

**UPDATE ON DENGUE VACCINES
AND
PEDIATRIC ASPECTS OF DENGUE**

Professor Usa Thisyakorn, M.D.

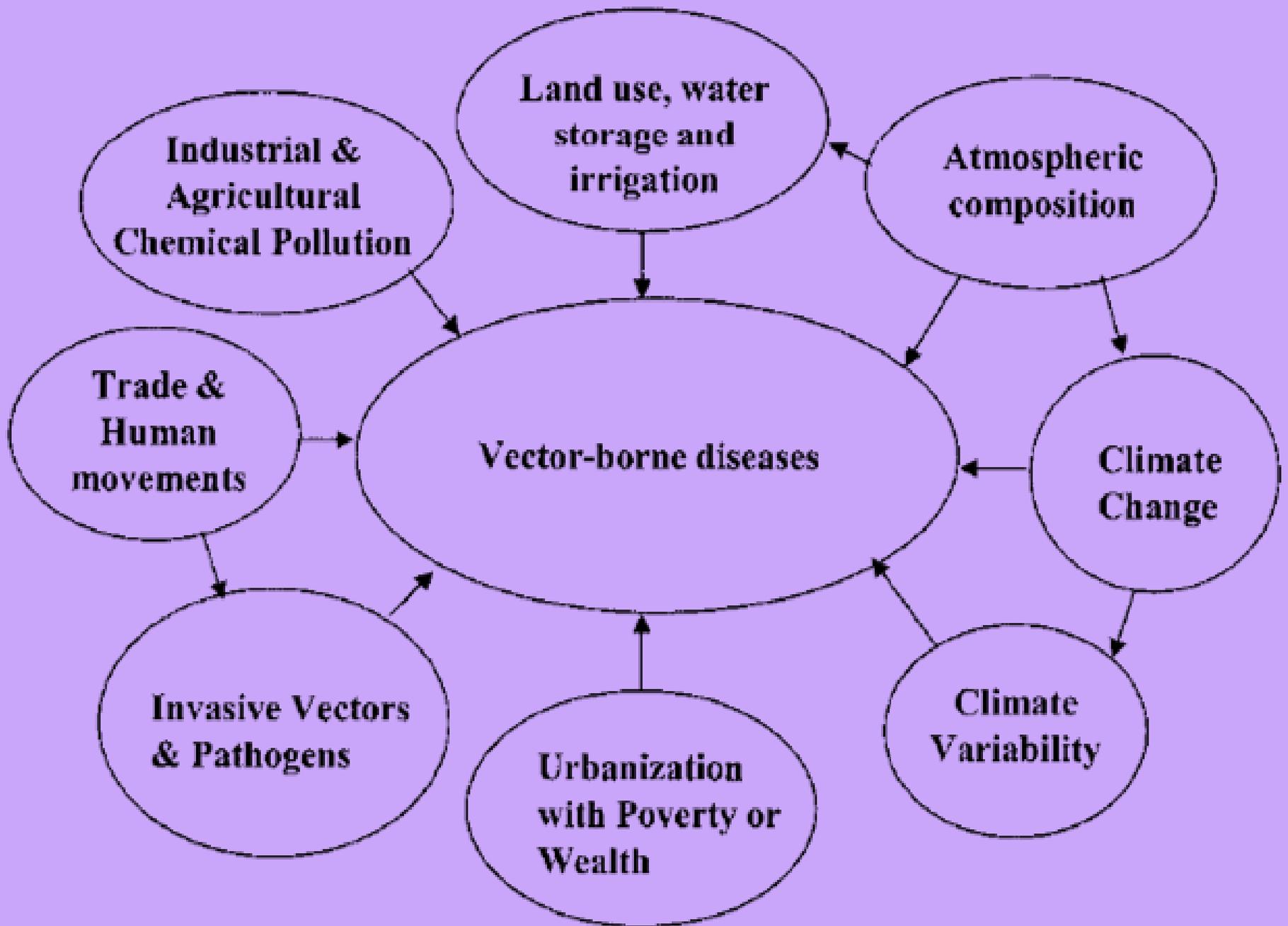
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DENGUE

