher, bleeding and organ involvement were more common.

Severe dengue as classified by WHO 2009 consisted on 3 key components; severe plasma leakage, severe bleeding and severe organ involvement. Presence of any one of these constituted severe disease. Dengue is a dynamic illness, to achieve good outcome in dengue management is to start with early diagnosis, followed by close monitoring and appropriate early intervention. Cardiac suppression has been demonstrated in many studies, optimal fluid replacement is an area to research on, particularly involving patient s with pre-existing cardiac and renal illnesses.

Clinical predictors and case management of severe dengue in Singapore

National Centre for Infectious Diseases

Prof Leo Yee-Sin
Clinical Director Communicable Disease Centre CDC
Executive Director National Centre for Infectious Diseases NCID
Singapore



National Centre for Infectious Diseases

2.5 billion people -40% of world population – are at risk of dengue

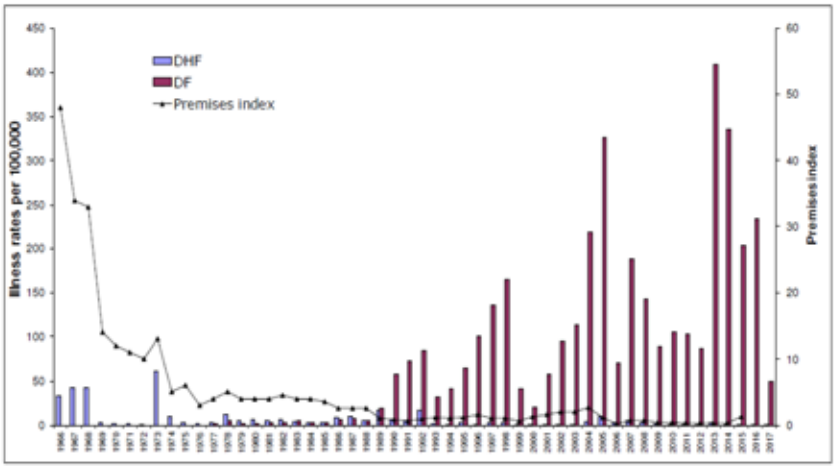
100 million dengue virus infections worldwide every year

Half a million with severe dengue

Singapore

National Centre for Infectious Diseases

Notified DF/DHF per 100,000 population and Premises Index



Despite vector control, low breeding index, Singapore faces successive waves of dengue epidemic

Predominantly adult dengue and increasingly more senior adults

Increasing recognition of atypical dengue

National Centre for Infectious Diseases

World Health Organisation 1997

It is not necessary to hospitalize all patients with suspected DHF, since shock develops in only about one-third. The finding of a continuing drop in the platelet count concurrent with a rise in the haematocrit is an important indicator of the onset of shock. So that early signs of shock can be recognized,

Indications for hospitalization

Hospitalization for bolus intravenous fluid therapy may be necessary where significant dehydration (>10% of normal body weight) has occurred and rapid volume expansion is needed. Signs of signficant dehydration include:

- Tachychardia
- Increased capillary refill time (>2s)
- Cool, mottled or pale skin
- Diminished peripheral pulses
- Changes in mental status
- Oliguria
- Sudden rise in haematocrit or continuously elevated haematocrit despite administration of fluids
- Narrowing of pulse pressure (<20 mmHg (2.7 kPa))
- Hypotension (a late finding representing uncorrected shock).

Recognition of hypovolemia

TTSH 2004 dengue cohort

National Centre for Infectious Diseases

Table 2. Significant univariate and multivariate factors associated with the development of DHF during hospitalization (DF n = 1855; DHF n=82)

	Univariate factors		Multivariate factors	
Variables	Odds Ratio	95% CI	Odds Ratio	95% CI
Presence of bleeding	40.8	24.0, 69.2	237.6	51.9, 1087.1
Rash	1.61	1.03, 2.53		
Pulse pressure, mmHg	0.98	0.95, 0.99		
Lymphocyte proportion, %	0.98	0.96, 0.99	0.94	0.89, 0.99
Platelets, $x10^3/\mu l$	0.99	0.98, 0.99		
Urea, mmol/L	1.10	1.01, 1.22	1.31	1.12, 1.55
Total protein, g/L	0.89	0.85, 0.93	0.79	0.71, 0.87
Alanine transaminase, IU/L	1.001	1.001, 1.003		
Aspartate transaminase, IU/L	1.001	1.001, 1.002		
Gamma glutamyl transpeptidase, IU/L	1.002	1.001, 1.003		

Bleeding

Lymphocyte %

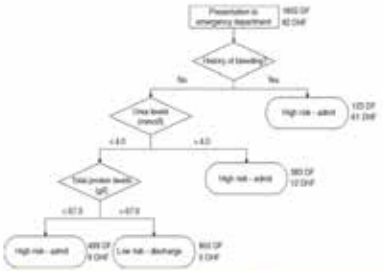
Urea

Total protein

LeeVJ et al Journal of Clinical Virology 42 (2008)34

Research to support clinical management

National Centre for Infectious Diseases



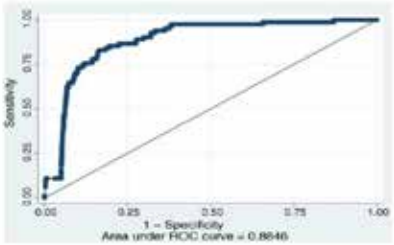


Fig. 1. Receiver-operating characteristic curve of the final multiple logistic regression model for predictors of DHF.

$$\ln\frac{p_i}{1-p_i} = 11.70 + 5.47x_{1i} - 0.24x_{2i} + 0.27x_{3i} - 0.07x_{4i}$$

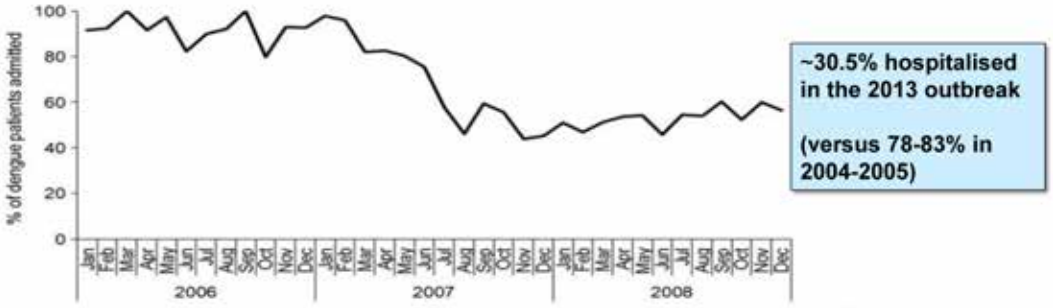
- Implemented March 2007
- New criteria:
  - *Platelet ≤50,000/mm³*
  - *Hematocrit ≥50%*
  - *BP ≤90/60 mmHg*
  - *Postural drop in BP >20mmHg*
  - *Pulse ≥100/min*
  - *Bleeding (except petechiae)*
  - *Clinically unwell status*
  - ***Fulfill predictive model(s)***

Lee, V.J. *et al. Trop. Med. Int. Health* **14**, 1154-1159 (2009).

Safety and cost savings of reducing adult dengue hospitalization in a tertiary care hospital in Singapore

National Centre for Infectious Diseases

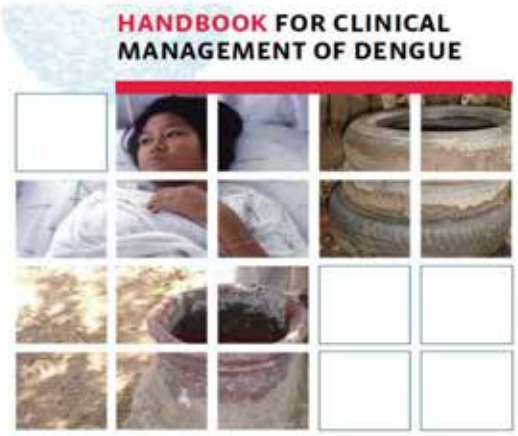
Linda K. Lee[a,*], Arul Earnest[b], Luis R. Carrasco[c], Tun L. Thein[a], Victor C. Gan[a], Vernon J. Lee[d], David C. Lye[a,d] and Yee-Sin Leo[a,d]



Trans R Soc Trop Med Hyg 2013; 107:37-42

Results: There was a 33.0% mean decrease in inpatients after the new criteria were implemented compared with the period before ($p < 0.001$). The proportion of inpatients with DHF increased significantly from 31.7% in 2006 to 34.4% in 2008 ($p = 0.008$); 68 DHF cases were managed safely on an outpatient basis after compared with none before implementation. DHF inpatients had more serious signs such as clinical fluid accumulation (15.5% vs 2.9% of outpatients), while most DHF outpatients had hypoproteinemia (92.7% vs 81.3% of inpatients). The eight intensive care unit admissions and five deaths during this time period all occurred among inpatients. The new criteria resulted in a median cost saving of US$1.4 million to patients in 2008.

National Centre for Infectious Diseases



Switzerland, 2008) agreed that 'dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome'.

Expect the unexpected
"Atypical" presentations

World Health Organization TDR for research on diseases of poverty

Dengue management

National Centre for Infectious Diseases

Enhance care at community

Primary Care

Febrile phase

- **Early recognition / suspicion of dengue**
- **POCT / rapid combined Ag/Abs**
- **Daily monitoring**
- **Early recognition of warning signs**

Admission criteria

Secondary Care Hospitalization — **Hospitalisation**

Critical phase

- Adequate trained staff
- Lab support
- Adequate consumables

Fluid management

Tertiary Care ICU

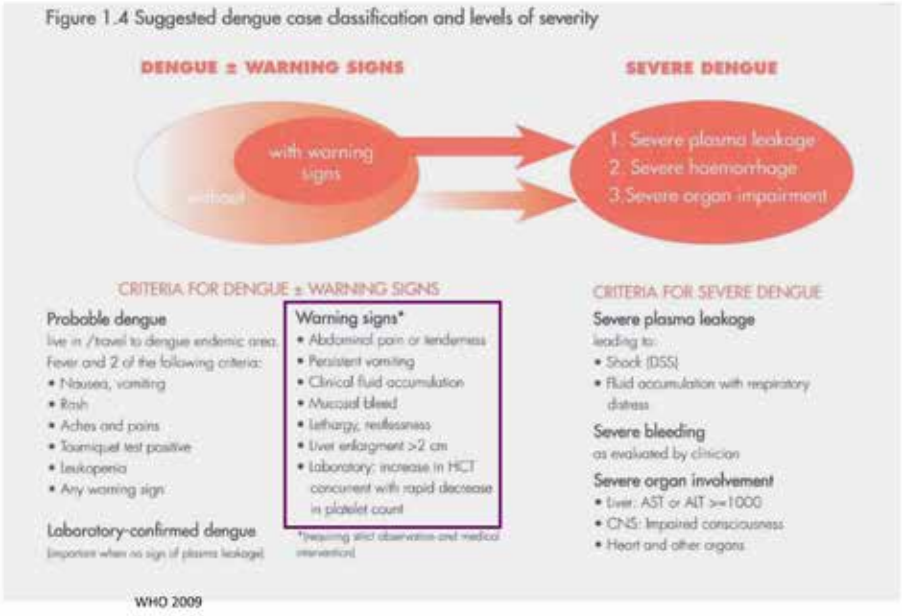
Specialized dengue care unit

Final Outcome

Recovery

WHO 2009

National Centre for Infectious Diseases



Utilities and Limitations of the World Health Organization 2009 Warning Signs for Adult Dengue Severity

Tun-Linn Thein[1,2*], Victor C. Gan[1,2], David C. Lye[1,2], Chee-Fu Yung[1], Yee-Sin Leo[1,2]

National Centre for Infectious Diseases

Table 3. Performance of warning signs (WS) for predicting dengue hemorrhagic fever (DHF) (n = 1507).

PLOS NTD 2013;7:e2023

Warning signs	Sn	Sp	PPV	NPV
Individual WS				
Abdominal pain or tenderness	0.29	0.73	0.17	0.85
Persistent vomiting	0.06	0.93	0.16	0.82
Hepatomegaly	0.01	0.99	0.20	0.81
Hematocrit rise and rapid platelet count drop	0.09	0.92	0.17	0.83
Clinical fluid accumulation	0.02	0.98	0.18	0.83
Mucosal bleeding	0.42	0.88	0.31	0.93
Lethargy*	0.33	0.55	0.28	0.61
WS count*				
Any number of seven WS*	0.87	0.18	0.30	0.77
Any number of six WS (without lethargy)	0.81	0.57	0.19	0.96
One WS	0.64	0.70	0.18	0.95
Two WS	0.44	0.89	0.25	0.95
Three WS	0.21	0.96	0.27	0.95
Four WS	0.04	0.98	0.14	0.94

Predicting DHF

NPV 0.96 in the absence of any WS

> 3 WS specific but not sensitive

Utilities and Limitations of the World Health Organization 2009 Warning Signs for Adult Dengue Severity

Tun-Linn Thein[1,2*], Victor C. Gan[1,2], David C. Lye[1,2], Chee-Fu Yung[1], Yee-Sin Leo[1,2]

National Centre for Infectious Diseases

Table 4. Performance of warning signs (WS) for predicting severe dengue (SD) (n = 1507).

Warning signs	Sn	Sp	PPV	NPV
Individual WS				
Abdominal pain or tenderness	0.21	0.72	0.09	0.87
Persistent vomiting	0.08	0.93	0.18	0.85
Hepatomegaly	0.00	0.99	0.06	0.84
Hematocrit rise and rapid platelet count drop	0.05	0.94	0.09	0.89
Clinical fluid accumulation	0.02	0.98	0.16	0.87
Mucosal bleeding	0.17	0.82	0.10	0.89
Lethargy*	0.34	0.56	0.17	0.76
WS count*				
Any number of seven WS*	0.96	0.18	0.15	0.96
Any number f six WS (without lethargy)	0.71	0.55	0.10	0.97
One WS	0.58	0.69	0.12	0.96
Two WS	0.32	0.88	0.12	0.96
Three WS	0.15	0.95	0.12	0.96
Four WS	0.04	0.98	0.25	0.96
Five WS	0.02	1.00	0.09	0.96

Predicting severe dengue

NPV 0.97 in the absence of any WS

PLOS NTD 2013;7:e2023

RESEARCH ARTICLE Open Access

Utility of warning signs in guiding admission and predicting severe disease in adult dengue

Yee-Sin Leo[1,2,3*], Victor C Gan[1], Ee-Ling Ng[1], Ying Hao[1], Lee-Ching Ng[4], Kwoon-Yong Pok[4], Federico Dimatatac[1], Chi-Jong Go[1] and David C Lye[1,5]

National Centre for Infectious Diseases

Prospective study

Enrolment site: Communicable Disease Centre, CDC

Jan 2010 to Sept 2012

Include outpatients and inpatients (2 cohorts: emergency dept ED and Outpatient cohort)

Febrile, > 18 years old

Confirmed dengue by PCR and NS1 (WHO standard)

Leo *et al. BMC Infectious Diseases* 2013, **13**:498

Dengue research Clinic managed by 3 well-trained Medical officers

RESEARCH ARTICLE Open Access

Utility of warning signs in guiding admission and predicting severe disease in adult dengue

Yee-Sin Leo[1,2,3*], Victor C Gan[1], Ee-Ling Ng[1], Ying Hao[1], Lee-Ching Ng[4], Kwoon-Yong Pok[4], Federico Dimatatac[1], Chi-Jong Go[1] and David C Lye[1,5]

National Centre for Infectious Diseases

BMC Infectious Diseases

Table 4 Performance of individual warning signs in predicting DHF and SD in outpatients

Warning sign	DHF I-IV (N = 70)				DHF II-IV (N = 43)				SD (N = 13)			
	Sn	Sp	PPV	NPV	Sn	Sp	PPV	NPV	Sn	Sp	PPV	NPV
Abdominal pain (N = 88)	31	78	25	83	37	78	18	91	38	77	6	97
Persistent vomiting (N = 16)	7	96	31	82	9	96	25	89	23	96	19	97
Clinical fluid accumulation (N = 1)	1	100	100	82	0	100	0	89	0	100	0	97
Mucosal bleeding (N = 154)	61	64	28	88	100	67	28	100	62	60	5	98
Hepatomegaly (> 2 cm) (N = 2)	1	100	50	82	0	99	0	89	0	99	0	97
↑ in hematocrit; rapid ↓ of platelet (N = 10)	14	100	100	84	9	98	40	89	31	98	40	98
Any warning sign (N = 203)	79	52	27	91	100	52	21	100	100	48	6	100
Two warning signs (N = 61)	33	88	38	85	47	88	33	93	46	85	10	98
Three warning signs (N = 7)	6	99	57	82	9	99	57	89	8	98	14	97

Leo *et al. BMC Infectious Diseases* 2013, **13**:498

Mucosal bleeding the most common WS

NPV for severe disease in absence of any WS was 100%

RESEARCH ARTICLE Open Access

Utility of warning signs in guiding admission and predicting severe disease in adult dengue

Yee-Sin Leo[1,2,3*], Victor C Gan[1], Ee-Ling Ng[1], Ying Hao[1], Lee-Ching Ng[4], Kwoon-Yong Pok[4], Federico Dimatatac[1], Chi-Jong Go[1] and David C Lye[1,3]

National Centre for Infectious Diseases

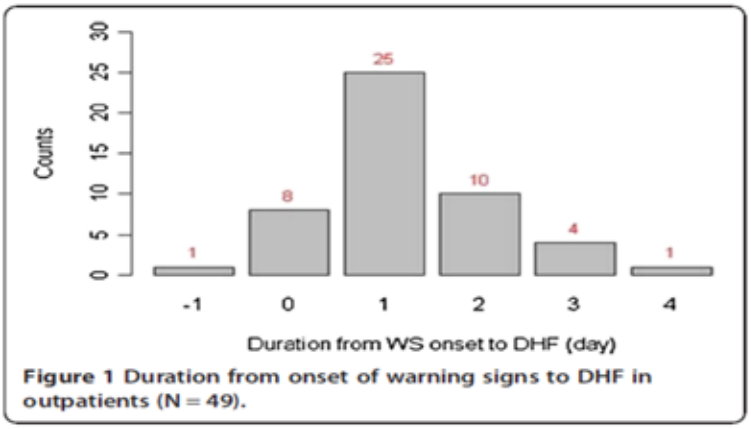


Figure 1 Duration from onset of warning signs to DHF in outpatients (N = 49).

Majority had WS 1 day prior to onset of severe illness

Leo *et al. BMC Infectious Diseases* 2013, **13**:498

RESEARCH ARTICLE Open Access

Utility of warning signs in guiding admission and predicting severe disease in adult dengue

Yee-Sin Leo[1,2,3*], Victor C Gan[1], Ee-Ling Ng[1], Ying Hao[1], Lee-Ching Ng[4], Kwoon-Yong Pok[4], Federico Dimatatac[1], Chi-Jong Go[1] and David C Lye[1,3]

National Centre for Infectious Diseases

BMC Infectious Diseases

Table 4 Performance of individual warning signs in predicting DHF and SD in outpatients

Warning sign	DHF I-IV (N = 70)				DHF II-IV (N = 43)				SD (N = 13)			
	Sn	Sp	PPV	NPV	Sn	Sp	PPV	NPV	Sn	Sp	PPV	NPV
Abdominal pain (N = 88)	31	78	25	83	37	78	18	91	38	77	6	97
Persistent vomiting (N = 16)	7	96	31	82	9	96	25	89	23	96	19	97
Clinical fluid accumulation (N = 1)	1	100	100	82	0	100	0	89	0	100	0	97
Mucosal bleeding (N = 154)	61	64	28	88	100	67	28	100	62	60	5	98
Hepatomegaly (> 2 cm) (N = 2)	1	100	50	82	0	99	0	89	0	99	0	97
↑ in hematocrit; rapid ↓ of platelet (N = 10)	14	100	100	84	9	98	40	89	31	98	40	98
Any warning sign (N = 203)	79	52	27	91	100	52	21	100	100	48	6	100
Two warning signs (N = 61)	33	88	38	85	47	88	33	93	46	85	10	98
Three warning signs (N = 7)	6	99	57	82	9	99	57	89	8	98	14	97

Leo *et al. BMC Infectious Diseases* 2013, **13**:498

Mucosal bleeding the most common WS

NPV for severe disease in the absence of any WS was 100%

RESEARCH ARTICLE Open Access

Utility of warning signs in guiding admission and predicting severe disease in adult dengue

Yee-Sin Leo[1,2,3*], Victor C Gan[1], Ee-Ling Ng[1], Ying Hao[1], Lee-Ching Ng[4], Kwoon-Yong Pok[4], Federico Dimatatac[1], Chi-Jong Go[1] and David C Lye[1,5]

National Centre for Infectious Diseases

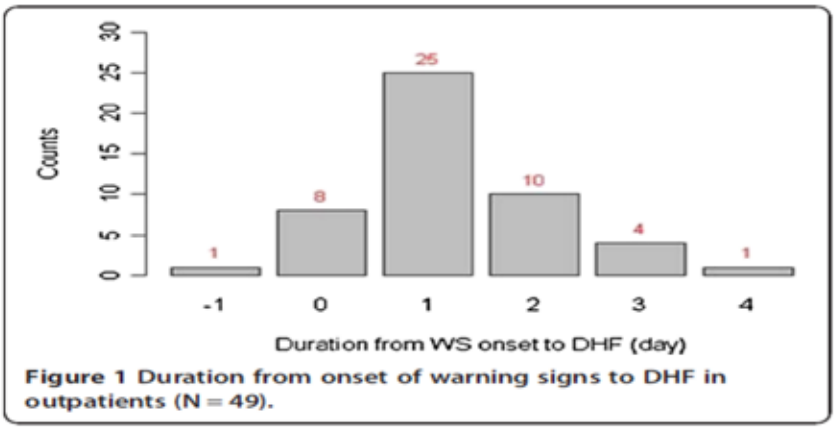


Figure 1 Duration from onset of warning signs to DHF in outpatients (N = 49).

Majority had WS 1 day prior to onset of severe illness

Leo *et al. BMC Infectious Diseases* 2013, 13:498

Capillary permeability, age and DHF

National Centre for Infectious Diseases

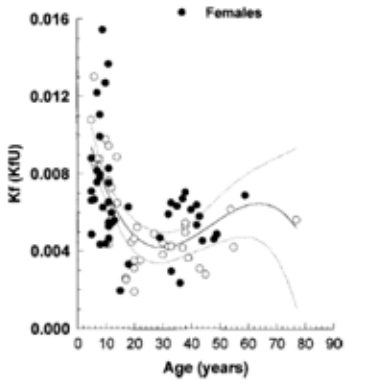


Figure 3 K_f **data obtained from 89 healthy Vietnamese volunteers aged 5 to 77 years**

Gamble Clin Science 2000; 98: 211-16

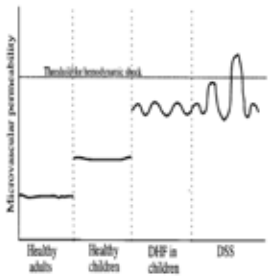
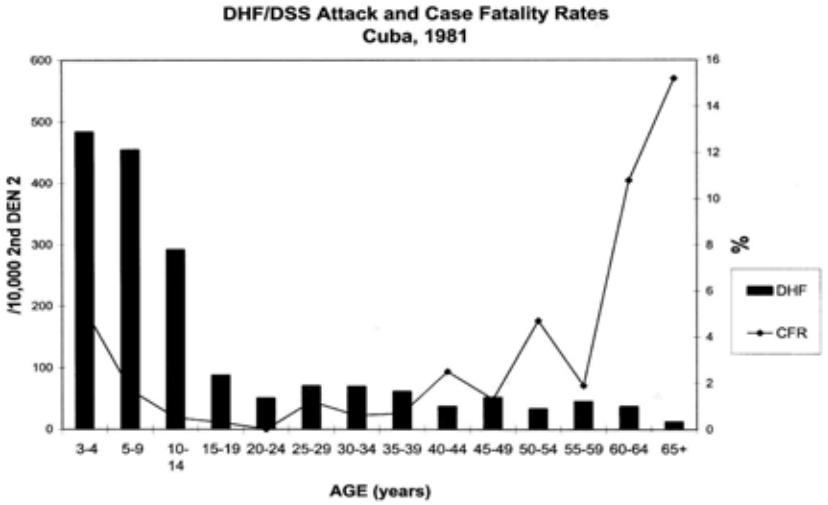


Figure 4. Hypothetical patterns of microvascular permeability with time for uninfected adults, uninfected children, and children with dengue hemorrhagic fever (DHF) with and without hemodynamic shock.

Bethell CID 2001; 32: 243-53

DHF – age in 2º Infection, 1981 Cuba Outbreak

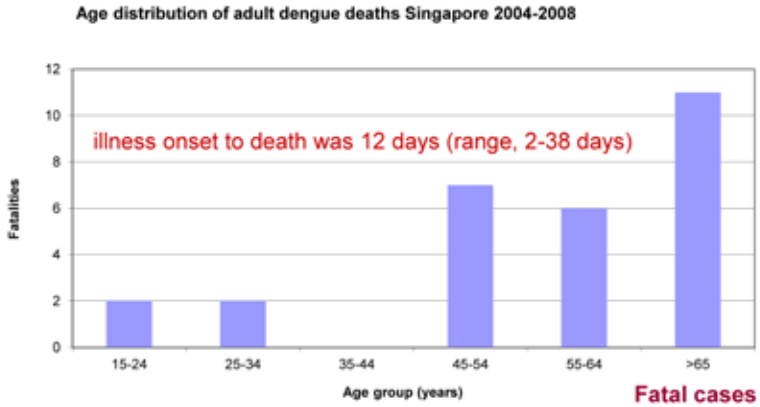
National Centre for Infectious Diseases



Guzman IJID 2002; 6:118

Retrospective dengue mortality study 2004-2008 Singapore

National Centre for Infectious Diseases



5 public hospitals

N=28

PCR / NS1 +v

Probable Dengue in 32.1% (Sensitivity) – WHO 1997
Probable Dengue in 78.6% (Sensitivity) – WHO 2009

96.4% had at least one warning sign

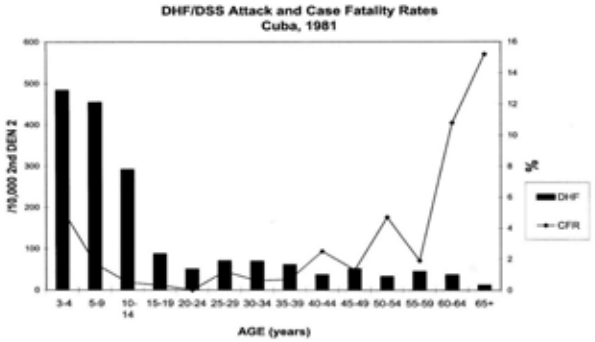
Fatal cases mostly involved older adults

Median age 59

3 out of 4 had co-morbidity

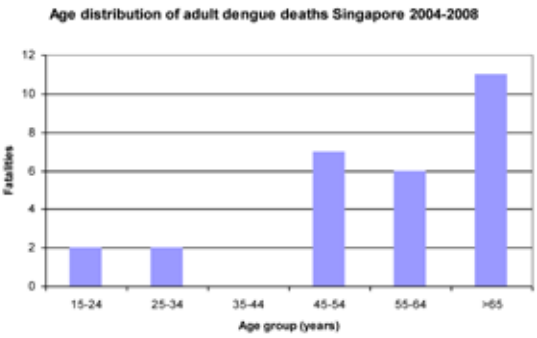
Leo YS et al. BMC ID 2011;11:123

National Centre for Infectious Diseases



DHF – age in 2º Infection, 1981 Cuba Outbreak

Guzman IJID 2002;6:118



Confirmed adult dengue deaths in Singapore: 5-year multi-center retrospective study

Leo YS et al. BMC ID 2011;11:123

Older adults with dengue have more atypical presentations, more organ involvement, more pre-existing comorbidities, higher mortality, require higher index of suspicion to diagnose, closer monitoring and careful management

Dengue-Related Deaths in Puerto Rico, 1992–1996: Diagnosis and Clinical Alarm Signals

National Centre for Infectious Diseases

Jose G. Rigau-Pérez[a] and Miriam K. Laufer[a]

Table 2. Frequency and onset of clinical alarm signals for impending dengue shock in patients with fatal cases of dengue, Puerto Rico, 1992–1996.

Clinical alarm signal	Patients with clinical alarm signal, by laboratory test results for dengue: Negative — Proportion of patients	Negative — Percentage (95% CI)	Positive — Proportion of patients	Positive — Percentage (95% CI)	Time from clinical alarm signal to deterioration of the patient's condition, median days (range)
Severe abdominal pain	0/8	0 (0–37)	6/23	26 (10–48)	0 (0–1)
Persistent vomiting	0/8	0 (0–37)	3/23	13 (3–34)	0 (0–4)
Abrupt change in temperature	0/8	0 (0–37)	1/23	4 (0.1–22)	0
Abnormal mental status[a]					
At admission	0/8	0 (0–37)	4/23	17 (5–39)	0 (0–2)
Shortly before death	5/8	62 (24–91)	15/22[b]	68 (45–86)	…

[a] Disoriented, combative, or obtunded.
[b] One patient was sedated for mechanical ventilation, and mental status was not evaluable.

16/23 (75%) had co-morbidities

Signals usually noted on the day of deterioration.

Clinical Infectious Diseases 2006; 42:1241–6

Assessment of Microalbuminuria for Early Diagnosis and Risk Prediction in Dengue Infections

Nguyen Thi Hanh Tien[1], Phung Khanh Lam[1], Huynh Thi Le Duyen[1], Tran Van Ngoc[3], Phan Thi Thanh Ha[4], Nguyen Tan Thanh Kieu[1], Cameron Simmons[1,2], Marcel Wolbers[1,2], Bridget Wills[1,2]*

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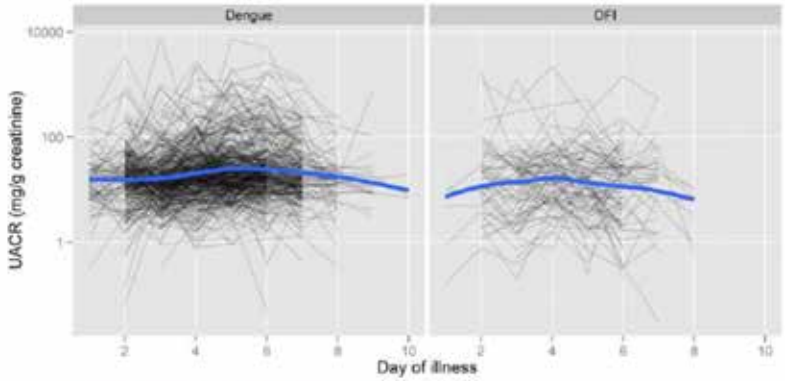


Considerable within-patient variation

Higher UACR values in dengue cases

Peak UACR values for dengue cases observed around day 5

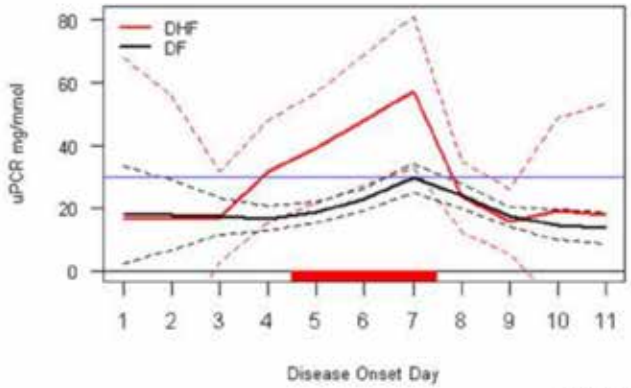
OPEN ACCESS Freely available online

PLOS

Predictive Value of Proteinuria in Adult Dengue Severity

Farhad F. Vasanwala[1,3], Tun-Linn Thein[2,3], Yee-Sin Leo[2,3,4]*, Victor C. Gan[2], Ying Hao[2], Linda K. Lee[2], David C. Lye[2,3]

National Centre for Infectious Diseases



PADS prospective study

168 dengue cases

34 DHF

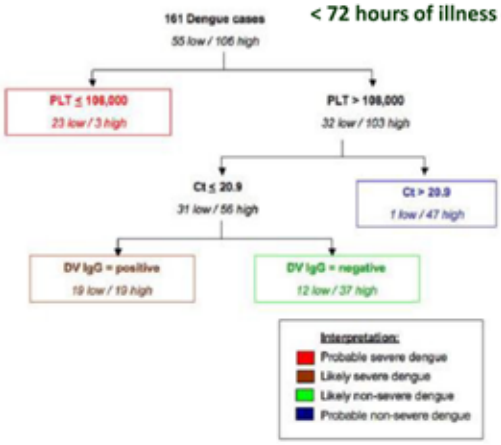
Decision Tree Algorithms Predict the Diagnosis and Outcome of Dengue Fever in the Early Phase of Illness

Lukas Tanner[1*], Mark Schreiber[1*], Jenny G. H. Low[2], Adrian Ong[2], Thomas Tolfvenstam[3], Yee Ling Lai[4], Lee Ching Ng[4], Yee Sin Leo[2], Le Thi Puong[5], Subhash G. Vasudevan[1], Cameron P. Simmons[6], Martin L. Hibberd[3], Eng Eong Ooi[7*]

National Centre for Infectious Diseases

< 72 hours of illness onset

PLOS NTD 2008;2:e196



Decision Node Feature	OR	95% CI (OR)	p value
Platelet count ≤ 108,000/mm³	24.7	20.9, 29.2	< 0.001
Ct ≤ 20.9	26.0	18.0, 37.5	< 0.001
DV IgG = positive	3.1	2.0, 4.8	< 0.05

Severity

-Platelet nadir <50,000/ul

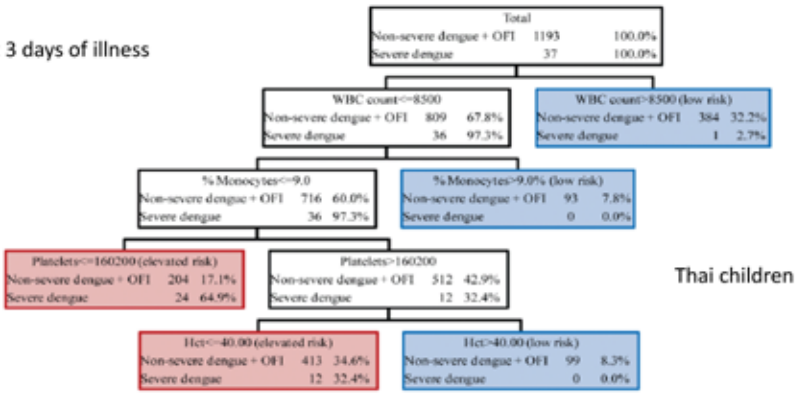
- hospitalized

Prediction of Dengue Disease Severity among Pediatric Thai Patients Using Early Clinical Laboratory Indicators

James A. Potts[1], Robert V. Gibbons[2], Alan L. Rothman[1], Anon Srikiatkhachorn[1], Stephen J. Thomas[2], Pra-on Supradish[3], Stephenie C. Lemon[4], Daniel H. Libraty[1], Sharone Green[1*], Siripen Kalayanarooj[3]

National Centre for Infectious Diseases

First 3 days of illness



Thai children

Figure 1. CART algorithm #1 for identifying patients who subsequently developed severe dengue (defined as WHO criteria for dengue shock syndrome, DSS) using clinical laboratory data obtained within the first three days of illness. Each node is shown with the selected splitting variable, the number of patients with severe/non-severe or OFI, and the proportion of each from the parent node. Terminal nodes are marked as 'elevated risk' of severe dengue illness, outlined in red, and 'low risk' of severe dengue, outlined in blue.

Potts, et al. PLOS NTD 2010;4:e769

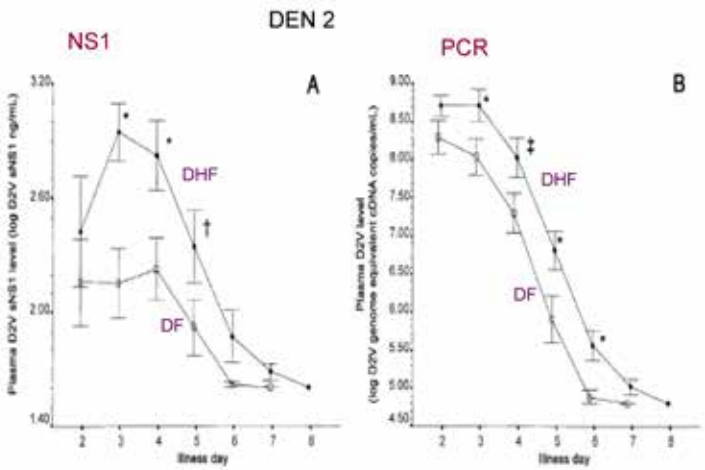


Figure 1. Plasma levels of free dengue-2 virus (D2V) secreted NS1 (sNS1) protein (*A*) and dengue-2 viral RNA (*B*) by day of illness in children with secondary D2V infections and dengue hemorrhagic fever (n = 18; ♦) or dengue fever (DF; n = 14; ○). Data are mean ± SE. **P* < .05, †*P* = .10, and ‡*P* = .06, all vs. DF.

Libraty DH et al. JID 2002;186:1165-8

National Centre for Infectious Diseases

ULTRASOUND MEASUREMENT OF GALLBLADDER WALL THICKENING AS A DIAGNOSTIC TEST AND PROGNOSTIC INDICATOR FOR SEVERE DENGUE IN PEDIATRIC PATIENTS

James A. Colbert, BA, Aubree Gordon, MA, MPH,† Rigoberto Roxelin, MD,‡ Sheyla Silva, MD,‡ Javier Silva, MD,‡ Crisanta Rocha, MD,‡ and Eva Harris, PhD†*

The Pediatric Infectious Disease Journal • Volume 26, Number 9, September 2007

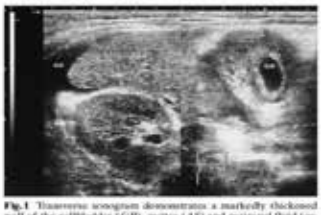


Fig. 1 Transverse sonogram demonstrates a markedly thickened wall of the gallbladder (*GB*), ascites (*AS*) and perirenal fluid (arrows). *RLL* right liver lobe, *RK* right kidney.

Melani W. Setiawan
Tatang K. Sunsi
Hanna Wulur
Djoharman Sugianto
Thomas N. Pool

Dengue haemorrhagic fever: ultrasound as an aid to predict the severity of the disease

Pediatr Radiol (1998) 28: 1–4

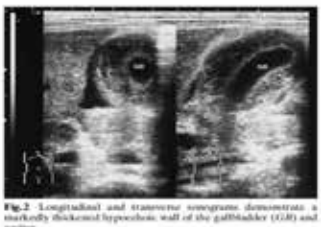


Fig. 2 Longitudinal and transverse sonograms demonstrate a markedly thickened hypoechoic wall of the gallbladder (*GB*) and ascites

The Predictive Diagnostic Value of Serial Daily Bedside Ultrasonography for Severe Dengue in Indonesian Adults

Meta Michels[1,*], Uun Sumardi[2], Quirijn de Mast[1], Hadi Jusuf[2], Mita Puspita[2], Intan Mauli Warma Dewi[2], Sylvia Sinarta[2], Bachti Alisjahbana[2], André J. A. M. van der Ven[1]

PLOS Neglected Tropical Diseases June 2013 | Volume 7 | Issue 6 | e2277

National Centre for Infectious Diseases

Association Between Increased Vascular Nitric Oxide Bioavailability and Progression to Dengue Hemorrhagic Fever in Adults

Tun-Linn Thein,[1] Joshua Wong,[1] Yee-Sin Lee,[1,2,3] Eng-Eong Ooi,[4] David Lye,[1,2] and Tsin W. Yeo[1,2]

The Journal of Infectious Diseases®

可测量血管扩张能力

心疾仪器或成检测骨痛溢血热症新指标

Blood vessel link to severe dengue

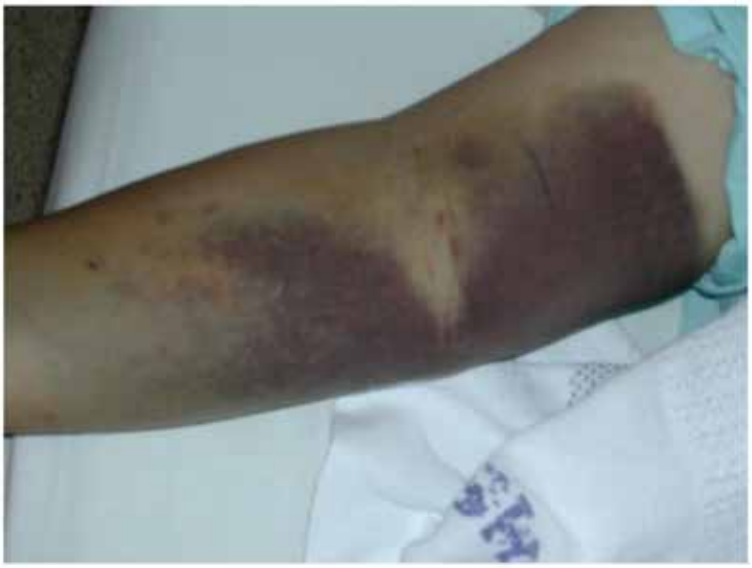
Patients with healthy vessels 'more likely to get serious form of disease'

Table 2. Multivariate Cox Regression Model Used to Predict Dengue Hemorrhagic Fever

Variable	Adjusted OR (95% CI)	*P* Value[a]
RHI at enrollment	4.15 (1.32–13.03)	.02
Fever day at enrollment	0.73 (.48–1.09)	.12
Age	1.03 (.94–1.14)	.52
BMI	1.03 (.68–1.56)	.90

Non-invasive technique to predict dengue severity

National Centre for Infectious Diseases



Bleeding in dengue fever

Percentage of Admissions & Number of Local Death Cases due to Dengue (2003 – 2014*)

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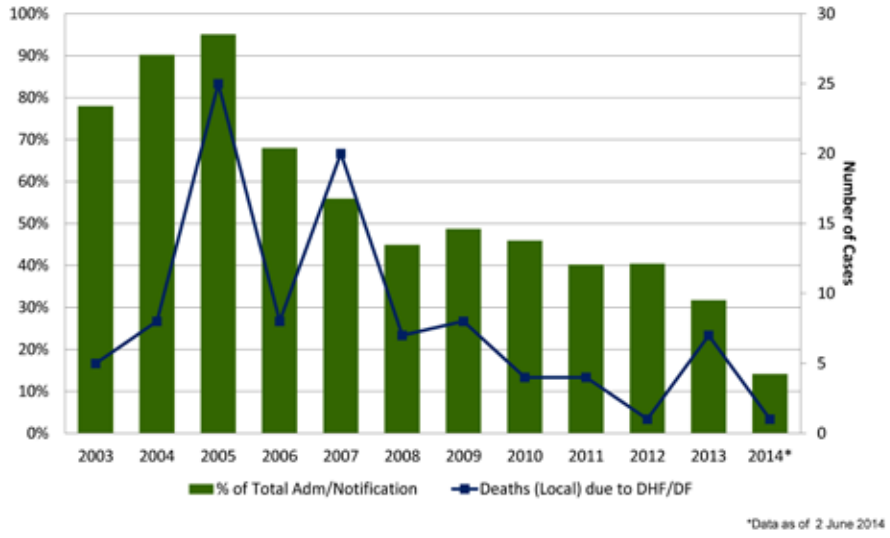

*Data as of 2 June 2014

No dengue mortality – a necessary stretch goal

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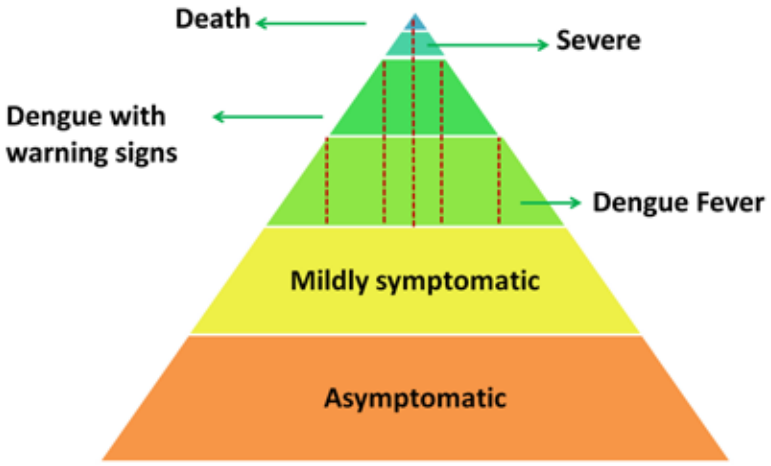

National Centre for Infectious Diseases

NCID – functionally go-live in April 2018

Building ready in 2018-2019

Welcome to NCID Singapore

CHI
9-storey educational and training building

NCID
14-storey clinical building
330 beds

4 basements with 850 car park lots
Food and retail outlets

Session II

Dengue Vaccine

Moderator

Duane J Gubler

Emeritus Professor, Emerging Infectious Diseases, Duke-NUS Medical School, Singapore / Adjunct Professor, International Health, Johns Hopkins School of Hygiene and Public Health / Adjunct Professor, Infectious Diseases, Duke University Medical School, The United States

Moderator

Prof. Duane J Gubler

Position: Emeritus Professor / Adjunct Professor
Department / Organization: Emerging Infectious Diseases, Duke-NUS Medical School, Singapore / International Health, Johns Hopkins School of Hygiene and Public Health / Infectious Diseases, Duke University Medical School
Economy: The United States

Biography

Dr Duane J Gubler, ScD, FAAAS, FIDSA, FASTMH, is Emeritus 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, the Duke University School of Medicine and Duke Global Health Institute. He has spent his entire career working on tropical infectious diseases with an emphasis on dengue and other Aedes-transmitted diseases. He has extensive field experience in Asia, the Pacific, tropical America and Africa, and has published extensively on all aspects of dengue and other vector-borne infectious diseases, with over 350 publications and 2 books to his credit. 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, CDC in Fort Collins, Colorado for 15 years and Chair, Department of Tropical Medicine, Medical Microbiology and Pharmacology, University of Hawaii School of Medicine, in Honolulu for 5 years. He has and continues to serve on numerous WHO, national and international committees and study groups, and on the Scientific Advisory Boards of a number of companies and institutions. Prof Gubler was founding Chair, Board of Councillors, Pediatric Dengue Vaccine Initiative in Seoul, Korea, founding Chair, Partnership for Dengue Control in Lyon, France, and the Global Dengue and Aedes-transmitted Diseases Consortium in Seoul, Korea, for which he currently serves as Chairman. Prof Gubler is a Fellow, Infectious Disease Society of America, Fellow, American Association for the Advancement of Science, and Fellow and Past President of the American Society of Tropical Medicine and Hygiene.