**The most important
arthropod-borne
viral disease of humans**



Economic costs of dengue are significant and likely to be even higher than estimated

- **Direct**

- Medical care
- Surveillance and reporting
- Prevention
 - Vector control and education

- **Indirect**

- Premature mortality
- Lost productivity (work/school) during infection
- Lost productivity of those caring for infected people

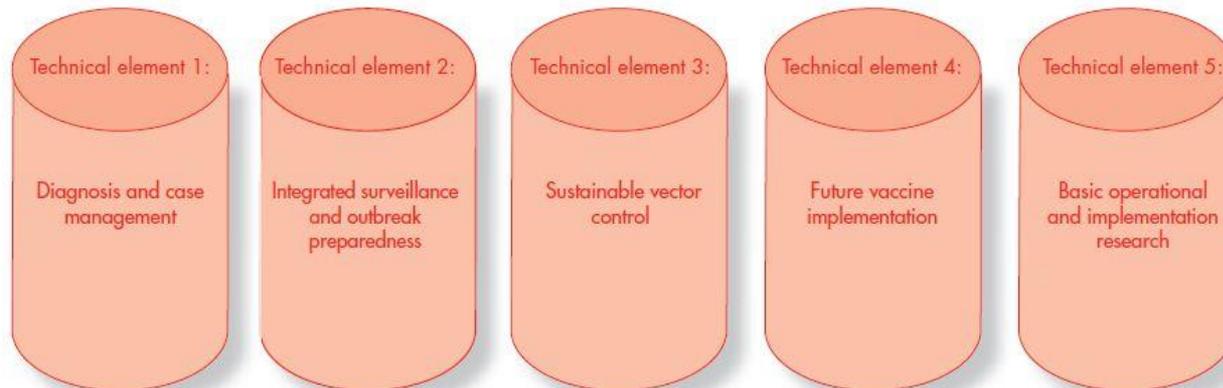
Global strategy for dengue prevention & control, 2012-2020

GOAL:
TO REDUCE THE BURDEN OF DENGUE

OBJECTIVES:

- To reduce dengue mortality by at least 50% by 2020*
- To reduce dengue morbidity by at least 25% by 2020*
- To estimate the true burden of the disease by 2015

* The year 2010 is used as the baseline.



ENABLING FACTORS FOR EFFECTIVE IMPLEMENTATION OF THE GLOBAL STRATEGY:

- advocacy and resource mobilization
- partnership, coordination and collaboration
- communication to achieve behavioural outcomes
- capacity-building
- monitoring and evaluation

PREVENTION

▼ **Control of mosquito**

▼ **Vaccine**



CHANGE IN CLIMATE HELPING MOSQUITOES THAT CARRY THE DISEASE THRIVE

Record dengue epidemic looms

PARITTA WANGKIAT

» Thailand could face one of the largest dengue fever epidemics yet with the Public Health Ministry anticipating that over 120,000 people could contract the virus this year.

That would surpass the number of infections during the major outbreak in 2010.

Last winter's warm temperatures and sporadic rainfall were obvious signs that a major dengue outbreak was due this year, health officials say.

More than 28,000 cases of dengue fever were reported between October to December last year even though winter is not the peak season for the disease.

The number of dengue cases continued to rise from January, with nearly 82,000 reported infections and 78 fatalities as of Friday, public health permanent-secretary Narong Sahamethapat said. Most of the fatalities were aged between 15-24 years.

The figure is three times higher than the same period last year, said Dr Narong, who heads the ministry's anti-dengue efforts.

Two major dengue outbreaks have been recorded in Thailand, with more than 170,000 cases reported in 1986, and 118,700 people infected in 2010.