Publications

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- Musso, D, Rodriguez-Morales, AJ, Levi, JE, Lormeau, VMC, Gubler, DJ. 2018. Re-cent Arboviral Black Swan Events: Lessons Learned from the Pacific and Tropical America, Lancet Infect. Dis, In Press.
- Kuno, G, Mackenzie, JS, Junglen, S, Hubálek, Z, Plyusnin, A, and Gubler, DJ. 2017. Vertebrate Reservoirs of Arboviruses: Myth, Synonym of Amplifier, or Reality? Viruses, 9, 185; doi:10.3390/v9070185
- Gubler, DJ, Vasilakis, N, and Musso, D. 2017.History and Emergence of Zika Virus, JID 2017:216 (Suppl 10).

NOTE

Session II

Dengue Vaccine

Speaker

In-Kyu Yoon
Director, Global Dengue & Aedes-Transmitted Diseases Consortium (GDAC), International Vaccine Institute, Republic of Korea

Stephen Whitehead

Senior Associate Scientist, Laboratory of Infectious Diseases, NIAID, NIH, The United States

Anna Durbin
Professor, Johns Hopkins Bloomberg School of Public Health, The United States

Michael Malison
Adjunct Professor, Department of International Health, Rollins School of Public Health, Emory University, The United States

Ta-Wen Yu
Regional Medical Head, Regional Medical Affairs, Sanofi Pasteur, Singapore

Speaker

Dr. In-Kyu Yoon

Position: Director

Department / Organization: Global Dengue & Aedes-Transmitted Diseases Consortium (GDAC), International Vaccine Institute

Economy: Republic of Korea

Educational Background

- Fellowship, Allergy-Immunology, Walter Reed Army Medical Center, Washington, DC, USA (Jul 2004 - Jun 2006)
- Internship and Residency, Internal Medicine, Walter Reed Army Medical Center, Washington, DC, USA (Jul 1993 - Jun 1996)
- Doctor of Medicine (MD), New York University School of Medicine, New York, NY, USA (Aug 1989 - May 1993)
- Bachelor of Science (BS), Paleobiology, Yale University, New Haven, CT, USA (Aug 1984 - May 1988)

Professional Career

- Director, Dengue and MERS Programs, International Vaccine Institute (IVI), Seoul, Korea (Aug 2017 – current)
- Deputy Director General of Science, IVI, Seoul, Korea (Nov 2015 - Jul 2017)
- Chief, Virology, Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand (Aug 2012 - Jul 2015)
- Deputy Chief and Director of Field Operations, Virology, AFRIMS, Bangkok, Thailand (Jul 2006 - Jul 2012)
- Clinical Investigator, Walter Reed Army Institute of Research, Silver Spring, MD, USA (Nov 2002 - Jun 2004)
- Medical Director, Primary Care Associates, Portsmouth Regional Hospital, Portsmouth, NH, USA (May 2001 - Oct 2002)
- Attending Physician, Portsmouth Regional Hospital, Portsmouth, NH, USA (Oct 2000 - Oct 2002)
- Attending Physician, Munson Army Health Center, Fort Leavenworth, KS, USA (Sep 1999 - Sep 2000)
- Chief, Internal Medicine Service, 121st General Hospital, US Army, Seoul, Korea (Jul 1997 - Aug 1999)
- Attending Physician, 121st General Hospital, US Army, Seoul, Korea (Aug 1996 - Aug 1999)

Publications

- Yoon IK, Thomas SJ. Encouraging results but questions remain for dengue vaccine. Lancet Infect Dis. 2018 Feb;18(2):125-126
- Lim SK, Lim JK, Yoon IK. An Update on Zika Virus in Asia. Infect Chemother. 2017 Jun;49(2): 91-100.
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- Salje H, Lessler J, Maljkovic Berry I, Melendrez M, Endy T, Kalanarooj S, A-Nuegoonpipat A, Chanama S, Sangkijporn S, Klungthong C, Thaisomboonsuk B, Nisalak A, Gibbons RV, Iamsirithaworn S, Macareo L, Yoon IK, Sangarsang A, Jarman R, Cummings D. Dengue diversity across spatial and temporal scales: local structure and the impact of host population size. Science 2017 Mar 24;355(6331):1302-6.
- Hunsawong T, Wichit S, Phonpakobsin T, Poolpanichupatam Y, Klungthong C, Latthiwongsakorn N, Thaisomboonsuk B, Im-Erbsin R, Yoon IK, Ellison DW, Macareo LR, Srikiatkhachorn A, Gibbons RV, Fernandez S. Polytopic vaccination with a live-attenuated dengue vaccine enhances B-cell and T-cell activation, but not neutralizing antibodies. Heliyon 2017 Mar 21;3(3):e00271.

Speech Abstract

Dengue Vaccine: Current Situation and Public Health Impact

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 urban centers result in significant morbidity and mortality, along with a break down in primary health care as hospitals and clinics become overloaded. The disease thus imposes significant economic and public health costs in endemic countries. Despite public health efforts to control the disease in the past 50 years, dengue epidemics have increased in frequency and magnitude as both the mosquito vectors and the viruses have continued to expand their geographic distributions. Recent advances in dengue research have resulted in development of new tools that show promise for use in dengue prevention and control. These include vaccines, such as Sanofi Pasteur's recently licensed Dengvaxia® (or CYD-TDV), and six other dengue vaccines in various phases of human clinical trials. Dengvaxia® is a tetravalent live attenuated chimeric vaccine consisting of a 17D yellow fever backbone with dengue virus (DENV) pre-membrane and envelope proteins from the four different DENV serotypes. Dengvaxia® has undergone phase III clinical trials in Asia and Latin America, demonstrating good efficacy against serotypes 3 and 4, and lower efficacy against serotypes 1 and 2. Notably, an increased risk of dengue hospitalization was seen in vaccinated children aged 2-5 years during the third year of the Asian phase III trial, leading to an age indication of 9-45 years old (or 9-60 years old depending on the country) in the 20 countries where the vaccine has been registered. In November 2017, Sanofi Pasteur announced that individuals of any age without evidence of prior dengue infection had an increased risk of hospitalized and severe dengue from natural infection after receiving Dengvaxia®. As a result, in April 2018, WHO SAGE recommended an update to the existing WHO recommendations, emphasizing the role of direct testing of potential Dengvaxia® recipients prior to vaccine administration. The experience with Dengvaxia® has led to key lessons learned, which are being noted by other vaccine developers. These lessons include the need to address the possibility of vaccine-induced disease enhancement. Two dengue vaccine candidates are currently in 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 of three serotypes, while the fourth serotype consists of a DENV-DENV chimera. The Butantan Institute, which is the sponsor of Butantan-DV (TV003) in Brazil, received regulatory approval in December 2015 to begin a phase III trial in Brazil. These efforts are being driven by the large potential public health impact of even moderately effective dengue vaccines, as long as the possible risk of enhancement is adequately addressed.

Dengue vaccines: Current situation and public health impact

In-Kyu Yoon, M.D.
Director, GDAC
International Vaccine Institute
3 May 2018

DENGUE VACCINE INITIATIVE + PDC PARTNERSHIP FOR DENGUE CONTROL = gdac GLOBAL DENGUE+AEDES-TRANSMITTED DISEASES CONSORTIUM

Mission: To promote the development and implementation of innovative and synergistic approaches for prevention and control of dengue and other Aedes-transmitted diseases

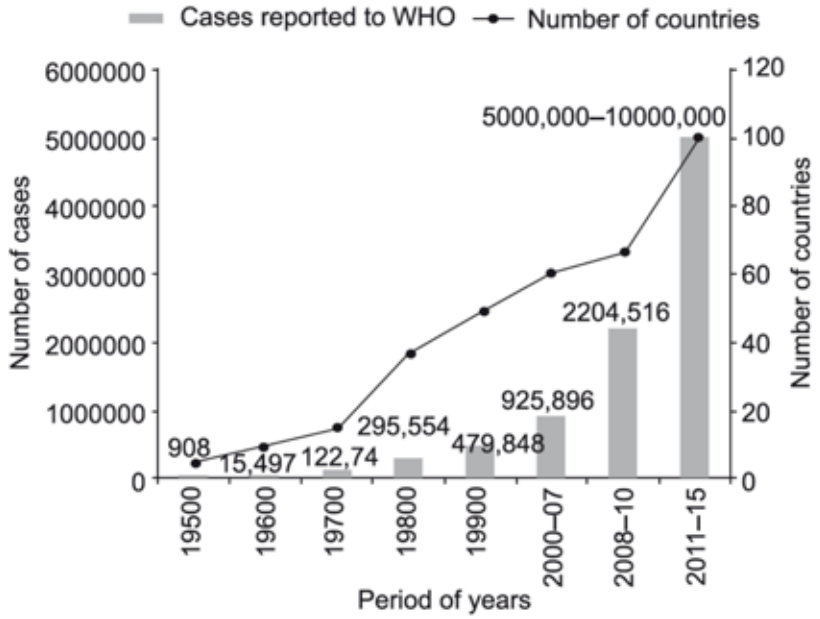
GLOBAL DENGUE & AEDES-TRANSMITTED DISEASES CONSORTIUM
Chair: Duane Gubler
Director: In-Kyu Yoon

WHO	International Vaccine Institute	Sabin Vaccine Institute	International Vaccine Access Center	Partnership for Dengue Control
(close collaborator)	• Vaccine introduction • Epidemiology • Laboratory testing • Modelling • Policy and access • Vaccine development • Regulatory support	• Communications and advocacy	(at Johns Hopkins Univ) • Health economics • Vaccine development • Regulatory support	• Integrated vaccine/vector control • Diagnostics • Surveillance • Clinical management • Pathogenesis • Therapeutics

Outline

- Dengue burden
- Dengvaxia® experience and lessons learned
- Dengue vaccine pipeline
- Takeda and Butantan dengue vaccine candidates
- Potential public health impact
- Conclusions

Global dengue burden continues to rise



Adapted from SEARO; J Vector Borne Dis. 2016 Oct-Dec;53(4):293-304.

Global burden of disease study 2013 & 2015

- Modelled incidence from officially reported cases
  - Adjusted for under-reporting based on published expansion factors (14 countries)
- Modelled mortality from vital registration, verbal autopsy, and surveillance data
- Estimated **58.4** million symptomatic cases (23.6-121.9 million) in 2013 [Stanaway JD et al. Lancet Infect Dis. 2016 Jun;16(6):712-23]
  - **21.1** million in Southeast Asia alone
- From 2005 to 2015, dengue deaths increased by **48.7%** (15.1-90.9), resulting in 18,400 deaths (11,800-22,700) in 2015 [Lancet. 2016 Oct 8;388(10053):1459-1544]

❖ **One of few infectious diseases with increasing mortality trend**

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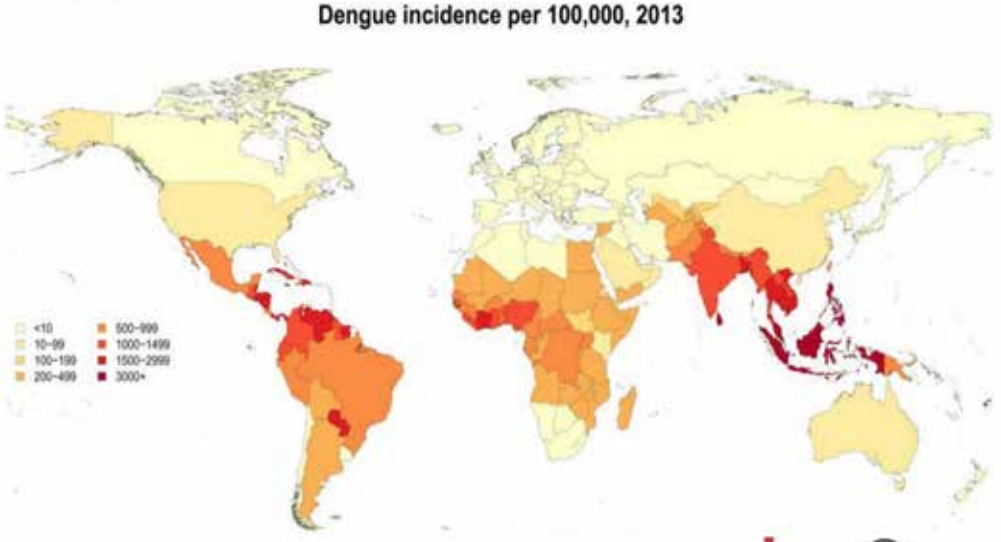
Highest incidence rates are in Asia



Stanaway JD et al. Lancet Infect Dis. 2016 Jun;16(6):712-23

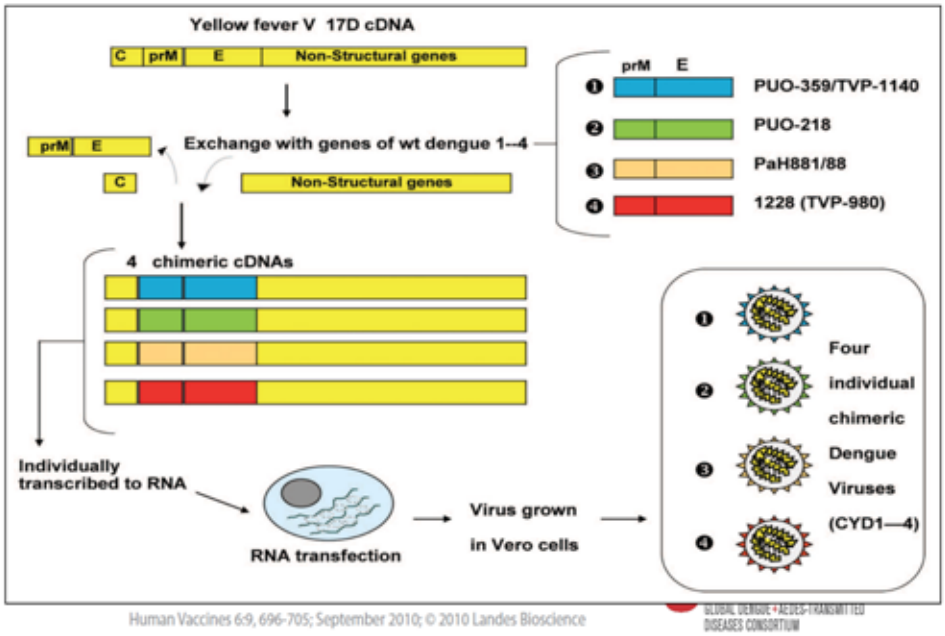
7

Promising new tools being developed

- Vaccines
- Mosquito control
- Surveillance and mapping
- Diagnostic assays
- Biomarkers for disease severity
- Antiviral drugs
- Therapeutic antibodies

8

Sanofi Pasteur's Dengvaxia® (CYD-TDV)



Dengvaxia® and seroprevalence

Seroprevalence in target age group (9 years +)	Vaccination recommended?
>70%	Yes
50-70%	Impact may be lower
<50%	No

- CYD-TDV performs differently in seropositive vs. seronegative individuals
- Lower impact in populations <50% seroprevalence
- Possible harm in very low transmission settings (~10%)
- Safety signal of increased hospitalization observed in 2-5 year olds in phase III trial
- Increased risk: age and/or serostatus at baseline

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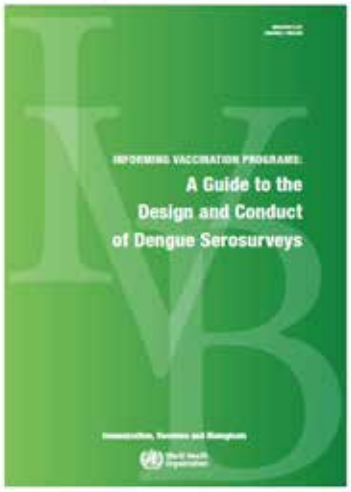
Support for country decision-making on Dengvaxia®

Serosurvey guide to inform vaccination



Global dengue transmission map

http://www.who.int/immunization/research/development/dengue_vaccines/en

Dengvaxia® safety summary

- CYD-TDV is well-tolerated
- SAEs similar across CYD/Placebo in Phase III trials
- No non-dengue safety signals identified
- An elevated risk of hospitalized dengue in CYD group was seen in 2-5 year-olds in Year 3 (**RR=7.5**)
  - **Risk diminishes in Years 4 and 5**
  - During entire study follow up (up to 5 years), there was an excess of hospitalized dengue cases in this group, but it was not statistically significant
  - Not seen consistently in older age groups
  - **Understanding potential factors associated with increased relative risk of hospitalized and severe dengue among some trial participants is priority**

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SP announcement on Dengvaxia® (29 Nov 2017)

- "Based on up to six years of clinical data, new analysis **[using dengue/ Yellow fever NS1 Ab test]** evaluated long-term safety and efficacy of Dengvaxia® in people who had been infected with dengue prior to vaccination and those who had not. The analysis confirmed that Dengvaxia® provides persistent protective benefit against dengue fever in those who had prior infection. **For those not previously infected by dengue virus, however, the analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection**."

- "Based on the new analysis, Sanofi will propose that national regulatory agencies update the prescribing information, known as the label in many countries, requesting that healthcare professionals **assess the likelihood of prior dengue infection in an individual before vaccinating**. Vaccination should only be recommended when the potential benefits outweigh the potential risks (in countries with high burden of dengue disease). For individuals who have not been previously infected by dengue virus, vaccination should not be recommended."

13

WHO position paper in July 2016

- Countries should consider introduction of CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease
  - Indicated by seroprevalence of approximately 70% or greater
  - 50-70% is acceptable but impact may be lower
- Important research and implementation questions remain
  - Efficacy of shorter dosing intervals
  - Safety in pregnant women
  - Validation of **age-stratified surveillance data** to infer seroprevalence
  - **Duration** of protection
  - Risk of severe dengue especially in vaccinated **seronegative** persons

WHO SAGE recommendation update in Apr 2018

- Emphasis on **direct testing of potential vaccine recipients** of all ages prior to Dengavaxia® administration
- Further details are pending publication of WHO SAGE recommendations

Lessons learned for 2nd generation vaccines

- **Early clinical studies are valuable to evaluate infectivity of vaccine viruses**, which relates to development of **type-specific immunity versus heterotypic immunity**
- **Neutralization tests** still represent our best assay of immunogenicity for dengue vaccines; however, they do not distinguish between type-specific antibodies, transient heterotypic antibody, and long-lasting heterotypic antibody…**Research assays are complementary**
- **Controlled human infection model** (CHIM) Phase I trials can provide initial proof-of-concept that a vaccine has clinical benefit

16

Lessons learned for 2nd generation vaccines

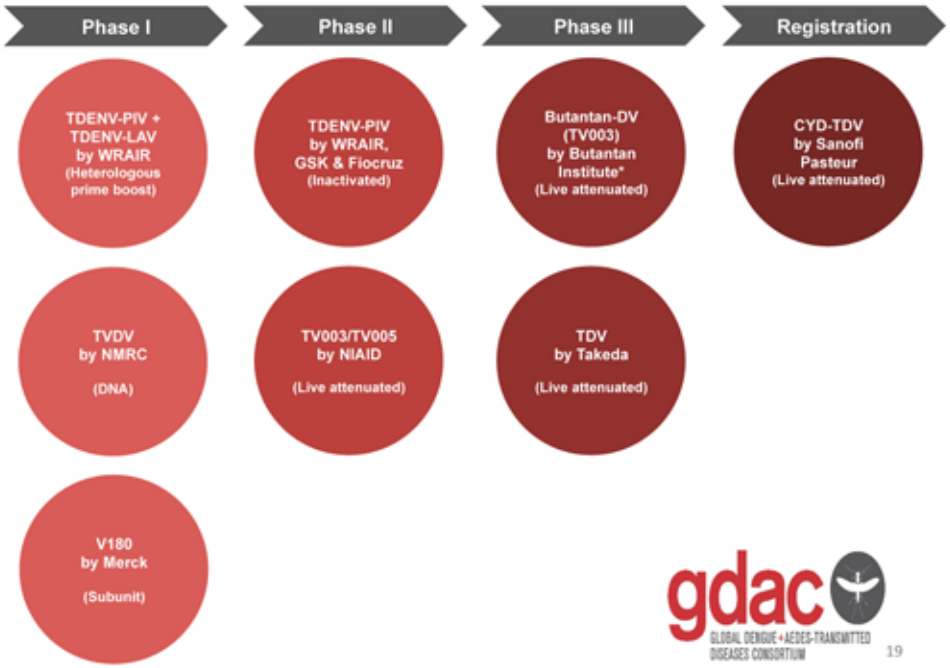
- **Dengue serostatus** at baseline remains an important variable, and safety and efficacy by serostatus should be presented in a stratified analysis…**Need for pre-vaccination blood samples**
- **Co-circulating flaviviruses**, in particular Zika, require close scrutiny
- Immunogenicity and efficacy results should be interpreted in context of potential **transient heterotypic immunity that could wane over time…Need for prolonged active surveillance**
- For licensure, vaccine efficacy will need to be demonstrated based on clinical outcomes (**no correlate yet**)

17

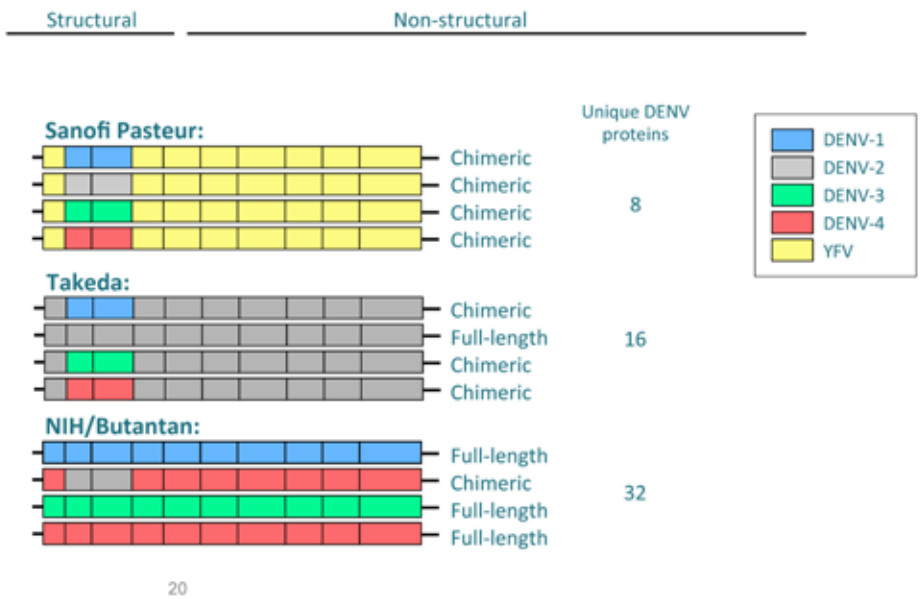
Dengue vaccine pipeline

Sponsor/ Developer	Design (ALL tetravalent)	Name
Sanofi Pasteur	Live recombinant (chimera with YF17D backbone)	Dengvaxia® (CYD-TDV)
Takeda	Live recombinant (chimera with DENV-2 backbone)	TDV
US NIH Brazil (Butantan) Vietnam (Vabiotech) India (Panacea, Serum Institute, Indian Immunologicals) Taiwan (Medigen Biotech) Merck (Excl: US, Can, EU, Chi, Jpn)	Live recombinant (full length or DENV-2 chimera with DENV-4 backbone)	TV003/TV005
GSK/ Fiocruz/ US Army	Inactivated whole virus	TDENV-PIV DPIV
Merck	Recombinant protein subunit (80% E protein)	V180
US Navy	DNA (plasmid)	TVDV
US Army	Heterologous prime-boost (inact whole + live atten)	TDENV-PIV + TDENV-LAV