The dengue prevention operation is at its most intense during the rainy season — from this month to September — when mosquitoes breed rapidly.

"But this disease cannot be controlled just through the work of the ministry," Bureau of Epidemiology director Pasakorn Akarasewi said. "It needs a chain of actions."

Dr Pasakorn said the disease control programme needs to work with other agencies and with local communities.

At the start of this year, the cabinet ordered various ministries, such as the



SPRAY AND KILL: A public health worker sprays insecticide to kill mosquitoes in the Huai Kwang area earlier this month.

surveillance programme, which aims to terminate the breeding grounds for dengue-carrying mosquitoes.

Hospitals nationwide are also on alert. So-called "dengue corners" have been set up at hospitals to screen patients with dengue-like symptoms to make a fast and efficient diagnosis.

"But the level of disease control efficiency is different in each area," Dr Pasakorn said.

According to public health reports,

including Chiang Mai, Chiang Rai and Mae Hong Son.

A number of cases are also being found in northeastern provinces such as Phetchabun and Loei.

Most cases are reported in remote communities which are difficult to reach, such as those in mountainous areas where disease prevention knowledge is poor and the vector control and surveillance programme is absent.

Some of these areas are inhabited by

The key activity in the dengue prevention programme is vector control, authorities say. Weak vector control at community levels allows *Aedes* mosquitoes, the carriers of dengue fever, to reproduce rapidly.

Society of Strengthening Epidemiology president Rungrueng Kitphati said changes in the climate might have helped the *Aedes* mosquitoes in "growing stronger and living longer".

Many Southeast Asian countries,

rainfall, and such conditions benefit the dengue-carrying mosquitoes, he said.

Scientists have found that the *Aedes* mosquito's life span has increased from one to two months.

Normally, the mosquitoes feed in the day, but Thailand's warmer climate allows them to feed at night too, Dr Rungrueng said. He suspects the changing climate has played a part in the changes in the mosquitoes' life cycle and behaviour.

Urbanisation and more waste man-

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Potential breeding habitats (indicated in dotted circle) of *Ae. aegypti* and *Ae. albopictus* in an indoor situation



Potential breeding habitats of *Ae. aegypti* and *Ae. albopictus* in an outdoor situation



INTEGRATED VECTOR MANAGEMENT

- **Advocacy, social mobilization and legislation**
- **Collaboration within the health sector and with other sectors**
- **Integrated approach to disease control**
- **Evidence-based decision-making**
- **Capacity-building**

<http://apps.who.int/tdr/svc/publications/training-guideline-publications/dengue-diagnosis-treatment>