Dengue vaccine pipeline status



Two live atten. candidates in phase III trials



TDV (Takeda)

- DENV/DENV chimeric live tetravalent vaccine based on attenuated DENV-2 backbone
- Has been evaluated in multiple trials in dengue-naïve and exposed subjects, addressing:
  - Delivery routes (SQ, IM, ID)
  - Vaccine formulations (high, low dose)
  - Scheduling (one vs two doses)
- Phase II trial in 1800 children 2-17 y.o. in 3 dengue endemic countries
  - 18-month interim results encouraging
- In Phase III multi-center evaluation (NCT02747927)
  - DB-RCT trial in children 4-16 years, placebo controlled
  - 0.5 ml TDV SQ day 1 and day 90
  - Countries: Brazil, Colombia, Dom. Republic, Nicaragua, Panama, Philippines, Sri Lanka, Thailand
  - Preliminary efficacy results in Q1 2019

21

TV003/TV005 (US NIH)

- DENV attenuated by deletions in 3'UTR or DENV/ DENV chimerization (DENV-2 component)
- TV003 contains 3log10 PFU/component, TV005 contains 10x fold dose of rDENV2/4Δ30
- Extensively studied in Phase I trials, including human challenge studies
- Elicits transient viremia in most subjects (≈75%)
- For all 4 components, no boost observed with 2nd dose

22

Butantan-DV (Butantan)

- Butantan-DV (equivalent to TV003)
- Phase III trial (NCT02406729)
  - DB-RCT multi-site in Brazil
  - 2:1 ratio of vaccine:placebo
  - Single dose, lyophilized product
  - Age groups: 18-59 years, 7-17 years, 2-6 years
  - Study population N=16,944
  - Primary efficacy outcome is incidence density of symptomatic virologically confirmed dengue
  - Preliminary efficacy results in late 2018

23

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TV003/TV005 licensees

- Butantan (exclusive in Brazil)
  - Phase III ongoing
- Vabiotech (nonexclusive)
- Panacea, Serum Institute of India, Indian Immunologicals (nonexclusive)
- Medigen (nonexclusive)
- Merck (exclusive in US, Canada, EU, China, Japan)

24

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Impact of moderately effective vaccines

- Given burden of dengue, moderately effective vaccines can have large public health impact

25

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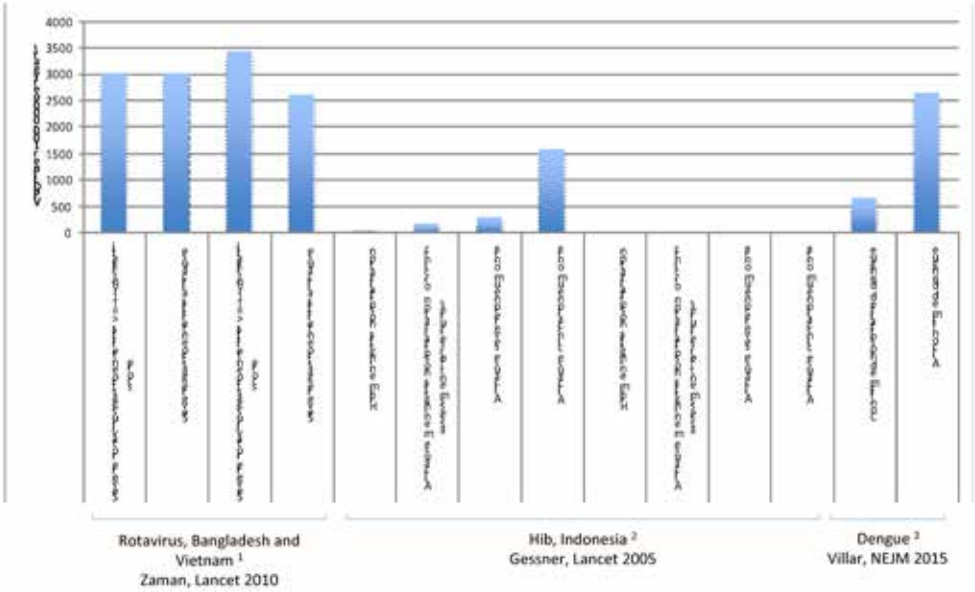
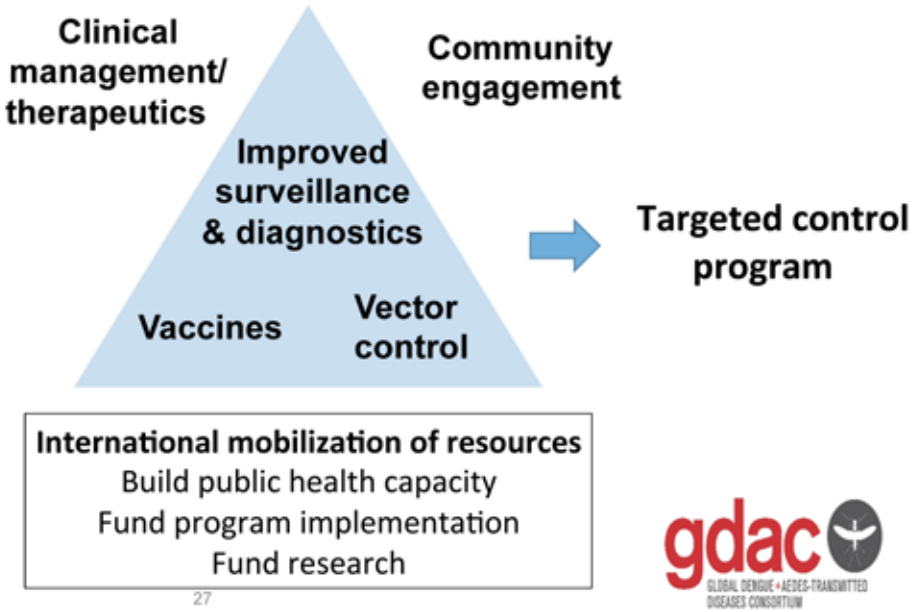
Dengvaxia® VPDI over 2-year period compared to other vaccines



1: Data for children followed from infant immunization to age 2 years; VDPI = cases / 100,000 persons years of observation
2: Data for children followed from infant immunization to age 2 years.;VDPI reported as PYO
3: Data calculated for persons 9-16 years of age and 2 year follow up period

Paradigm for using new tools: Integration and synergy



27

Conclusions

- Dengue burden is increasing globally, especially in Asia
- Dengvaxia® has moderate efficacy, and has caused concern due to increased risk of hospitalized and severe dengue in dengue naïve vaccine recipients
- Key lessons have been learned from Dengvaxia® experience
- Two other dengue vaccines, TDV (Takeda) and Butantan-DV (Butantan) are in phase III trials with preliminary results becoming available in near future
- Potential public health impact of even moderately effective dengue vaccine is large

28


Thank you
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Speaker

Dr. Stephen Whitehead
Position: Senior Associate Scientist
Department / Organization: Laboratory of Infectious Diseases, NIAID, NIH
Economy: The United States

Professional Career

- 23 years at NIAID Division of Intramural Research

Publications

- Gallichotte EN, Baric TJ, Yount BL Jr, Widman DG, Durbin A, Whitehead S, Baric RS, de Silva AM. Human dengue virus serotype 2 neutralizing antibodies target two distinct quaternary epitopes. PLoS Pathog. 2018 Feb 26;14(2):e1006934.
- Durbin AP, Whitehead SS. Zika Vaccines: Role for Controlled Human Infection. J Infect Dis. 2017 Dec 16;216(suppl10):S971-S975.
- Magnani DM, Rogers TF, Beutler N, Ricciardi MJ, Bailey VK, Gonzalez-Nieto L, Briney B, Sok D, Le K, Strubel A, Gutman MJ, Pedreño-Lopez N, Grubaugh ND, Silveira CGT, Maxwell HS, Domingues A, Martins MA, Lee DE, Okwuazi EE, Jean S, Strobert EA, Chahroudi A, Silvestri G, Vanderford TH, Kallas EG, Desrosiers RC, Bonaldo MC, Whitehead SS, Burton DR, Watkins DI. Neutralizing human monoclonal antibodies prevent Zika virus infection in macaques. Sci Transl Med. 2017. 9(410):eaan8184.
- Whitehead SS, Subbarao K. Which Dengue Vaccine Approach Is the Most Promising, and Should We Be Concerned about Enhanced Disease after Vaccination? The Risks of Incomplete Immunity to Dengue Virus Revealed by Vaccination. Cold Spring Harb Perspect Biol. 2017 Jul 17. pii: a028811.
- Whitehead SS, Durbin AP, Pierce KK, Elwood D, McElvany BD, Fraser EA, Carmolli MP, Tibery CM, Hynes NA, Jo M, Lovchik JM, Larsson CJ, Doty EA, Dickson DM, Luke CJ, Subbarao K, Diehl SA, Kirkpatrick BD. In a randomized trial, the live attenuated tetravalent dengue vaccine TV003 is well-tolerated and highly immunogenic in subjects with flavivirus exposure prior to vaccination. PLoS Negl Trop Dis. 2017. 11(5):e0005584.

Speaker

Prof. Anna Durbin

Position: Professor

Department / Organization: Johns Hopkins Bloomberg School of Public Health

Economy: The United States

Educational Background

- B.S./1983 University of Michigan, Ann Arbor, MI; Pharmacy
- M.D./1987 School of Medicine, Wayne State University, Detroit, MI; Medicine

Professional Career

- 1999-present: Department of International Health Johns Hopkins Bloomberg School of Public Health, Baltimore MD USA
- 1194-1999: Laboratory of Infectious Diseases, National Institutes of Health, Bethesda MD USA

Publications

- Kirkpatrick BD, Whitehead SS, Pierce KK, Tibery CM, Grier PL, Hynes NA, Larsson CJ, Sabundayo BP, Talaat KR, Janiak A, Carmolli MP, Luke CJ, Diehl SA, and Dur-bin AP. The live attenuated dengue vaccine TV003 elicits complete protection against dengue in human challenge model. Sci Transl Med 2016; 8(330). Cover story
- Durbin AP, Kirkpatrick BD, Pierce KK, Carmolli MP, Tibery CM, Grier PL, Hynes NA, Opert K, Jarvis AP, Sabudnayo BP, McElvany BD, Sendra E, Larsson CJ, Jo M, Lovchik J, Luke CJ, Walsh MC, Fraser EA, Subbarao K, and Whitehead SS. A 12-month interval dosing study in healthy adults indicates that a single dose of the NIAID live attenuated tetravalent dengue vaccine induces a robust neutral-izing antibody response. J Infect Dis 2016; Published online February 16, 2016; Editor's choice
- Whitehead SS, Durbin AP, Pierce KK, et al. In a randomized trial, the live attenu-ated tetravalent dengue vaccine TV003 is well-tolerated and highly immunogenic in subjects with flavivirus exposure prior to vaccination. PLoS Negl Trop Dis 2017;11:e0005584
- Durbin AP, Whitehead SS. Zika Vaccines: Role for Controlled Human Infection. J Infect Dis 2017;216:S971-S975
- Vannice KS, Wilder-Smith A, Barrett ADT, Carrijo K, Cavaleri M, de Silva A, Durbin AP, et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. Vaccine 2018

Speech Abstract

Update of Dengue Vaccine Development at the US NIH

Anna P. Durbin[1] and Stephen S. Whitehead[2]

[1]Johns Hopkins Bloomberg School of Public Health, [2]Laboratory of Viral Diseases, US NIAID

The Laboratory of Infectious Diseases at the National Institute of Allergy and Infectious Diseases at the US National Institutes of Health began developing a live attenuated tetravalent dengue vaccine in 1999. Hundreds of recombinant viruses were evaluated in rodent models to identify candidates that were attenuated for further evaluation in a non-human primate model. More than 20 monovalent candidates were evaluated in NHP to identify those that should be further evaluated in human clinical trials. We conducted 15 clinical trials in more than 700 subjects to determine which monovalent candidate vaccines should be combined and tested in tetravalent admixtures. The monovalent candidate vaccines were chosen based on their safety profile, infectivity (low human infectious dose 50%), and their immunogenicity in flavivirus-naïve individuals. Using this iterative process, we identified 2 tetravalent admixtures, TV003 and TV005 for evaluation in endemic areas. A single dose of either TV003 and TV005 induces trivalent or better seroconversion in more than 90% of flavivirus-naïve subjects. A single dose of either TV003 or TV005 administered to flavivirus-naïve subjects induce complete protection against DENV-2 challenge at 6-months in a controlled human infection model (CHIM). In addition, a single dose of TV005 administered to flavivirus-naïve subjects induced complete protection against DENV-3 in a second CHIM study (TV003 was not tested). TV003 and TV005 are being evaluated in Phase 2 clinical trials in Thailand and Bangladesh in subjects ages 1 year of age to 50. The vaccines have been well tolerated in dengue exposed and dengue naïve subjects in these studies. Immunogenicity data and virology data from the above studies will be presented. Based on the CHIM studies, the Instituto Butantan in Brazil chose TV003 as the live attenuated tetravalent dengue formulation for manufacture and clinical evaluation. TV003 is currently being evaluated in a Phase 3 efficacy trial enrolling 17,000 subjects throughout Brazil. The early formative studies, CHIM studies, and current clinical trials of TV003 and TV005 will be presented.

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JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Immunization Research

Update on the NIAID dengue vaccine

Anna P. Durbin

3 May 2018

APEC Meeting, Tainan Chinese Taipei

Important considerations for a dengue vaccine

- Four distinct DENV serotypes capable of causing the full spectrum of dengue illness
- Each serotype provides long-term homotypic immunity but only short-term heterotypic immunity
- **Antibody to the E protein is protective**
  - Is it sufficient?
  - Antibody is a correlate of protection for other flavivirus vaccines

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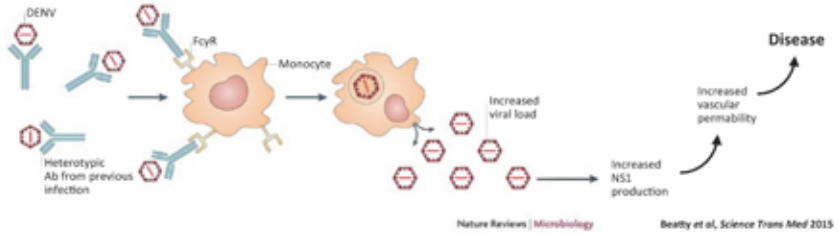
Dengue: critical issues for vaccine development

- Four DENV serotypes all capable of causing the full spectrum of disease (***need for a tetravalent vaccine***)
- Life-long homotypic protection afforded after infection but only short term (few months) heterotypic protection is afforded
- ***Secondary infection with a different serotype is strongly associated with severe disease***
  - Antibody-mediated enhancement of infection



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Important considerations for a dengue vaccine

- Sequential infection with different serotypes leads to broadly neutralizing antibody response
  - Rarely see symptomatic infection with third or fourth dengue infection
- However, secondary infection with a different serotype is strongly associated with severe disease
  - Antibody-mediated enhancement of infection

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Important considerations for a dengue vaccine

- **Dengue vaccine must protect against all four DENV serotypes**
  - Partial immunity to dengue is **BAD**
- Neutralizing antibody standard measure of immunogencity (no correlate of protection exists)
- No model of dengue disease that reproduces the disease seen in humans
  - Only natural hosts for DENV are mosquitoes, humans, and NHP

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Live dengue vaccines

- Could vaccine induce disease in those with pre-existing DENV antibody?
- Could vaccine be transmitted to community if vector present?
- Live vaccine – advantages
  - Presented in the context of both MHC class I and MHC class II
  - Induction of long-lived immunity with few doses: success of yellow fever vaccine, JE vaccine

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Status of LA vaccine development

- Sanofi Pasteur live attenuated tetravalent (LATV) dengue chimeric vaccine CYD
  - Chimeric based on YF17D vaccine
  - 3 doses given over 12 months
- Takeda (Inviragen) LATV chimeric vaccine based on DENV-2 backbone
  - 2 doses given 3 months apart
  - In phase 2 trials in Americas & Asia
  - Phase 3 trial started in Nov. 2016
- **NIH LATV vaccine attenuated by Δ30 mutation in 3´ UTR**
  - Single dose
  - In trials in Brazil, Thailand, Bangladesh
  - Licensed by the Butantan Institute in Brazil and in Phase 3 trial in Brazil

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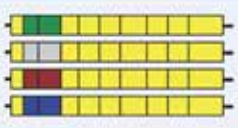
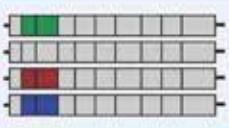
Live attenuated dengue vaccines

	Dengvaxia (Sanofi Pasteur)	TDV (Takeda)	TV003/TV005 (NIH/ Butantan)
Status	Licensed	Phase 3	Phase 3
# Doses	3 doses over 12 months (0, 6, 12)	2 doses (0, 3 months)	Single dose
Indicated age	9 - 45	Phase 3 age range 2 - <18	Phase 3 age range 2 - 59
Other	Seroprevalence ≥ 70%	?	?
Construct			

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Summary of Dengvaxia™

- All components are chimeric viruses
  - prM and E of DENV, NS protein or YF17D
- Requires 3 doses given over 12 months to induce antibody to all 4 DENV in dengue-naïve subjects
  - DENV-4 component immunodominant
  - Limited infectivity of DENV-1, DENV-2 components leading to poor immunogenicity of DENV-1 & DENV-2 components

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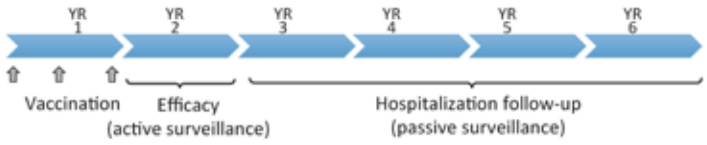
Efficacy and Long-term Safety of the CYD vaccine



- Year 2 efficacy analysis utilized active follow-up for virologically-confirmed dengue (VCD)
- Years 3, 4, 5, & 6 utilized passive surveillance for hospitalized follow-up (now active surveillance)
  - Subjects contacted ***at least*** once every 3 months
  - Seen once per year

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CYD14, Hadinegoro *et al.*, 2015, *NEJM*

Efficacy[1] of CYD-TDV

Trial	Region	Vaccine recipients enrolled	Age	Overall Efficacy (95% CI)	Efficacy, hospitalization	Efficacy, severe disease
CYD23[2]	Thailand	2,669	4-11	30.2 (-13.4-56.6)	Not reported	Not reported
CYD14[3]	SE Asia	6,851	2-14	56.5 (43.8-66.4)	67%	80%
CYD15[4]	Latin America	13,920	9-16	60.8 (52.0-68.0)	80%	91.7%

1. Per protocol analysis. Period of primary efficacy evaluation was > 28 days after the third dose to month 25 (12 month period)
2. Sabchareon, The Lancet, 2012
3. Capeding et al, The Lancet, 2014
4. Villar et al, NEJM, 2014

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11

Efficacy[1] of CYD-TDV

Trial	Region	Vaccine recipients enrolled	Age	Efficacy in seropositive at baseline	Efficacy in seronegative at baseline
CYD23[2]	Thailand	2,669	4-11	Not reported	Not reported
CYD14[3]	SE Asia	6,851	2-14	74.3 (53.2-86.3)	35.5 (-26.8-66.7)
CYD15[4]	Latin America	13,920	9-16	83.7 (62.2-93.7)	43.2 (-61.5-80)

Poorest efficacy against DENV-1 & DENV-2, best efficacy against DENV-4

1. Per protocol analysis. Period of primary efficacy evaluation was > 28 days after the third dose to month 25 (12 month period)
2. Sabchareon, The Lancet, 2012
3. Capeding et al, The Lancet, 2014
4. Villar et al, NEJM, 2014

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12

Vaccine-viremia induced by CYD

	Percentage of subjects with detectable viremia after a single dose (% by RT-PCR) in flavivirus-naïve subjects			
	DENV-1	DENV-2	DENV-3	DENV-4
CYD, Day 7 (n=12)	0 (0)	0 (0)	0 (17)	8 (50)
CYD, Day 7 (n=84)	0 (0)	1 (2)	0 (0)	2.1 (30)
CYD (n=25)	(0)	(4)	(0)	(52)
CYD (n=95)	(7.4)	(0)	(12.6)	(44.2)

- Efficacy against individual serotypes mirrors viremia induced by vaccine
- Viremia a measure of infectivity of each of the vaccine components

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Long-term Safety of the CYD vaccine

- Longer-term follow-up period is year 3 – 6
- Most current analyses based on data collected during:
  - Year 3 of 2 phase 3 trials (CYD14 and CYD15) and
  - Years 3 and 4 of the CYD23 extension study (CYD57) in Thailand
- Participants attended yearly clinic visits with regular contact (≥ 1 contact every 3 months by telephone, text message, or home visit)

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CYD14, Hadinegoro *et al.*, 2015, *NEJM*

Hospitalized VCD CYD14

	Vaccine Group			Control Group			
	VCD	Total subjects	Annual Incidence	VCD	Total subjects	Annual Incidence	Relative Risk
All	27	6,778	0.4	13	3387	0.4	1.04 (0.52-2.19)
2 - 5	15	1,636	0.3	1	813	0.1	7.45 (1.15-313.8)
6 - 11	10	3,598	0.3	4	1806	0.5	0.63 (0.22-1.83)
12 - 14	2	1,544	0.1	4	768	0.6	0.25 (0.02-1.74)

Hadinegoro NEJM 2015

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15

Summary of dengue vaccine Dengvaxia™

- Variable efficacy dependent on:
  - Age at vaccination
  - Dengue serostatus at vaccination
  - Serotype
  - Country
- Long-term safety follow-up demonstrated increased risk of hospitalization and severe dengue in vaccinated subjects compared to controls in year 3
  - **Highest risk in younger subjects (7.5-fold increase)**
  - Increased risk not observed in subjects ≥ 9 years old

16

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NIH LATV dengue vaccine

- Developed at the LID, NIH
- Phase I studies of **monovalent** candidates conducted at JHU & UVM
- Purpose: to identify candidates with the best
  - Safety profile
  - Immunogenicity profile
  - Infectivity profile
- Clinical trials began at JHU in 1999
- Monovalent vaccines extensively evaluated prior to inclusion in tetravalent admixture

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Development of TV003/TV005

1999 - 2012 | 2013 - 2017

100's of virus constructs	Pre-clinical candidates (monkeys)	Phase I monovalent (700+)	Phase I tetravalent (200+)	Phase II tetravalent (700+)	Phase III tetravalent (17,000+)
⇨	DEN1Δ30 DEN1/4 DEN1/4Δ30 DEN1/4Δ30(CME) DEN1mutF	DEN1Δ30	DEN1Δ30	DEN1Δ30	**DEN1Δ30**
	DEN2Δ30 DEN2Δ30-4995 DEN2/4 DEN2/4Δ30 DEN2/4Δ30(CME) DEN2-3'D4Δ30	DEN2/4Δ30 DEN2Δ30*	DEN2/4Δ30	DEN2/4Δ30	**DEN2/4Δ30**
	DEN3Δ30 DEN3/4 DEN3/4Δ30 DEN3/4Δ30(CME) DEN3/4Δ30(Sri Lanka) DEN3Δ86 DEN3Δ30/31 DEN3-3'D4Δ30	DEN3/4Δ30 DEN3Δ30/31 DEN3-3'D4Δ30	DEN3Δ30/31 DEN3-3'D4Δ30	DEN3Δ30/31	**DEN3Δ30/31**
	DEN4Δ30 DEN4Δ30-200,201 DEN4Δ30-436-437 DEN4Δ30-4995	DEN4Δ30 DEN4Δ30-4995 DEN4Δ30-200,201	DEN4Δ30 DEN4Δ30-200,201	DEN4Δ30	**DEN4Δ30**

Monovalent DENV vaccines

- All monovalent vaccines contain wild-type E protein
- Major attenuating mutation 30 nucleotide deletion in the 3´ UTR
- All attenuating mutations are outside of the structural and non-structural proteins
  - Except for the rDEN4Δ30-200, 201 (mutation in NS5)
- Vaccines for 3 of the 4 serotypes contain the wild-type NS proteins
  - Majority of T cell epitopes found in the NS proteins

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Viremia induced by monovalent vaccine components

Vaccine component	Dose (log_{10} PFU)	N	% viremia	Mean peak titer (log_{10} PFU/mL)	Mean # days of viremia
rDEN1Δ30	3	71	60	1.0 ± 0.08	3.3 ± 0.3
rDEN2/4Δ30	3	40	60	0.5 ± 0.03	3.3 ± 0.6
rDEN3/4Δ30	3	20	15	1.0 ± 0.3	4.3 ± 0.7
rDEN3/4Δ30	5	20	0	n/a	n/a
rDEN3Δ30/31	3	50	34	0.6 ± 0.1	3.2 ± 0.5
rDEN4Δ30	3	70	28	0.6 ± 0.1	3.1 ± 0.7

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20

Immunogenicity following single 10^3 PFU dose of monovalent DENV candidates

		Geometric mean antibody titer		
Vaccine	No. of subjects	Day 28	Day 42	% seroconversion
rDEN1Δ30	70	170	140	93
rDEN2/4Δ30	40	95	131	100
rDEN3/4Δ30	20	37	210	**30%**
rDEN3/4Δ30	20	25	210	**25%**
rDEN3Δ30/31	50	84	79	81
rDEN4Δ30	50	112	135	93

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Immunogenicity following single 10^3 PFU dose of monovalent DENV candidates

		Geometric mean antibody titer		
Vaccine	No. of subjects	Day 28	Day 42	% seroconversion
rDEN1Δ30	70	170	140	93
rDEN2/4Δ30	40	95	131	100
~~rDEN3/4Δ30~~	~~20~~	~~37~~	~~210~~	~~30%~~
rDEN3Δ30/31	50	84	79	81
rDEN4Δ30	50	112	135	93

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Tetravalent admixture

- All viruses contain wild-type structural proteins
- Contain wild-type NS from 3 of the 4 DENV serotypes
- All contain at least a 30 nt deletion in the 3' UTR

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23

NIH tetravalent DENV vaccine

Clinical measures of infectivity

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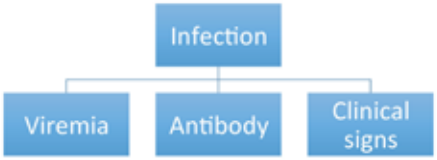
24

Vaccine infection summary

For live vaccines – infection is generally required for immune stimulation



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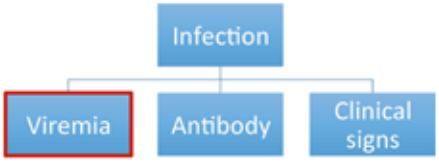
25

Vaccine infection summary

For live vaccines – infection is generally required for immune stimulation



TV003

Vaccine component	% with viremia	Mean peak titer	Maximum titer	Mean day of onset (range)	Mean duration in days (max)
DEN1	23	3.3 pfu/mL	5 pfu/mL	12 (8-15)	1.9 (3)
DEN2	5	3.0 pfu/mL	3 pfu/mL	9 (8-10)	1.0 (1)
DEN3	38	3.5 pfu/mL	5 pfu/mL	9 (7-14)	2.5 (7)
DEN4	33	3.4 pfu/mL	5 pfu/mL	10 (7-16)	2.2 (6)
Total %	75				

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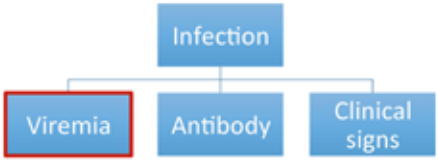
26

Vaccine infection summary

For live vaccines – infection is generally required for immune stimulation



TV005

Vaccine component	% with viremia	Mean peak titer	Maximum titer	Mean day of onset (range)	Mean duration in days (max)
DEN1	23	4 pfu/mL	50 pfu/mL	11 (8-15)	3 (7)
DEN2	20	3 pfu/mL	3 pfu/mL	9 (8-14)	2 (4)
DEN3	43	4 pfu/mL	10 pfu/mL	9 (8-14)	3 (9)
DEN4	23	6 pfu/mL	32 pfu/mL	8 (8-10)	3 (10)
Total %	70				

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27

Viremia induced by CYD

	Percentage of subjects with detectable viremia after a single dose (% by RT-PCR) in flavivirus-naïve subjects			
	DENV-1	**DENV-2**	**DENV-3**	**DENV-4**
TV003 (n=84)	**25**	**6**	**45**	**26**
TV005 (n=84)	**25**	**19**	**38**	**24**
CYD, Day 7 (n=12)	0 (0)	0 (0)	0 (17)	8 (50)
CYD, Day 7 (n=84)	0 (0)	1 (2)	0 (0)	2.1 (30)
CYD (n=25)	(0)	(4)	(0)	(52)
CYD (n=95)	(7.4)	(0)	(12.6)	(44.2)

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28

Immunogenicity of single dose TV003 & TV005 in flavivirus-naive adults

		% Seroconverted ($PRNT_{50}$ ≥ 10)			
	N	DENV-1	DENV-2	DENV3	DENV4
TV003	62	92	**85**	98	100
TV005	63	87	**98**	97	97
		Mean peak titer (GMT) ($PRNT_{50}$>10)			
TV003	62	56	55	105	184
TV005	63	35	99	99	154
		Subjects with antibody response, %, by valence			
		Tetravalent	Trivalent	Bivalent	Monovalent
TV003	62	**81**	**15 (96)**	4 (100)	0 (100)
TV005	63	**83**	**16 (99)**	1 (100)	0 (100)

Kirkpatrick et al ID 2015, 2016, and unpublished

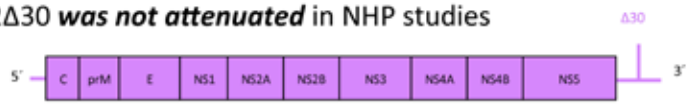
Drivers for development of Dengue CHIM

- Down selection of candidate vaccines before Phase 3 efficacy trials in endemic countries. Issues of vaccine acceleration and safety.
  - A dengue vaccine that fails to protect may not just fail to reduce disease incidence but ***may actually pose a greater risk of more severe disease*** to those vaccinated over time (Dengvaxia)
- Platform upon which to understand immune correlates of protection.
  - Clear CoP are important for bridging studies for future or second generation vaccines.
  - Need to understand immunologic responses in naïve vs. experienced individuals.
  - Explore development and components of protective responses
- Testing of therapeutics.

30

Dengue Controlled Human Infection Model (D-CHIM) for DENV-2

- Developed from DENV-2 Tonga/74 virus that was described as a naturally attenuated DENV (caused milder illness, lower viremia outbreak in Kingdom of Tonga)
  - Tonga/74 is different DENV-2 genotype (American) than strain in TV003 vaccine (Asian)
- DHIM developed using a DENV-2 virus initially developed as a vaccine candidate but failed in preclinical evaluation
  - DEN2Δ30 ***was not attenuated*** in NHP studies



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31

DENV-2 CHIM Summary

- Induced viremia in 100% of subjects
  - Viremia easily measured (100-fold higher than LLQ for DENV-2)
- Induced clinical signs and symptoms consistent with majority of DENV infections (asymptomatic or mild infection)
  - Rash in 80% of subjects (50% moderate intensity)
  - Neutropenia in 20 - 40% of subjects
    - Moderate in 2 subjects (ANC nadir = 500-749/mm^3)
    - Mild in 2 subjects (ANC nadir = 750-999/mm^3)
- **No subject developed fever, elevated LFTs, or signs vascular leak**

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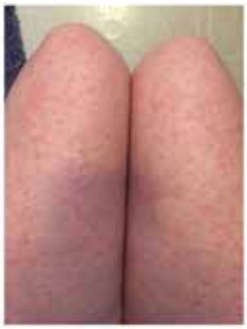
32

D-CHIM: Rash induced by challenge viruses



DENV challenge

DENV challenge

Typical DENV vaccine rash

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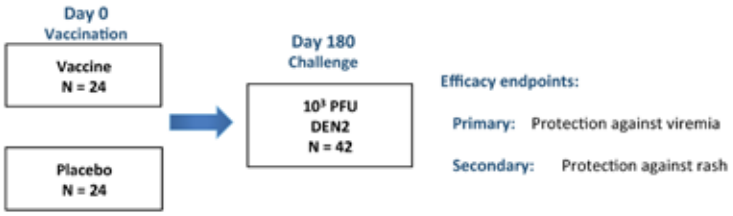
DHIM utilized to evaluate protective efficacy of candidate LATV dengue vaccines

- LATV dengue vaccines TV003 and TV005 were both evaluated for efficacy against DENV-2 challenge (48 each cohort)
- 6 months later all received 1,000 PFU DENV-2
  - ***Primary efficacy endpoint is protection against viremia with DENV-2*** (60% efficacy at a power of 0.8)



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TV003 & TV005 completely protect against viremia and rash induced by DENV-2

Cohort	N	Frequency of viremia	P value	Frequency of rash	P value
TV-003	21	0%	<0.0001	0%	<0.0001
Placebo	20	100%		80%	
TV005	21	0%	<0.0001	0%	<0.0001
Placebo	21	100%		100%	

Kirkpatrick et al (2017) Science Transl. Med

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Viremia post-challenge

		Viremia post-challenge with DEN2Δ30				
Cohort	N	Frequency of viremia	Mean peak Viremia (log_{10} PFU/mL)	Viremia range	Mean day of onset	Mean duration (days)
TV-003	21	0%	n/a	n/a	n/a	n/a
Placebo	20	100%	2.3 ± 0.1	1.5 – 2.9	4.7 ± 0.6	5.6 ± 0.5
TV005	21	0%	n/a	n/a	n/a	n/a
Placebo	21	100%	2.2 ± 0.2	0.5 – 3.2	4.95 ± 0.5	4.6 ± 0.4

- DEN2Δ30 induces consist level, onset, and duration of viremia. Viremia ~ 100-fold higher than vaccine-induced viremia
- Virus was not detected by quantitative or digital drop PCR in subjects who had previously received TV003

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36

DENV-2 Challenge Study

What do the challenge studies tell us?

What do the challenge studies tell us?

The vaccine is 100% efficacious against DEN2 infection
TV003 chosen for the Phase 3 trial based on DHIM

Because of the high level of efficacy, definition of a correlate of protection may not be possible.

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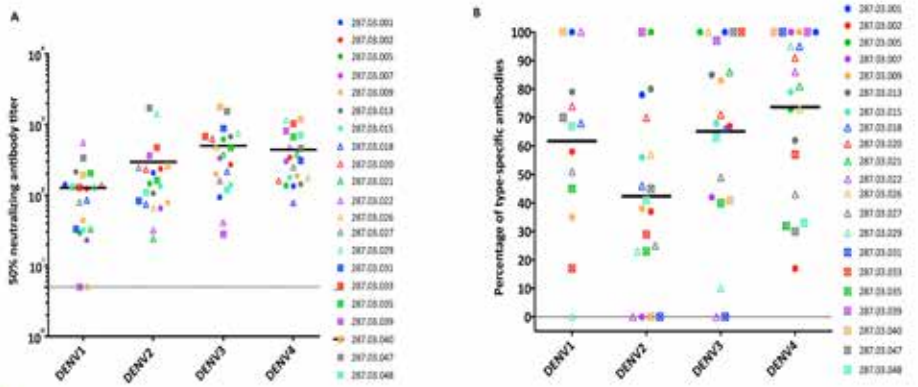
Antibody-depletion assay demonstrates high proportion of neutralizing antibody is homotypic



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Usha Nivartha, UNC

CIR300 - Trivalent DENV exposure followed by challenge

- Do we need a ***homotypic tetravalent*** immune response to protect?
- Infected 18 flavivirus-naïve subjects with trivalent admixture of DEN1Δ30, DEN3Δ30/31, and DEN4Δ30 (components of TV003 &TV005)
  - Included 6 placebo recipients (infectivity controls)
- 6 months later challenged all with DENV-2
- Protection against DENV-2 viremia was the primary endpoint
  - Protection against rash was the secondary endpoint

39

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Post-challenge endpoints

	Trivalent (N = 15)	Control (N = 6)	P value	Efficacy
Culture vir.	27%	100%	0.004	73%
PCR viremia	80%	100%	0.526	20%
Rash	27%	83%	0.029	68%

		% viremic	Mean peak titer (log_{10} PFU/mL)	Max titer (log_{10} PFU/mL)	Mean Onset	Mean Duration
Culture	Placebo	100	2.3	2.8	6.3	3.8
	Trivalent	27	2.4	3.5	7.3	2.8
PCR	Placebo	100	6.1	6.5	3.3	8.0
	Trivalent	80	5.2	7.2	5.8	5.4

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CIR300 Protection (per protocol analysis)

Subject	DEN2 PRNT Day 180	DEN2 PRNT Peak (by day 270)	Fold rise	Mean Fold rise	Viremia	Rash
300.01.003	4	27	7x			
300.01.007	4	62	16x			
300.01.008	4	64	16x			
300.01.004	4	167	42x	50x		
300.01.019	4	220	55x			
300.01.002	4	792	198x		Yes	
300.01.016	9	124	14x			
300.01.013	11	1049	93x		Yes	
300.01.011	14	641	47x		Yes	Yes
★ 300.01.012	17	15	0.9x			
300.01.023	19	407	21x	27x		
300.01.020	32	485	15x			Yes
300.01.021	55	631	11x		Yes	Yes
★ 300.01.009	81	294	3.6x			

Enhancing antibody?
Low quality antibody?
Cell-mediated immunity?

Frequency of viremia
in sero (+) vs. sero (-)
P = 0.559

Although the mean fold rise in antibody is 2-fold higher in sero (-) subjects there is no significant difference with sero (+) subjects

★ Sterile immunity? 14%
- No clinical signs
- No viremia (culture)
- Antibody boost <4-fold

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CIR300 Protection (per protocol analysis)

Subject	DEN2 PRNT Day 180	DEN2 PRNT Peak (by day 270)	Fold rise	Mean Fold rise	RNA Viremia	Rash
300.01.003	4	27	7x		Yes	
300.01.007	4	62	16x			
300.01.008	4	64	16x		Yes	
300.01.004	4	167	42x	50x	Yes	
300.01.019	4	220	55x			
300.01.002	4	792	198x		Yes	
300.01.016	9	124	14x		Yes	
300.01.013	11	1049	93x		Yes	
300.01.011	14	641	47x		Yes	Yes
300.01.012	17	15	0.9x			
300.01.023	19	407	21x	27x	Yes	
300.01.020	32	485	15x		Yes	Yes
300.01.021	55	631	11x		Yes	Yes
300.01.009	81	294	3.6x		Yes	

Enhancing antibody?
Low quality antibody?
Cell-mediated immunity?

Frequency of viremia
in sero (+) vs. sero (-)
P = 0.559

Although the mean fold rise in antibody is 2-fold higher in sero (-) subjects there is no significant with sero (+) subjects

★ Sterile immunity? 7%
- No clinical signs
- No viremia (culture)
- Antibody boost <4-fold

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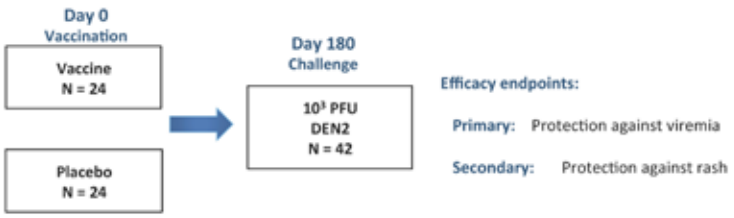
CIR300 – lessons learned

- Homotypic antibody important for protection against ***infection***
  - Tetravalent vaccination prevented detectable viremia (by culture or PCR) in 100% of vaccinated subjects
  - Trivalent vaccination was unable to prevent detectable viremia in 80% of subjects.
    - Trivalent vaccination induced only heterotypic antibody to DENV-2
- The cellular immune response is likely important for clearing virus if infection does occur
  - 8/12 subjects with detectable viremia by PCR did not achieve viremia detectable by culture
  - Cellular immune response pre- and post-challenge ongoing

CIR

DHIM utilized to evaluate protective efficacy of candidate LATV dengue vaccines

- LATV dengue vaccines TV005 was evaluated for efficacy against DENV-3 challenge (48 total)
- 6 months later all received 1,000 PFU DENV-3
  - ***Primary efficacy endpoint is protection against viremia with DENV-2*** (60% efficacy at a power of 0.8)



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44

TV005 completely protect against viremia and rash induced by DENV-3

Cohort	N	Frequency of viremia	P value	Frequency of rash	P value
TV005	21	0%	<0.0001	0%	<0.0001
Placebo	21	85%		100%	

Viremia post-challenge with DEN2Δ30						
Cohort	N	Frequency of viremia	Mean peak Viremia (PFU/mL)	Viremia range	Mean day of onset	Mean duration (days)
TV005	21	0%	n/a	n/a	n/a	n/a
Placebo	21	85%	8	3-158	4.6 ± 0.5	1.9 ± 0.4

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TV005 in the elderly

- Enrolled flavivirus-naïve older adults (50 – 70) years of age in the Baltimore area
- Received 1 dose of TV005 subcutaneously
- Monitored reactogenicity
- Collect samples for viremia ~ every other day through Study Day 16
- Calculated peak $PRNT_{50}$ through Study Day 90

CIR

TV005 in Elderly

- Enrolled 28 subjects ages 50 – 70
  - Mean age TV005 recipients: 58.6 ± 1.2
  - Mean age placebo recipients: 53.6 ± 1.9
- Followed ~ every other day for first 16 days
  - Viremia samples collected at these time points
- Adverse events collected through study day 28
  - Medically-attended and SAEs collected for duration of trial
- Serology time-points: Day 0, 28, 56, 90, and 180
  - Primary serologic endpoint was peak $PRNT_{50}$ through study day 90

CIR

Viremia induced by TV005 in the elderly

Vaccine component	No. TV005 recipients	No. viremic	Mean peak titer (log_{10} PFU/mL)	Mean day of onset of viremia	Mean duration in days
rDEN1Δ30	20	8 (40%)	1.2 ± 0.2	9.0 (4-11)	4.0 (1-8)
rDEN2/4Δ30		7 (35%)	0.6 ± 0.2	7.4 (4-11)	1.6 (1-5)
rDEN3Δ30/31		4 (20%)	0.5 ± 0.3	10.8 (10-11)	1.0 (all 1)
rDEN4Δ30		7 (35%)	0.8 ± 0.2	8.9 (7-11)	1.1 (1-2)
Total		13 (65%)			

2 subjects were viremic with all 4 viruses
1 subject was viremic with 3 viruses (rDEN1Δ30, rDEN2/4Δ30, and rDEN4Δ30)
5 subjects were viremic with 2 viruses (2 with rDEN1Δ30 & rDEN2/4Δ30; 2 with rDEN2/4Δ30 & rDEN4Δ30; 1 with rDEN2/4Δ30 and rDEN3Δ30/31)
5 subjects were viremic with 1 virus (4 with rDEN1Δ30 and 1 with rDEN4Δ30)

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Immunogenicity of single dose of TV005 in elderly flavivirus-naive adults

		% Seroconverted ($PRNT_{50} \geq 10$)			
	N	DENV-1	DENV-2	DENV3	DENV4
TV005	19	95	**95**	95	95
		Mean peak titer (GMT) ($PRNT_{50}>10$)			
TV005	19	66	351	79	245
		Subjects with antibody response, %, by valence			
		Tetravalent	Trivalent	Bivalent	Monovalent
TV005	19	**90**	**5 (95)**	0 (95)	5 (100)

Single dose of TV005 highly immunogenic in subjects > 50 years of age

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Summary of TV005 in the elderly

- TV005 was well tolerated – incidence and spectrum of adverse events similar to that seen in flavivirus-naïve adults 18 – 50
- Incidence and magnitude of viremia were well balanced
- Neutralizing antibody response was robust and well-balanced
- Trial supports evaluation of TV003 and TV005 in older population in dengue-endemic areas

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Phase II studies TV003/TV005

- **Bangkok, Thailand – AFRIMS & Phramongutkhlao (PMK) Hospital (NIAID) in 294 subjects**
  - Adults (18 – 50), 80 subjects (60 + 20 placebo)
  - Adolescents (13 -17), 70 subjects (50 + 20 placebo)
  - Children (5 – 12), 70 subjects (50 + 20 placebo)
  - Young children (1 – 4), 70 subjects (50 + 20 placebo)
- **Dhaka, Bangladesh – ICDDR,B (NIAID), 192 subjects**
  - Adult (18 – 50), 48 subjects (36 + 12 placebo)
  - Adolescents (11 – 17), 48 subjects (36 + 12 placebo)
  - Children (5 – 10), 48 subjects (36 + 12 placebo)
  - Young children (1 – 4), 48 subjects (36 + 12 placebo)

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Neutralizing antibody responses in Thai adults (N = 84)

% Seropositivity ($PRNT_{50} \geq 10$)

	Placebo (N=24)				Vaccinees (N=60)			
Group	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	88	92	88	67	**90**	**95**	**82**	**83**
Day 32-74	92	96	92	79	**100**	**100**	**98**	**100**

Neutralizing antibody GMT

	Placebo (N=24)				Vaccine (N=60)			
	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	79	89	91	21	**110**	**77**	**83**	**41**
Day 32-74	106	119	102	28	**422**	**337**	**261**	**214**
Mean fold rise (indiv)	1.4x	1.5x	1.3x	1.5x	**13x**	**30x**	**14x**	**31x**

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52

Neutralizing antibody responses in adult vaccinees

52% of subjects

	GMT				
Subject A	DEN1	DEN2	DEN3	DEN4	
Pre-vaccine	227	384	222	135	Strong Pre-immunity
Post-vaccine	235	446	322	210	
Fold rise	1.04x	1.16x	1.45x	1.55x	No boost

32% of subjects

	GMT				
Subject C	DEN1	DEN2	DEN3	DEN4	
Pre-vaccine	14	10	651	16	
Post-vaccine	193	111	4152	2122	
Fold rise	14x	11x	6x	135x	Boost to 4 types

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Neutralizing antibody responses in adult vaccinees

	GMT				
Subject E	DEN1	DEN2	DEN3	DEN4	
Pre-vaccine	8	10	3315	53	
Post-vaccine	128	247	3935	1502	
Fold rise	17x	24x	1.2x	19x	Boost to 3 types

The Exception:

	GMT				
Subject I	DEN1	DEN2	DEN3	DEN4	
Pre-vaccine	15	28	7	17	
Post-vaccine	25	52	11	12	
Fold rise	1.6x	1.8x	1.6x	0.7x	No boost

Vaccination error? Hypogammaglobulinemia?

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Neutralizing antibody responses in Thai adolescents (N = 70)

% Seropositivity ($PRNT_{50} \geq 10$)

	Placebo (N=20)				Vaccinees (N=50)			
Group	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	50	70	60	40	**62**	**76**	**58**	**54**
Day 32-74	70	70	60	50	**100**	**100**	**100**	**100**

Neutralizing antibody GMT

	Placebo (N=20)				Vaccine (N=50)			
	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	14	54	21	9	**21.8**	**57.7**	**20.6**	**11.5**
Day 32-74	20	65	31	13	**202**	**508**	**240**	**189**
Mean fold rise (indiv)	1.4x	1.2x	1.5x	1.4x	**7.8x**	**8.6x**	**11x**	**21.2x**

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55

Neutralizing antibody responses in Thai children (N = 26)

% Seropositivity ($PRNT_{50} \geq 10$)

	Placebo (N=8)				Vaccinees (N=16)			
Group	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	63	50	63	50	**25**	**19**	**19**	**13**
Day 32-74	63	63	63	63	**89**	**100**	**100**	**100**

Neutralizing antibody GMT

	Placebo (N=8)				Vaccine (N=16)			
	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	33	15	24	12	**10**	**6.2**	**5.5**	**5.3**
Day 32-74	63	51	50	22	**53**	**251**	**155**	**259**
Mean fold rise (indiv)	2.3x	3.5x	2.1x	1.8x	**5.2x**	**40.3x**	**28.1x**	**49.0x**

CIR

56

Neutralizing antibody responses in Thai young children (N = 70)

% Seropositivity ($PRNT_{50} \geq 10$)

	Placebo (N=20)				Vaccinees (N=50)			
Group	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	15	10	20	10	**18**	**22**	**12**	**16**
Day 32-74	15	15	20	10	**76**	**100**	**96**	**96**

Neutralizing antibody GMT

	Placebo (N=20)				Vaccine (N=50)			
	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	4	4	5	4	**6**	**5**	**4**	**4**
Day 32-74	6	4	5	5	**45**	**212**	**89**	**141**
Mean fold rise (indiv)	1.2x	1.1	1.0	1.0	**7.6x**	**41.0x**	**20.4x**	**33.3x**

CIR

Seropositivity post-vaccination in those seronaive & seropositive at baseline

% Seropositivity ($PRNT_{50} \geq 10$)

	Sero-naive vaccinees (n=43)				Sero-positive (n=117)			
Group	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	0	0	0	0	**82.1**	**90.1**	**72.6**	**71.8**
Day 32-74	77	100	97.7	97.7	**98.3**	**100**	**99.1**	**99.1**
	TETRA	TRI	BI	MONO	TETRA	TRI	BI	MONO
	31 (72.1%)	11 (97.7%)	1 (100%)		114 (97.4%)	2 (99.2%)	1 (100%)	

CIR

Rise in $PRNT_{50}$ post-vaccination by pre-vaccination serostatus

Neutralizing antibody GMT

	Seronaive vaccinees (n=43)				Seropositive (n=117)			
	DEN1	DEN2	DEN3	DEN4	DEN1	DEN2	DEN3	DEN4
Day 0	2.5	2.5	2.5	2.5	56.95	71.09	38.68	24.76
Day 32-74	42.49	222.63	86.61	162.61	71.1	407.35	272.20	238.25
Ratio	12.0	89.1	34.6	65.1	5.4	5.7	7.0	9.6

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59

Adverse event profile for adults (dose one)

Adults (18 – 50 years old):

			Frequency of indicated AE (%)												
Treatment	N	% reporting AE	ALT	Arth-ralgia	Rash	Fatigue	Fever	Head-ache	IS erythema	IS pain	Leuko-cytosis	Myalgia	Neutro-penia	Photo-phobia	Retro-orbital
003	30	63	3	10	13	17	17	30	23	17	3	13	3	0	17
005	30	83	3	7	40	33	13	33	27	37	10	23	0	3	7
Placebo	24	63	0	4	8	0	0	25	29	13	8	13	4	8	13
Comparison with placebo															
P-value* for 003		1.000	1.000	0.620	0.682	0.059	0.059	0.766	0.862	0.720	0.579	1.000	1.000	0.192	0.720
P-value* for 005		0.120	1.000	1.000	0.020	0.003	0.120	0.561	1.000	0.062	1.000	0.483	0.444	0.579	0.646
003 vs 005															
P-value*		0.143	1.000	1.000	0.039	0.232	1.000	1.000	1.000	0.143	0.612	0.502	1.000	1.000	0.424

* Fisher Exact test – Two tailed
Data only for vaccine-related AE's

Adverse event profile for adolescents and children (one dose)

Adolescents (13 – 17 years old):

			Frequency of indicated AE (%)												
Treatment	N	% reporting AE	ALT	Arth-ralgia	Rash	Fatigue	Fever	Head-ache	IS erythema	IS pain	Leuko-cytosis	Myalgia	Neutro-penia	Photo-phobia	Retro-orbital
005	50	74	2	14	18	30	28	42	20	28	2	24	0	4	21
Placebo	20	65	0	0	5	10	15	25	10	25	5	25	0	10	15
P-value*		0.560	1.000	0.180	0.262	0.122	0.359	0.274	0.487	1.000	0.493	1.000	1.000	0.573	0.743

Older children (5 – 12 years old):

			Frequency of indicated AE (%)												
Treatment	N	% reporting AE	ALT	Arth-ralgia	Rash	Fatigue	Fever	Head-ache	IS erythema	IS pain	Leuko-cytosis	Myalgia	Neutro-penia	Photo-phobia	Retro-orbital
005	50	64	2	6	22	10	18	18	14	22	0	14	2	2	8
Placebo	20	55	0	10	0	10	15	20	15	10	0	5	0	5	20
P-value*		0.589	1.000	0.619	0.027	1.000	1.000	1.000	1.000	0.322	1.000	0.424	1.000	0.493	0.213

Younger children (1 – 4 years old):

			Frequency of indicated AE (%)												
Treatment	N	% reporting AE	ALT	Anemia	Rash	Dec. activity	Fever	Head-ache	IS erythema	IS pain	Leuko-cytosis	Fussi-ness	Neutro-penia	Loss of appetite	Vomiting
005	50	96	0	12	14	4	30	6	12	18	0	22	2	8	16
Placebo	20	95	0	15	15	10	35	15	10	20	0	30	0	15	10
P-value*		1.000	1.000	0.708	1.000	0.573	0.777	0.343	1.000	1.000	1.000	0.543	1.000	0.399	0.713

* Fisher Exact test – Two tailed

DEN-01-IB: Systemic Adverse Reactions

Safety results up to 21 days after vaccination

		Dengue-naive adult participants				
	N	Rash	Headache	Myalgia	Arthralgia	RO pain
Brazil	80	70.0%	50.3%	20.0%	5.0%	7.5%
USA	40	55.0%	45.0%	7.5%	0.0%	5.0%
p-value		0.111	0.699	0.111	0.300	0.717

		Dengue-exposed adult participants				
	N	Rash	Headache	Myalgia	Arthralgia	RO pain
Brazil	80	49.3%	45.3%	21.3%	12.7%	12.0%
Thailand	30	13.0%	30.0%	13.0%	10.0%	17.0%
p-value		<0.001	0.194	0.424	0.540	0.548

CIR

Institute Butantan Phase 3 Trial

- Currently enrolling 16, 800 subjects in 14 sites throughout Brazil
  - Adults (18 – 49 years) N=5600
  - Adolescents (7 – 17 years) N = 5600
  - Children (2 – 6 years) N = 5600
- A single dose of TV003
- Endpoint is efficacy against virologically-confirmed dengue of any severity
- Prevaccination sample collected on all subjects
- 5-year safety follow-up

CIR

Butantan Phase III trial

- Adult cohort 100% enrolled
- Adolescent 62% enrolled
- Child cohort 25% enrolled
- Total enrollment > 11,000
- Low dengue season in 2016 – interim analysis criteria have not been met (minimum number of dengue cases)

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64

Study Team

JHU
- Cecilia Tibery
- Tama Grier
- Beulah Sabundayo
- Eve Ostrowski
- Andrea Melton
- Kawsar Talaat
- Noreen Hynes
- Helen He
- Yolanda Eby
- Wensheng Luo
- CIR Team

BMGF
- Lynda Stuart
- Ana Aguilar

UVM
- Beth Kirkpatrick
- Kristen Pierce
- Cathy Larsson
- Patty Lutton
- Cassandra Ventrone
- Marya Carmolli
- Sean Diehl
- Ben McElvany
- Dorothy Dickson
- Ellen Fraser
- Jason Botten
- John Boyson

LID/NIAID/NIH
- Steve Whitehead
- Margarita Ossorio Goldman

AFRIMS Thailand
- Louis Macarao
- Intararit Thidarat
- Veerachai Watanaveeradej

Instituto Butantan
- Alexander Precioso
- Ricardo Palacios
- Jorge Kalil

Funded by NIAID contract: No. HHSN272200900010C

65

CYD Efficacy trials

- **CYD23 (Phase 2b)**
  - Enrolled 4,002 children **ages 4-11** in Thailand
  - No protection against DENV-2 despite induction of DENV-2 antibodies
- **CYD14 (Phase 3)**
  - Enrolled 10,275 children **ages 2-14** in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Viet Nam)
  - 68% seropositive to dengue at baseline
- **CYD15 (Phase 3)**
  - Enrolled 20,869 children **ages 9 – 16** in 5 countries in Latin America (Mexico, Colombia, Brazil, Puerto Rico, and Honduras)
  - 80% seropositive to DENV at baseline
- Randomized 2:1, vaccine:placebo
- 3 doses given over 12 months (0, 6, and 12)

66

Efficacy of CYD-TDV by age and serostatus

	Age / Serostatus	Vaccine efficacy % (95% CI)
CYD14	2 – 5 years	33.7 (11.7; 50.0)
	6 - 11 years	59.5 (48.9; 68.0)
	12 -14 years	74.4 (59.2; 84.3)
	Seropositive	74.3 (53.2; 86.3)
	Seronegative	**35.5 (-26.8; 66.7)**
	Age / Serostatus	**Vaccine efficacy % (95% CI)**
CYD15	9 – 11 years	61.7 (52.3 – 69.3)
	12 – 16 years	67.6 (59.3 – 74.3)
	Seropositive	83.7 (62.2 – 93.7)
	Seronegative	**43.2 (-61.5 – 80.0)**

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67

Hospitalized VCD CYD15 yr 3

	Vaccine Group			Control Group			
All subjects	VCD	Total subjects	Annual Incidence	VCD	Total subjects	Annual Incidence	Relative risk (95% CI)
	16	13,268	0.1 (0.1-0.2)	15	6,630	0.2 (0.1-0.4)	0.53 (0.25-1.16)
9-11 yr	10	6,029	0.2 (0.1-0.3)	9	3,005	0.3 (0.1-0.6)	0.55 (0.20-1.54)
12-16 yr	6	3,598	<0.1 (0.0-0.2)	6	3,625	0.2 (0.1-0.4)	0.50 (0.13-1.87)

Hadinegoro NEJM 2015

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68

Hospitalized VCD by age

	Vaccine Group			Control Group			
Trial	VCD	Total subjects	Annual Incidence	VCD	Total subjects	Annual Incidence	Relative Risk
<9 years							
CYD14 (yr 3)	19	3,496	0.6 (0.4-0.9)	6	1740	0.4 (0.1-0.8)	1.58 (0.61-4.83)
CYD57 (yr 3)	19	1,338	1.5 (0.9-2.4)	6	665	1.0 (0.4-2.1)	1.57 (0.60-4.80)
CYD57 (yr 4)	5	1,338	1.0 (0.5-1.7)	12	665	1.8 (0.9-3.1)	0.54 (0.23-1.29)
≥ 9 years							
CYD14 (yr 3)	8	3,285	0.3 (0.1-0.5)	6	1646	0.5 (0.2-1.0)	0.57 (0.18-1.86)
CYD15 (yr 3)	16	13,268	0.1 (0.1-0.2)	15	6,630	0.2 (0.1-0.4)	0.53 (0.25-1.16)
CYD57(yr 3)	3	793	0.4 (0.1-1.2)	5	407	1.3 (0.4-3.1)	0.31 (0.05-1.58)
CYD57 (yr 4)	3	793	0.4 (0.1-1.1)	5	407	1.2 (0.4-2.8)	0.31 (0.05-1.58)

Hadinegoro NEJM 2015

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69

Severe Hospitalized Confirmed Dengue Year 3

Trial	Age	Vaccine group n/N	Control group n/N	RR
CYD14	< 9	8/19	0/6	Could not be calculated
CYD57	< 9	4/19	0/11	Could not be calculated
CYD14	> 9	3/8	1/7	1.50 (0.12 – 78.9)
CYD57	> 9	0/3	0/5	n/a
CYD15	> 9	3/16	5/15	Not reported
	Pooled RR	18/65	6/45	1.50 (0.60 - 3.79)

Excess number of cases of severe disease observed in year 3 in CYD recipients compared to placebo in CYD14 and CYD57 (caveat: small numbers)

Hadinegoro NEJM 2015

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70

WHO SAGE recommendations

- Countries should consider the introduction of CYD-TDV only in geographic settings (national or subnational) with high endemicity, as indicated by seroprevalence of ~ 70% or greater in the age group targeted for vaccination
  - 9 – 45 years of age
- Not recommended where the seroprevalence is < 50%

CIR

71

Summary of dengue vaccine Dengvaxia™

- Additional analysis of post-vaccination samples determined increased risk of hospitalization in years 3 – 6 was related to being dengue-naïve at the time of vaccination.
- SAGE will re-review data in April 2018

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72

The Δ30 mutation

- 30 contiguous nucleotides removed from the 3' UTR
- Similar stem loop structure found in all DENV

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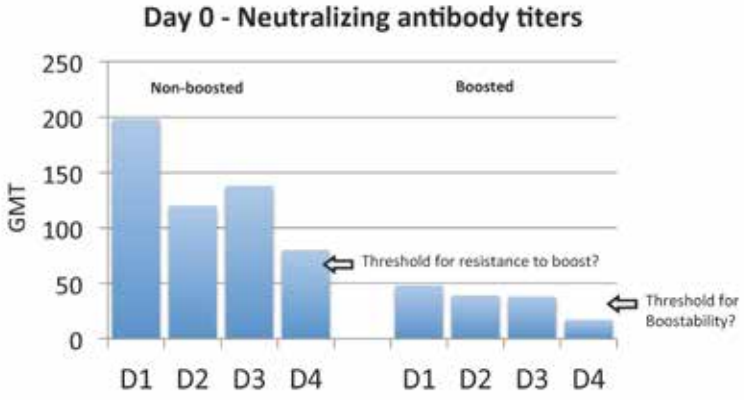
73

Neutralizing antibody responses in Thai adult vaccinees



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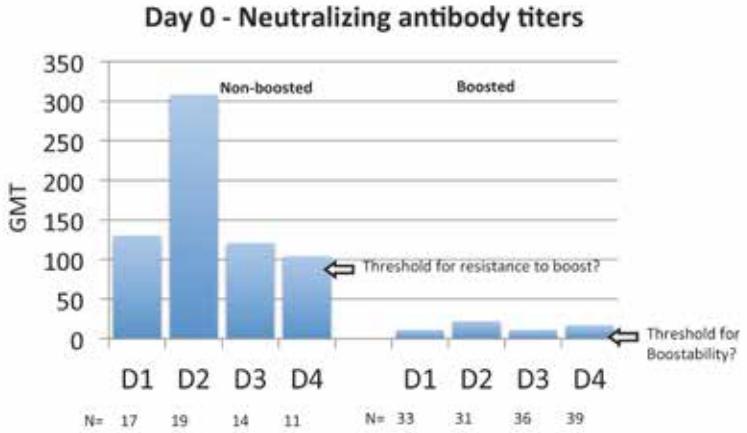
74

Neutralizing antibody responses in Thai adolescent vaccinees



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75

Speaker

Prof. Michael Malison

Position: Adjunct Professor

Department/ Organization: Department of International Health, Rollins School of Public Health, Emory University

Economy: The United States

Educational Background

- MPA 1990 (Kennedy School of Government, Harvard University)
- MD 1978 (University of Miami)
- BA 1973 (Catholic University of America)

Professional Career

- Board Certified – General Preventive Medicine and Public Health CDC Medical Epidemiologist 1981-2013
- Resident Advisor to the Chinese Taipei FETP 1984-1988
- Emory University Adjunct Faculty 1984-present
- Board Member, American Bureau for Medical Advance in China Consultant, Medigen Vaccine Biologics Corp Chinese Taipei (2017 – present)

Publications

- Setliff R, Porter JE, Malison M, Frederick S, and Balderson TR. Strengthening the Public Health Workforce: Three CDC Programs that Prepare Managers and Leaders for the Challenges of the 21st Century. J Pub Health Management Pract 2003; 9(2): 91-102.
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- Do MH, Bui TTH, Phan VT, Nguyen HL, Duong TA, Le BC, Pham TTL, Nguyen MH, Nguyen PT, Malison MD. Strengthening Public Health Management Capacity in Vietnam – Preparing Local Public Health Workers for New Roles in a Decentralized Health System. J Pub Health Management & Pract 2018;24(2 Supp): S74-S81.

Speech Abstract

Dengue Drivers, Restrainers, and the role of Biomedical Interventions

In the past two decades, the global incidence of dengue has steadily increased driven mainly by urban growth, the improper disposal of solid waste (especially plastics), and cheap global travel. For the first time, several new promising biomedical interventions are on the horizon that will potentially reduce dengue transmission; these include several vaccine candidates as well as Wolbachia-infected mosquitos that are less efficient hosts for the dengue virus. While these interventions are potential game-changers, we mustn't neglect the social and environmental factors that drive the global spread of dengue as well as other arboviruses like Zika virus. Chinese Taipei is an example of a country that is providing leadership in both in dengue vaccine production as well as solid waste recycling. Hopefully, other countries will recognize the value of developing a similar approach that combines biomedical interventions specific to dengue with programs that address the underlying social and environmental determinants of multiple infectious diseases including dengue.

Speaker

Dr. Ta-Wen Yu

Position: Regional Medical Head

Department / Organization: Regional Medical Affairs, Sanofi Pasteur

Economy: Singapore

Educational Background

- Medical Degree, Grad Dip in Occupational Medicine

Professional Career

- 8 years of clinical practice, mainly in paediatrics and oncology
- Over 10 years of experience in vaccines within the industry

Publications

- Burden of hospitalized childhood community-acquired pneumonia: A retrospective cross-sectional study in Vietnam, Malaysia, Indonesia and the Republic of Korea
  Hum Vacc Immunother 2017 (https://doi.org/10.1080/21645515.2017.1375073)
- Safety and reactogenicity of the combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae type b (DTPa-IPV/Hib) vaccine in healthy Vietnamese toddlers: an open-label, phase III study
  Hum Vacc Immunother 2015 (http://www.tandfonline.com/doi/pdf/10.1080/21645515.2015.1084451)
- Safety and Reactogenicity of the 10-valent Pneumococcal Non-Typeable Haemophilus influenzae protein D-Conjugate Vaccine (PHiD-CV) Co-administered with DTPa-HBV-IPV/Hib in Vietnamese Infants
  BMC Infectious Diseases 2013, 13:95 (http://www.biomedcentral.com/1471-2334/13/95)

Speech Abstract

Update of Dengue vaccine developed by Sanofi Pasteur

Overview

Dengue is the most common mosquito-transmitted viral infectious disease. It continues to pose a significant public health threat to individuals living in endemic countries where the virus causes 390 million dengue infections each year, of which 96 million are symptomatic with 500,000 resulting in severe disease. The World Health Organization (WHO) state dengue is a major public-health concern throughout tropical and sub-tropical regions of the world. The WHO introduced an Integrated Management Strategy for Dengue Prevention and Control (IMS-dengue) to help strengthen national programs.

The first dengue vaccine (CYD-TDV / Dengvaxia® developed by Sanofi Pasteur) was registered in 2015 for use in individuals living in dengue endemic areas (9-60 years depending on license) and has been licensed in 20 countries and introduced in public immunization programs in the Philippines and Brazil.

While initial results using the recommended PRNT50 indicated that CYD-TDV performed better in those who had previous dengue infection than those who did not have a previous dengue infection, additional long-term follow-up data and especially post-hoc analyses using a newly developed research assay, a dengue Anti-NS1 IgG Elisa (NS1 Supplemental Analyses) provided additional insights on vaccine performance. These analyses indicated that for those with past dengue infection prior to vaccination (seropositive) there is a persistent protection against symptomatic dengue, including hospitalization and severe dengue disease 5 years after the first injection, while in those with no previous dengue infection before vaccination (seronegative) there is a short-term protection and a relative increased risk of hospitalization due to dengue and severe dengue cases. The onset of increased risk was mainly during the 3rd year following the first injection. The newly-generated data was shared by Sanofi with regulators and WHO.

In April 2018, WHO's Strategic Advisory Group of Experts (SAGE) on Immunization met in Geneva to review the recommendations on the dengue vaccine by the reconvened Dengue Working Group (DWG). The DWG reviewed new data on the long-term follow-up of dengue vaccine recipients, including data generated by additional laboratory testing and analysis related to the long-term safety and efficacy of CYD-TDV Phase 3 trial participants. In particular, the group was asked to review the

differential performance of the CYD-TDV vaccine in subjects seronegative versus seropositive at the time of vaccination. The DWG came to the overall conclusion that CYD-TDV still has a potential public health role, in the absence of currently available alternative solutions to combat the expanding problem of the global dengue burden. The challenge is how best to use CYD-TDV to maximize the public health impact, and minimize harm.

Presentation objectives

The purpose of the presentation is to review:

- Licensure status update
- Dengue vaccine Clinical Development Plan results
- Dengue vaccine Long-term follow-up results
- NS1 Supplemental analyses results
- Updated SAGE recommendations

NOTE

Session III

New Technology Development in Vector Surveillance and Control

Moderator

Ching-Len Liao
Investigator and Director, National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Chinese Taipei

Moderator

Dr. Ching-Len Liao

Position: Investigator and Director

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Economy: Chinese Taipei

Educational Background

- PhD, Department of Microbiology and Immunology, School of Medicine, University of Southern California.

Professional Career

- 2009-present Professor, Department of Microbiology and Immunology, NDMC.
- 2014-present Director, National Institute of Infectious Diseases and Vaccinology, NHRI.
- 2015-present Director, National Mosquito-Borne Diseases Control Research Center, NHRI.

Publications

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Session III

New Technology Development in Vector Surveillance and Control

Speaker

Cheong-Huat Tan
Research Scientist, Environmental Health Institute,
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Kun-Hsien Tsai
Associate Professor,Institute of Environmental Health,
National Taiwan University, Chinese Taipei

Wu-Chun Tu
Professor, Medical Entomology Laboratory, Department of
Entomology, National Chung Hsing University, Chinese Taipei

Speaker

Dr. Cheong-Huat Tan
Position: Research Scientist
Department / Organization: Environmental Health Institute, National Environment Agency
Economy: Singapore

Educational Background

- Doctor of Philosophy (Biological Sciences). 2016. Monash University (Australia).
- Master of Science (Entomology and Molecular Parasitology). 2008. University Malaysia Sarawak (Malaysia)
- Bachelor of Science (Zoology). 1995. University of the Philippines (Republic of the Philippines).

Publications

- TAN CH, Tan LK, Hapuarachchi HC, Lai YL, Wong, PSJ, Yap G, Mak KW, Wong, WY, Leo YS, Wong CW, Ng LC. (2018). Viral and Antibody Kinetics, and Mosquito Infectivity of an Imported Case of Zika Fever Due to Asian Genotype (American Strain) in Singapore. Viruses 10:44.
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Speaker

Dr. Kun-Hsien Tsai

Position: Associate Professor

Department / Organization: Institute of Environmental Health, National Taiwan University

Economy: Chines Taipei

Educational Background

- Ph.D. in Department of Entomology, College of Bioresources and Agriculture, National Taiwan University, Chinese Taipei

Professional Career

- Deputy director, Department of Public Health, CPH, NTU (2017.08 ~)
- Associate Professor, Institute of Environmental Health & Department of Public Health, CPH, NTU (2016.08 ~ present)
- Assistant Professor, Institute of Environmental Health & Department of Public Health, CPH, NTU (2012.08~2016.07)
- Deputy director, Global Health Center, NTU (2016.08~2017.07)
- Adjunct Research Fellow, Global Health Center, NTU (2012.08~2016.07)
- Joint Appointment Research Fellow, Infectious Diseases Research and Education Center, MOHW-NTU (2012.08~present)
- Advisor, Centro Nacional de Endemias, Ministerio da Saude, DRSTP, West-Central Africa (2014.01~2016.12)
- Short-term expert advisor, Taiwan Anti-malaria Advisory Mission, DRSTP, West-Central Africa (2011.01~ 2016.12)

Publications

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Speech Abstract

Field Experience on Ecological Control of Dengue and Malaria Vectors

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Malaria and dengue fever are the two most important mosquito-borne infectious diseases around the world. With the successful elimination of malaria since 1965, the politics, economics, and society of Chinese Taipei have made great progress. However, globalization and urbanization have also resulted in the growing threat of dengue fever. Looking back at the history, we reflected on the battles against dengue and malaria, a concept of integrated vector management with eco-friendly approaches, WILD technology, derived from Wide, Integrated, Long-term, and Deep-going, was proposed. To practice this idea, we have launched four field works to evaluate the long-term effect of these ecological control tools. For example, studies have been conducted in Chinese Taipei to examine the results of biological control using native copepods in flooded basement and vegetation garden, auto-dissemination of pyriproxyfen (insect growth regulator) by Aedes mosquitoes for cryptic source, and attractive larvicidal ovi-trap containing boric acid solution for vector density surveillance. In Sao Tome and Principe, a nation in West-Central Africa, the performance of Bacillus thuringiensis subsp. israelensis (Bti) in controlling malaria vector Anopheles coluzzii (formerly Anopheles gambiae M form) has been investigated as well. Our findings suggested that the above tools were not only feasible and sustainable for long-term interventions but valuable to be promoted in diverse environment.

Key words: dengue, malaria, copepod, pyriproxyfen, larvicidal ovi-trap, Bti, biological control

APEC Conference on Severe Dengue Prevention and Strategies for Reducing Disease Burden

Asia-Pacific Economic Cooperation

Field experience on ecological control of dengue and malaria vectors

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[2] Infectious Diseases Research and Education Center, the Ministry of Health and Welfare and National Taiwan University

Introduction

- Mosquito-borne diseases
  - malaria, lymphatic filariasis, and arboviruses such as dengue virus and Zika virus
  - no vaccines or drugs is available for most of these diseases
- Mosquito control
  - vector control is the main form of prevention
  - the limitations of traditional insecticide-based strategies is insecticide resistance
- Sustainable and eco-friendly strategies
  - Environmental methods and biological control are alternatives to chemical control
    - Cost, reliable……

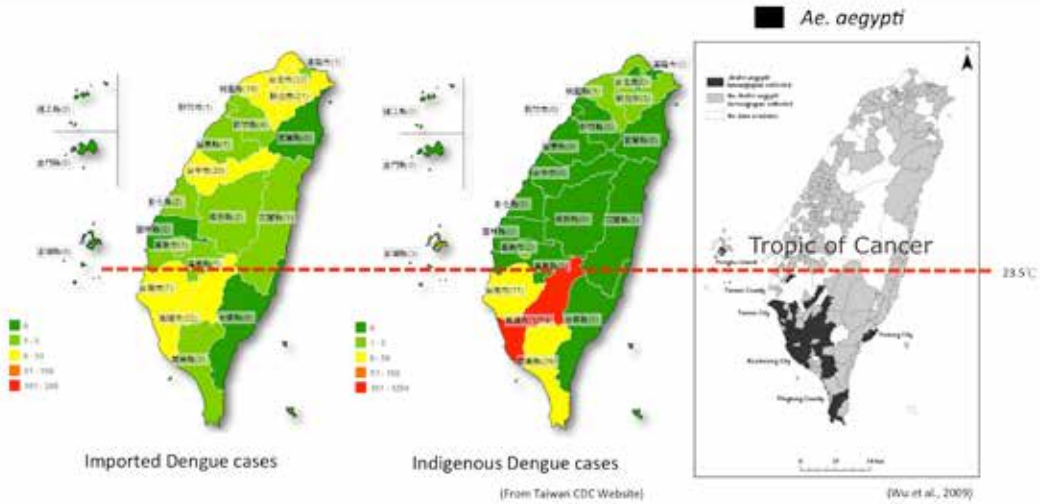
Mosquito diversity in Chinese Taipei

- Mosquito species
  - 16 Genus 132 species were recorded (Lien 2004)
- Disease vector
  - *Ae. aegypti*
  - *Ae. albopictus*
  - *Cx. tritaeniorhynchus*
  - *An. minimus*
- Nuisance
  - *Cx. quinquefasciatus*
  - *Cx. pipiens* form *molestus*
  - *Ar. subalbatus*
- Feeding host and behavior
  - ecological information is limited

Aedes aegypti

Larvae siphon

Dengue Cases and Vector Distribution in Chinese Taipei



Imported Dengue cases

Indigenous Dengue cases

(From Taiwan CDC Website)

(Wu et al., 2009)

Integrated Dengue Fever Vector Control

- Environmental Management
  - Environmental manipulation, Environmental modification, Changes to human habitats and behavior
- Chemical Control
  - Larvicides, pupacidide, adulticides
- Biological Control
  - Biocide *Bti*, IGR, larvivorous fish, copepods
- Genetic Technology
  - Population suppression, Population replacement
- Personal Protection
  - Mosquito net and mosquito repellent

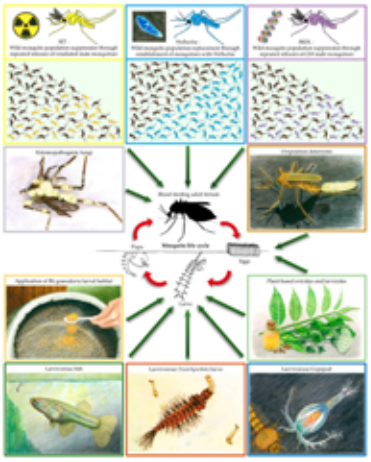


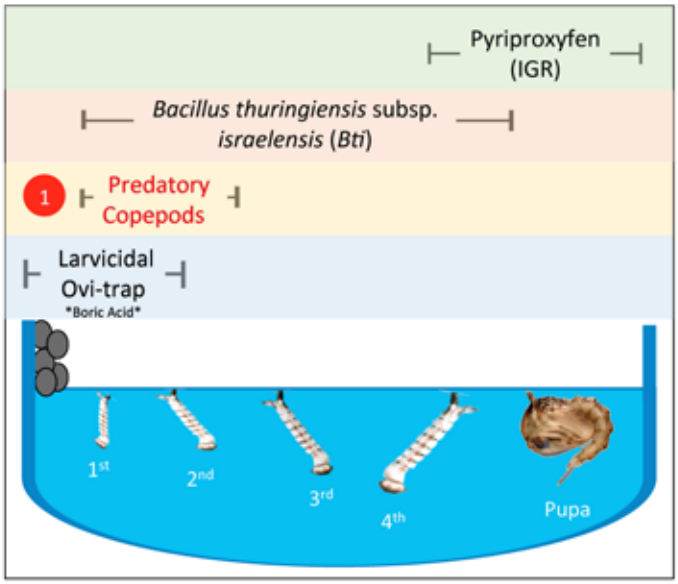
Fig. Mosquito biocontrol strategies targeting different stages of the mosquito lifecycle. (Benelli et al., 2016)

Source reduction: from containers to buildings

SB05Tokyo Student Session
building a sustainable future

WILD Technology
- Wide
- Interactive
- Long-term
- Deep-going

(Archilife Research Foundation, Sustainable Building 2005)



- Eco-friendly
- Environment sustainable
- Effective predator
- Easy mass production
- Inexpensive
- Indigenous species
- Species specific
- Unaffected by *Bti* & pesticide

Fig. Immature control methods in this study

Nation-wide surveillance of copepods

- Four major species of copepods with highly predatory efficiency
  - *Mesocyclops aspericornis, M. pehpeiensis, M. woutersi, M. ogunnus*

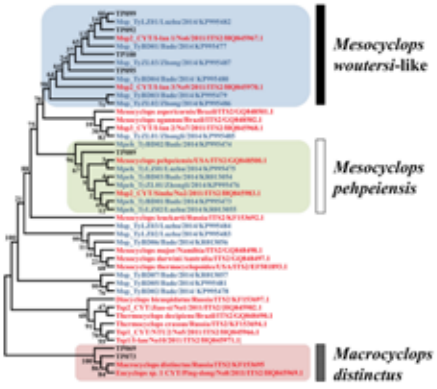


Fig. Phylogentic tree of copepods collected in northern based on ITS-2 gene sequence.

Fig. Surveillance of copepods in field.

● 2011~2014 ● 2013~2016

Predation Efficiency in Laboratory

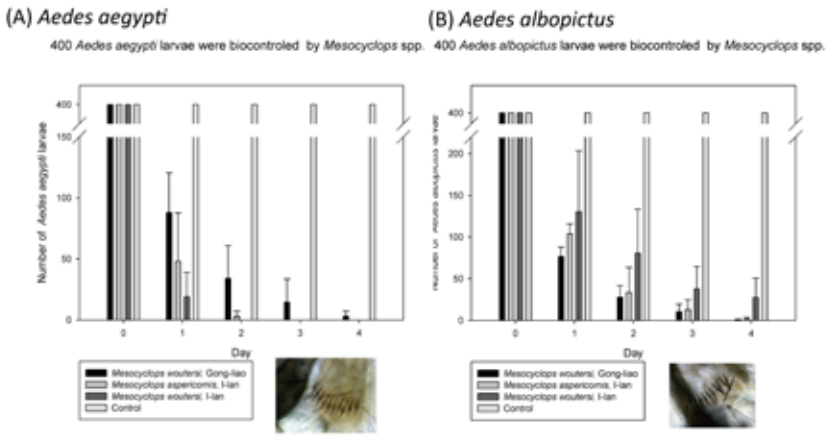


Fig. The change of (A) *Ae. aegypti* and (B) *Ae. albopictus* larval population within 96 hours under the predation of 10 *Mesocyclops*.

Table Follow-up survival rate of copepods among four types of flooded basements from March 2012 to December 2013

Types	No. observation sites	No. site with survival copepods*	Survival rate (%)
TSV[a]	3	0	0
CSV[b]	8	1	12.5
CMV[c]	9	5	55.6
CLV[d]	4	3	75.0
Total	24	9	37.5

* Site with stable population of both pregnant female adult and nauplius, and appearance of copepods with at least one time per season were treated as survival.
[a] TSV: small volume of turbid water
[b] CSV: small volume of clear water
[c] CMV: medium volume of clear water
[d] CLV: large volume of clear water

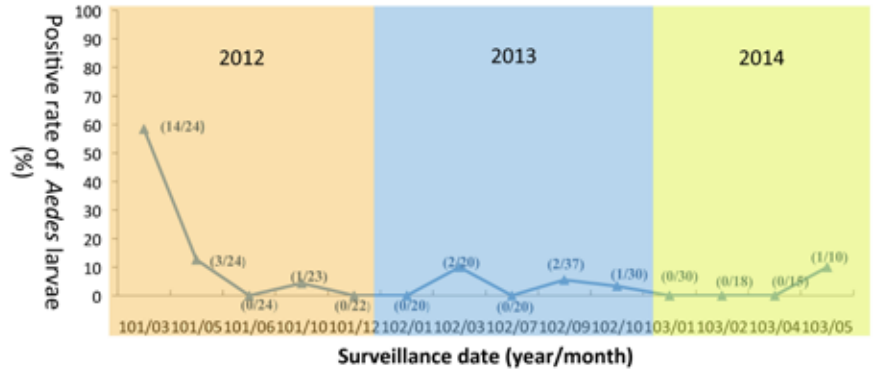
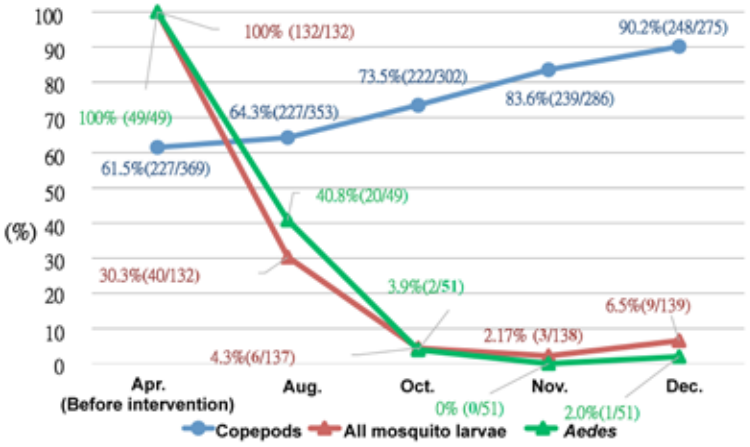
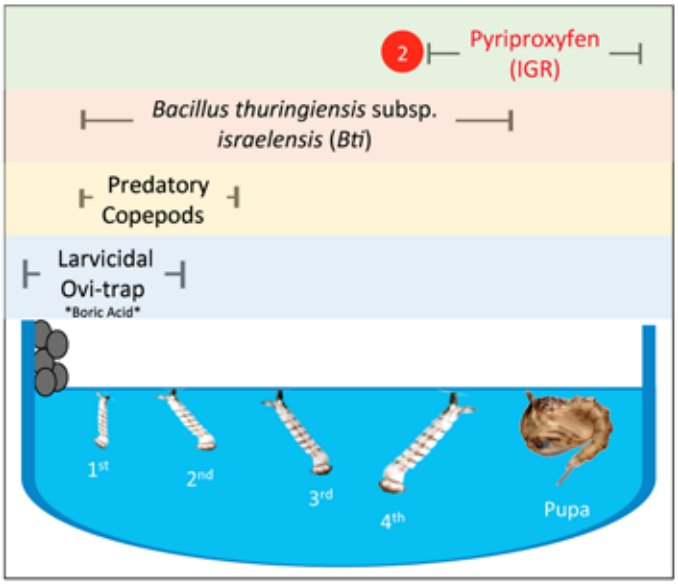


Fig. The positive rate of larvae breeding sites after introducing local predatory copepods. The numbers on broken line graph means (no. breeding site with *Aedes* larvae/total breeding site).



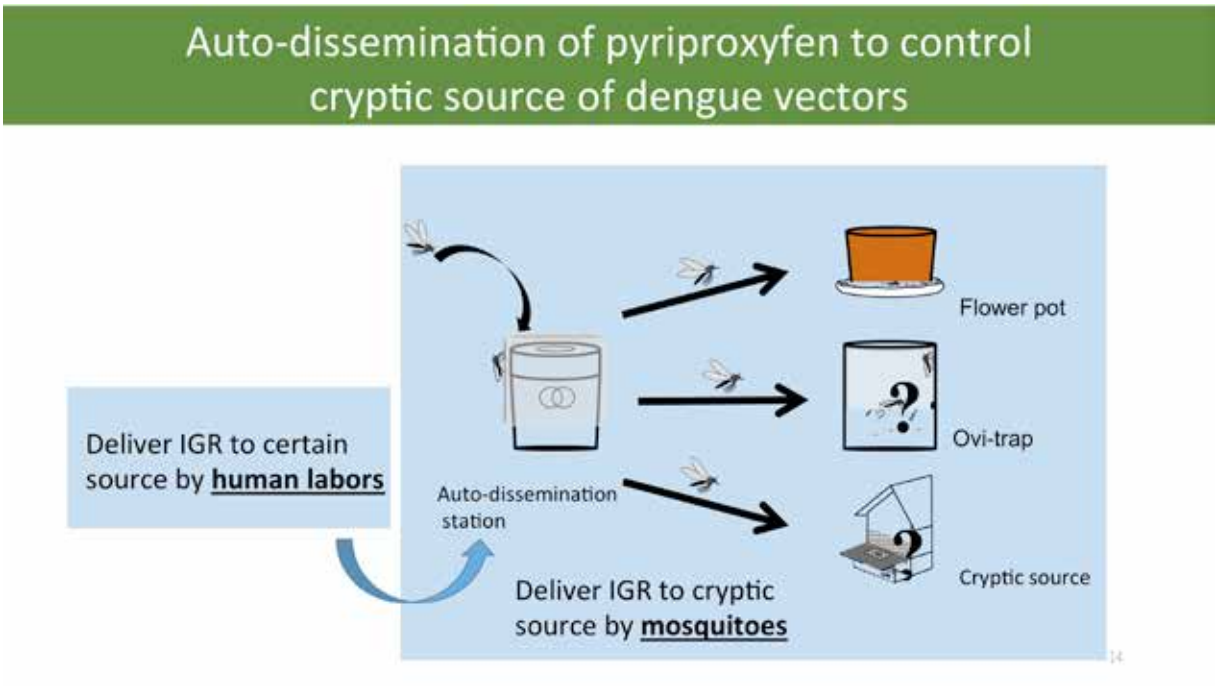
- **Coverage of copepods: 61.5%➔90.2%**
- **Appearance of mosquito larvae**
  Total: 132➔9 (↓93.1%)
  ***Aedes* mosquito: 49➔1 (↓ 97.9%)**

Fig. Evaluation of coverage and control efficiency by copepods after delivering artificially of copepods in water containers in agricultural environment.



- Pyriproxyfen (PPF)
  - a juvenile hormone analogue that interferes with insect morphogenesis, embryogenesis and reproduction
  - a conventional mosquito pupacide, has a unique mode of action that also sterilises adult mosquitoes (unable to produce viable offspring) via direct contact

Fig. Immature control methods in this study



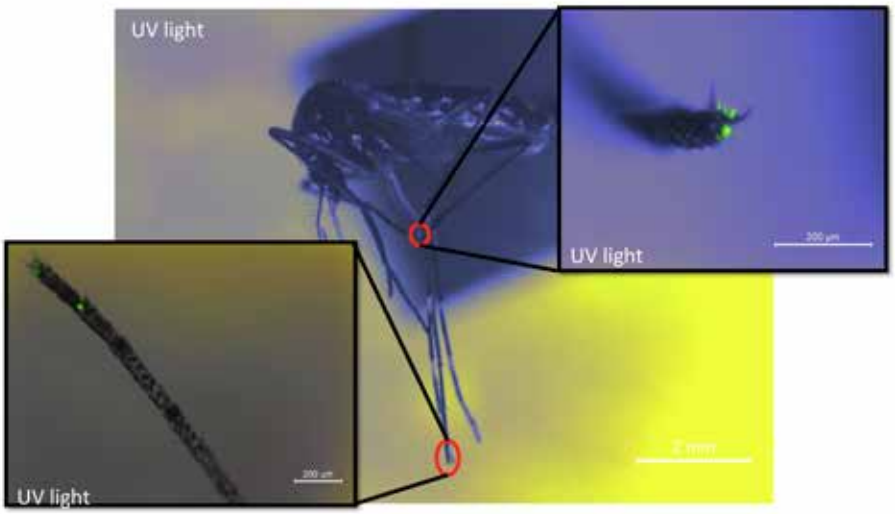
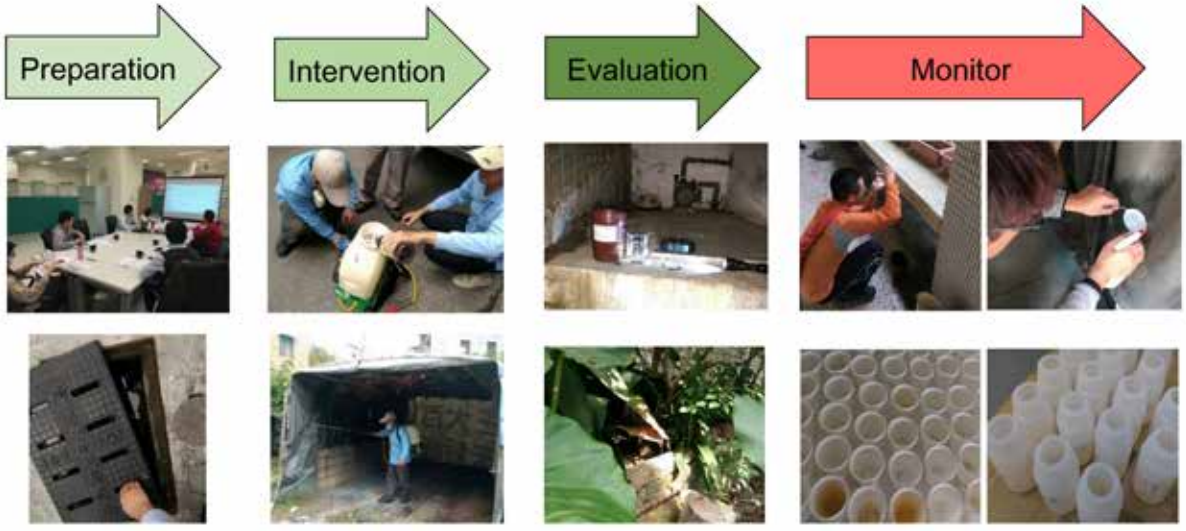


Fig. Observation of mosquito tarsus carrying PPF by luminous powder kit

15

Field study at Kaohsiung City



16

Fig. PPF dissemination stations and locations of monitoring traps

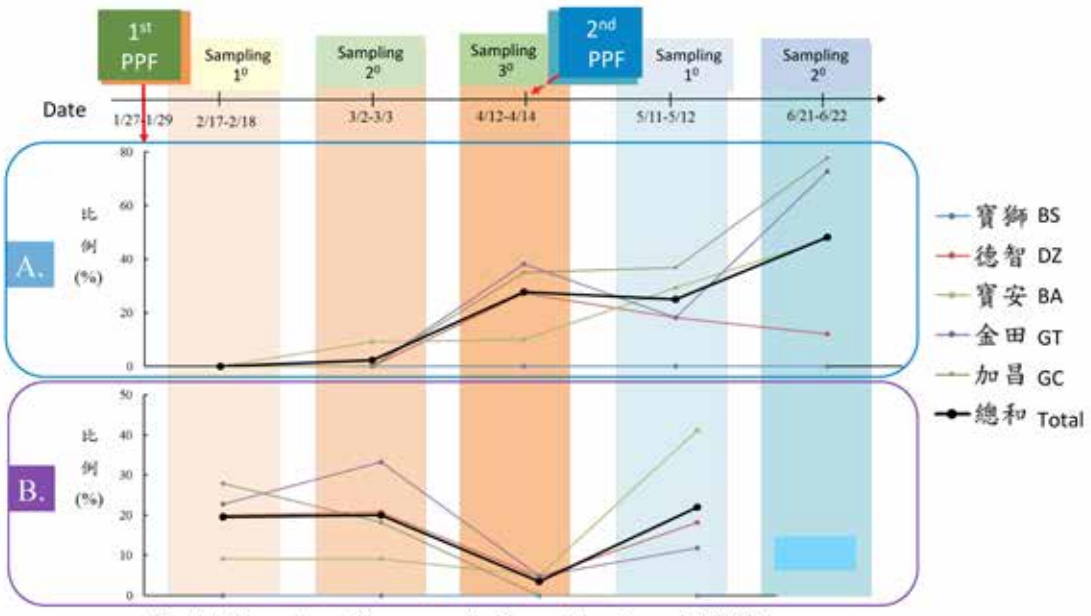


Fig. (A) Percentage of eggs occupied in container in each Li (里);
(B) Percentage of effective dosage of PPF (IE%>50) in field water samples.

Table Bioassay of residual effect of PPF after 33 days

Area		No. PPF station	IE%	
			> 50	≦50
三民區 SanMin Dis.	德智里 DZ	5	5	0
	寶安里 BA	5	1	4
楠梓區 NanZi Dis.	金田里 GT	4	2	2
	加昌里 GC	3	0	3
Total		17	8	9
%		100.0	47.1	52.9

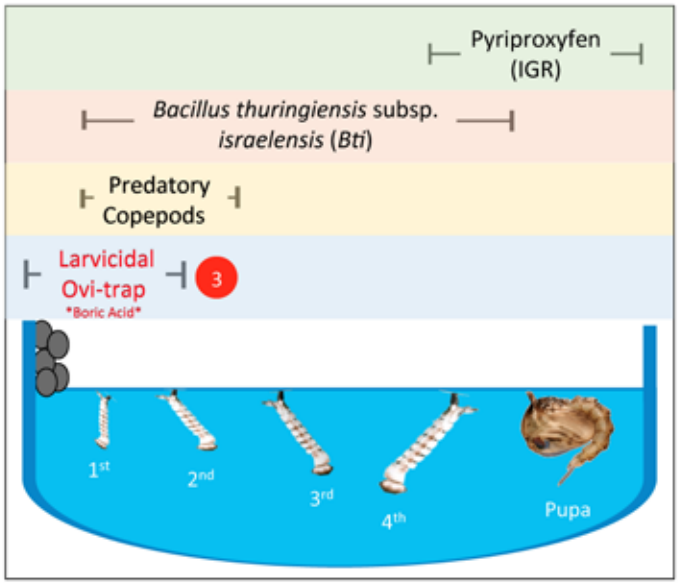


Fig. Immature control methods in this study

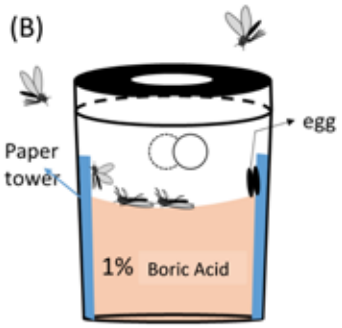


Fig. Diagram of larvicidal ovid-trap

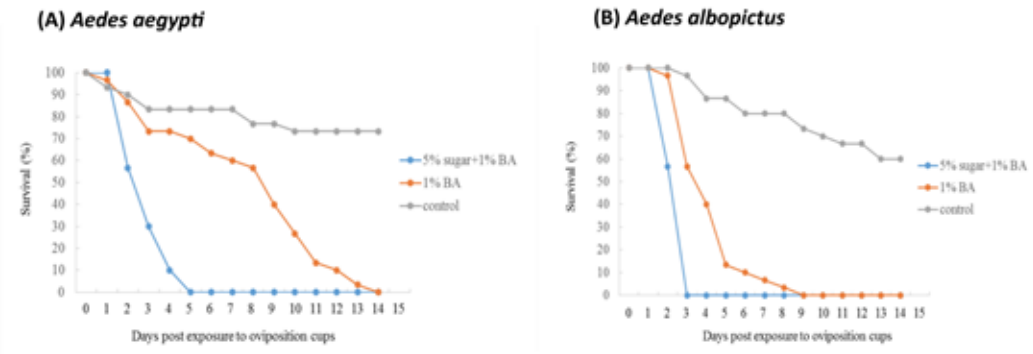


Fig. Laboratory evaluation of survival curve of female mosquitoes living in larvicidal ovi-trap which containing 1% boric acid (A) *Aedes aegypti* and (B) *Aedes albopictus*

21

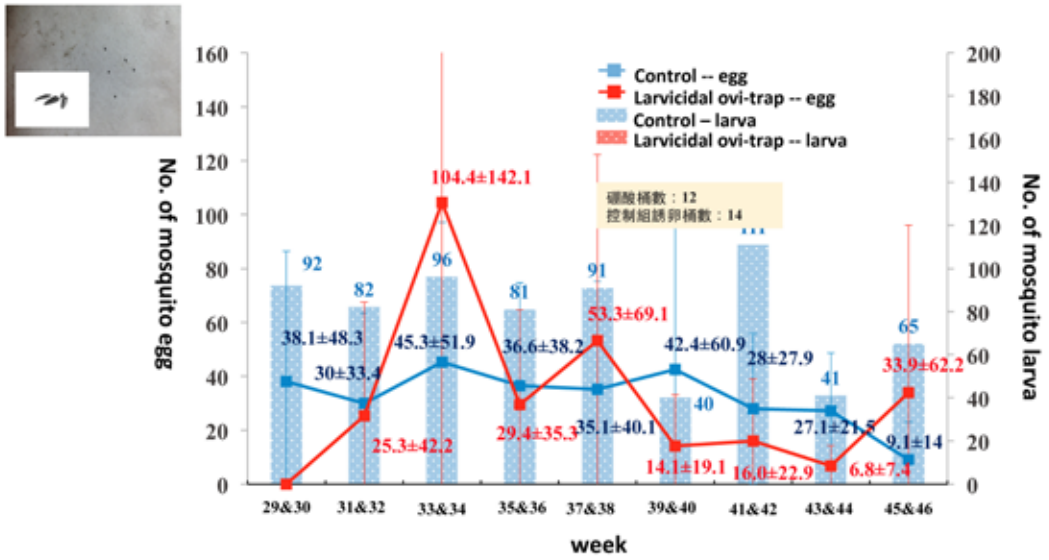


Fig. Field trials of larvicidal ovi-trap in Kaohsiung City

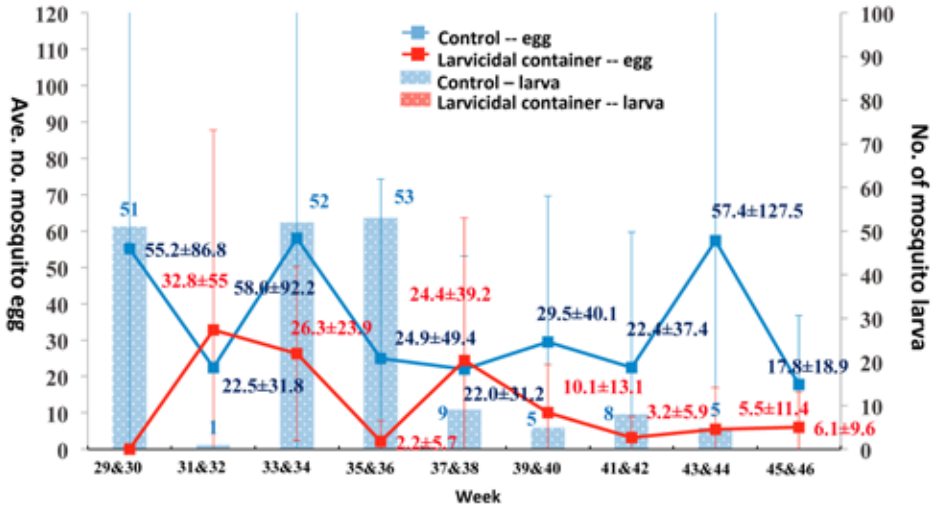
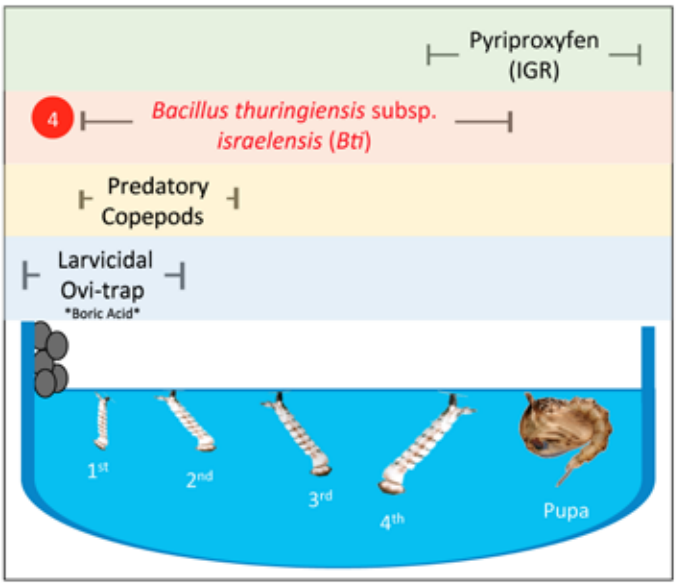


Fig. Field trials of larvicidal ovi-trap in Tainan City



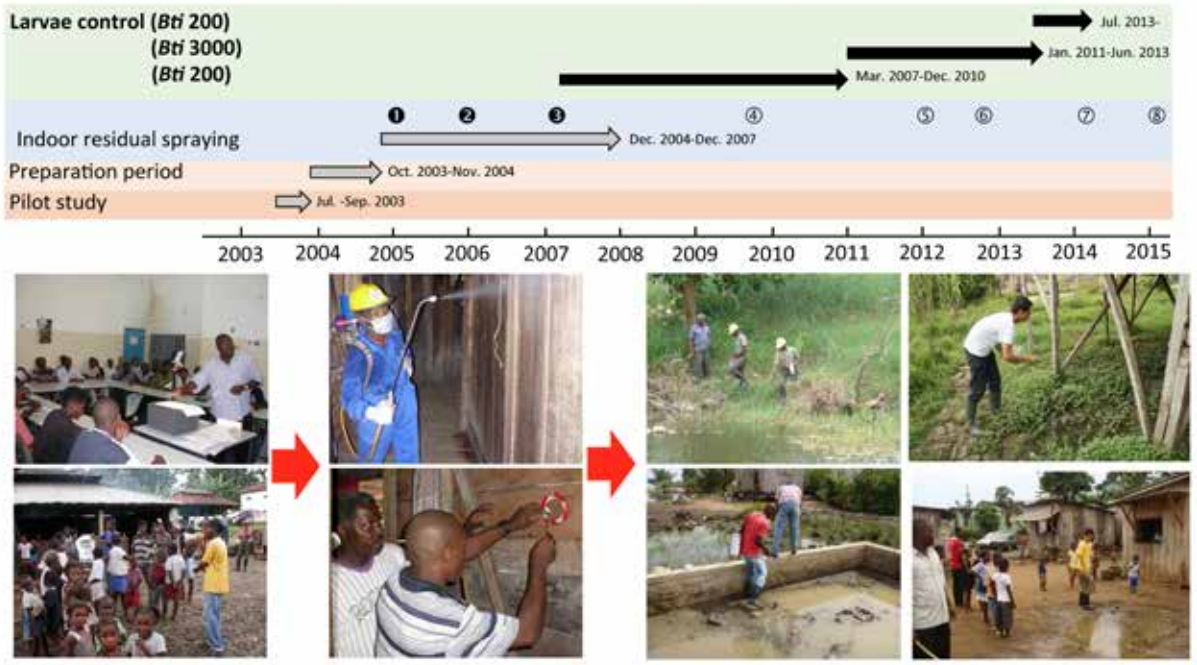
Bti

- is a naturally occurring bacterium found in soils
- contains spores that produce toxins that specifically target and only affect the larvae of the mosquito, blackfly and fungus gnat.
- has no toxicity to people and is approved for use for pest control in organic farming operations
- no documented resistance to *Bti* as a larvicide

Fig. Immature control methods in this study

Fig. Map of the Democratic Republic of São Tomé and Príncipe (DRSTP)

Map of the Democratic Republic of São Tomé and Príncipe (DRSTP) (left panel). Sampling sites are listed below. 1: Praia Gamboa, 2: Riboque, 3: Trindade, 4: Praia Melao, 5: Ribeira Afonso, 6: Zandrigo, 7: Angolares, 8: Emolve, 9: Micolo, 10: Conde, 11, Neves, 12: Generosa.



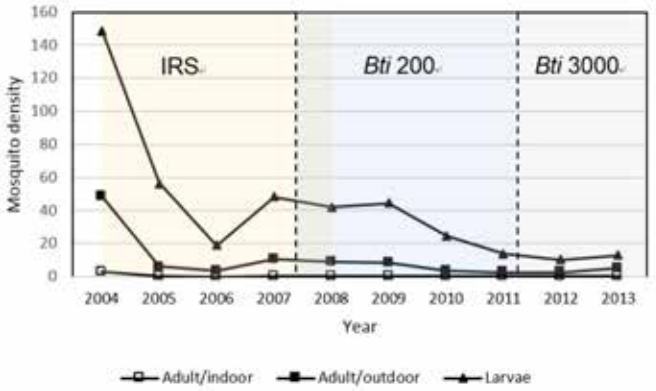


Fig. Yearly trends of average mosquito density in São Tomé in 2004-2013

The mosquito densities for Adult/indoor or Adult/outdoor are represented by the number of mosquitoes/house/hour/month. The larval density is represented by the number of mosquitoes/person/hour/month.

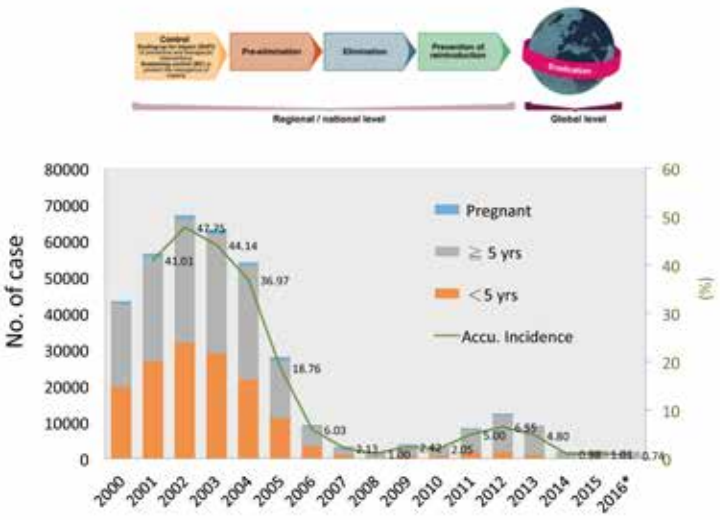


Fig. Malaria epidemiology in the DRSTP during 2000 to 2016.

Conclusion

- Chemical control
  - Pyriproxyfen
    - Auto-dissemination
- Biological Control
  - Larvivorous fish
  - *Bacillus thuringiensis* subsp. *israelensis* (*Bti*)
    - Lower down the cost by developing native fertilizer industry
  - Copepods
    - Applied in agricultural area

- Larvicidal ovi-trap with boric acid
  - For surveillance as well as ATSB

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➢ **Dr. Tsai's Lab. (NTU)**
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- Ying-An Chen
- Ying-Chieh Lee (G)
- Cheng-Yen Tsai (G)

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- Dr. Wer-Jer Wu
- Dr. Chin-Chi Huang

➢ **Department of Health, Kaohsiung City Government**

➢ **Department of Health, Tainan City Government**

➢ **Taiwan Anti-Malaria Advisory Team in DRSTP**
- Dr. Jih-Ching Lien
- Lien-Fen Tseng
- Chien-Fu Cheng
- The health workers in São Tomé and Principe

Thank you for your attention ~

Speaker

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Professional Career

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- Taiwan Apicultural Society, Chairman (Current)
- Taiwan Entomological Society, Member of Board of Supervisors (Current)
- Taiwan Environment Pest Association, Member of Board of Directors (Current)

Publications

- Lee-Jin Bong, Wu-Chun Tu, Kok-Boon Neoh, Chin-Gi Huang, Rou-Xing Ting 2018. The Effect of Insecticidal Stress on Reproductive Output of Susceptible and Field Strains of Aedes aegypti (Diptera: Culicidae). Journal of Medical Entomology. 55(1): 36-42.
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- Wang Xi, Wu-Chun Tu, En-jiong Huang, Yen-Hou Chen, and Wen-Bin Yeh. 2016 Identification of disease-transmitting mosquitoes: development of species-specific probes for DNA chip assay using mitochondrial COI and ND2 genes and ribosomal internal transcribed spacer 2. Journal of Medical Entomology. 2016, 1-7.
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- Yang, M. J., W.Y. Lin, R. F. Hou, C. H. Lin, C. L. Shyu, and W. C. Tu. * 2013. Enhancing antimicrobial activities of mastoparan-B by amino acid substitutions. Journal of Asia Pacific Entomology 16: 349-355.

Speech Abstract

New Approach of Mosquito Vector Surveillance and the Application of Environment Management

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Dengue fever is one of the most important mosquito-borne viral diseases in the world. More than 50 million dengue patients were reported each year. Recently, dengue fever become a serious threat in Chinese Taipei. In 2015, 43,784 of dengue cases were reported in Chinese Taipei, of which 43,419 were local infection. The two major dengue vectors in Chinese Taipei are Aedes aegypti and Ae. albopictus. Ae. aegypti is distributed in the southern part of Chinese Taipei. ChiaYi county, where the Tropic of cancer passes through, is the northern most boundary of its distribution. Ae. albopictus is distributed below 1500 meters latitude in the whole island. More than 95% of dengue cases occurred in the areas where Ae aegytpi is distributed, suggesting that Ae. aegypti control is prioritized matters on prevention/control dengue program in Chinese Taipei. Dengue fever is a mosquito-borne infectious disease. Therefore, the vector control is the main approach for dengue control. The best strategy for dengue prevention/control is using integrated vector management (IVM).

A successful IVM requires a complete/systematic operation, which includes the implementation of container reduction, community participation, chemical control, and vector surveillance. Among them, the density monitoring of vectors is an important parameter in IVM. It directly links the risk of dengue fever outbreak, and according to the vector surveillance information we obtained to understand the changes of vector population, spatial distribution, and play an early warning.

The vector surveillance methods include house index, container index, Breteau index, larval index, and adult index. Among them, the Breteau index has more objective reference value and is widely used, it is also the method recommended by the WHO. However, these are all passive monitoring methods, the monitoring data are easily affected by the quality and experience of the implementers. In addition, densely populated cities and three-dimensional buildings cause changes in the breeding sites of vector mosquitoes. In addition, the inspectors are not likely to enter the building for survey, resulting the low level of the Breteau index. Thus indicating that this survey method is no longer suitable for modern cities. In addition, the WHO recommends that urban communities with a Breteau index below 5 may consider an alternative approach with ovitrap surveillance.

Ovitrap surveillance is an active type of survey method. It is based on the habit of gravid female mosquito who searching for oviposition in containers. Certain number of ovitraps were placed in specific monitoring sites, and the positive rate of ovitraps and the trapped eggs were examined regularly.

No any vector index is absolutely accurate. However, relative reference values can be obtained as long as the method is consistent. Therefore, the use of ovitrap is simple, small, convenient to operate, and can be widely distributed in the community with regular high-frequency inspections. The dynamics of vector mosquito population will be observed immediately.

In 2016, the National Mosquito-Borne Diseases Control Research Center began to promote the ovitrap approach as regular dengue vector surveillance in southern Chinese Taipei where the highest risk areas of dengue, including Tainan City, Kaohsiung City, and Pingtung County. The smallest administrative district “Li” is used as a monitoring unit, it set aside 10 ovitraps in each unit, and regularly check the positive rate and calculate the number of eggs every week.

The purpose of vector surveillance is dengue early warning. In case if there isn’t a match for real-time environmental management system, it lose its early warning effectiveness. We designed a surveillance-management dengue control system. According to the surveillance data, the positive rates (PR) of ovitap were divided into three parts, PR>60%, 60%>PR>30%, amd PR<30%. The egg number (EN) were divided into three parts , EN>500, 500>EN>250, EN<250. \Based on 3 by 3 grid concept, the survey data were divided into nine management bases. The first level of priority management is PR>60% with EN>500, the second is PR>60% with 500>EN>250, and the following were ranked according to the PR and EN.
In addition, we develop a management information system for dengue vector control. A website was built to calibrate each survey site on the global positioning system, and different gradient colors were used to show the change in egg number of ovitrap. The data is updated once a week, and management reports were generated synchronously.

This dengue vector management system is based on surveillance data as index. Updates of the website every week allowed us to provide vector control reference to the charged unit of government, and immediately initiates environmental management or chemical control according to the surveillance results. This system has been implemented for more than one year and has become an important tool for dengue vector control in Tainan. This system was used to monitor eight high dengue risk districts in Tainan, with a total 288 “Li” and 3,456 ovitrap.

Regular ovitrap surveillance can be used as a basis for accurate management and as an evaluation reference for vector control effectiveness. 63.3% of the monitored districts in Tainan showed significant reduction after mobilizing environmental management with previous detection of positive rate above 60% and egg number >500.

Vector surveillance is important for mosquito-borne diseases control program, it can predict disease outbreak, serve as vector management index, and evaluate the effectiveness of vector control. It can understand the spatial distribution of vector mosquitoes in community of cities. Our survey data show that the distribution of Ae. aegypti is highly correlated with residential density, housing density, and the vegetation area in city. Except regular routine monitoring, ovirtap surveillance can also be temporarily deployed in the event of an outbreak as a basis for the evaluation of the effectiveness of vector control actions. This system is also possible to identify the mosquito density information of the area where the imported patient stay, and immediately estimate the risk and plan the vector control action.

In the past two years we have confirmed that the dengue fever is preventable. There are many reasons for successful prevention or control of dengue fever. Among then, the ovitrap surveillance plays a critical role. The most importance of all is the joint efforts of the government and community who work together on the environment management of source reduction.

Closing Remarks Speaker

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Economy: Chinese Taipei

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- MPH (Epidemiology), National Taiwan University, Chinese Taipei
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Professional Career

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- Deputy Health Commissioner, Taipei County Health Department
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Publications

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