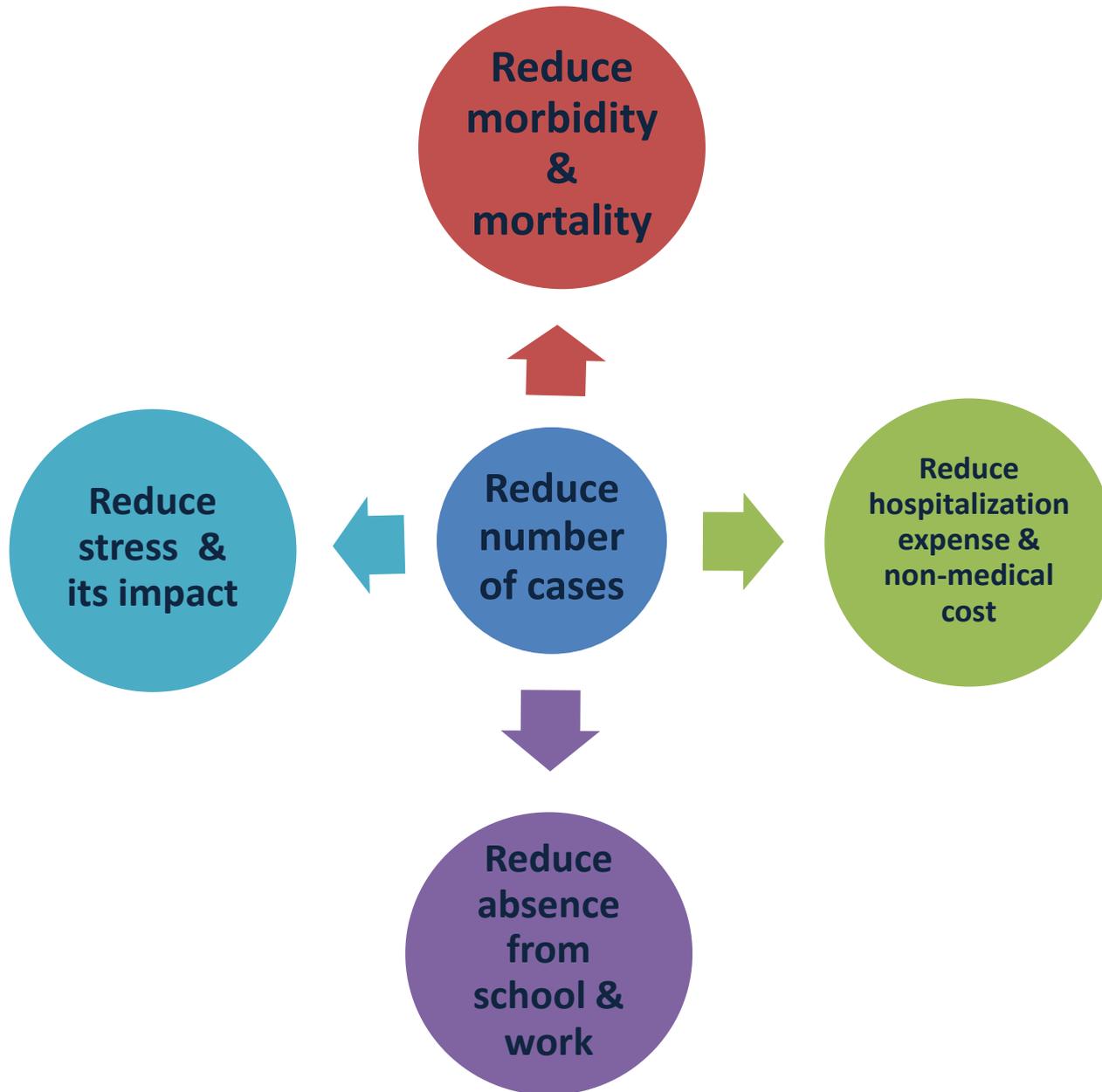
DONT
MAKE DR
USA
WORRY!

Dengue Vaccine

The complexity of developing a dengue vaccine development

- Need for a tetravalent vaccine with not just one but four immunogens that will give a balanced immune response whereby a protective long-lasting immunity is induced against all four viruses simultaneously (balancing viral interference, immunogenicity, and reactogenicity).
- Lack of immune correlate of protection since the mechanism of protective immunity against DEN infection is only partially understood. It is assumed that neutralizing antibodies are the main effector of protection against DEN infection.
- Lack of a suitable animal model that recapitulates human disease and can be used to evaluate candidate vaccines.
- Potential immunopathogenesis, including antibody-dependent enhancement implementation.
- Need for long-term follow-up.
- Need for testing in both Asia and the Americas.
- Ideally, can be tested against all four DEN serotypes.
- The exact location, timing and serotype/genotype composition of dengue epidemics varies from year to year and is somewhat unpredictable.

INDIVIDUAL BENEFITS



PUBLIC HEALTH BENEFITS

- **1. Save cost for mosquito control**
- **2. Save hospital beds for non-dengue cases**
- **3. Save ICU beds for other critical cases**
- **4. Save hospital expense for dengue patients**
- **5. Reduce absence from work for both patients and relatives**
- **6. Reduce negative impact on tourism**

Dengue Vaccines:

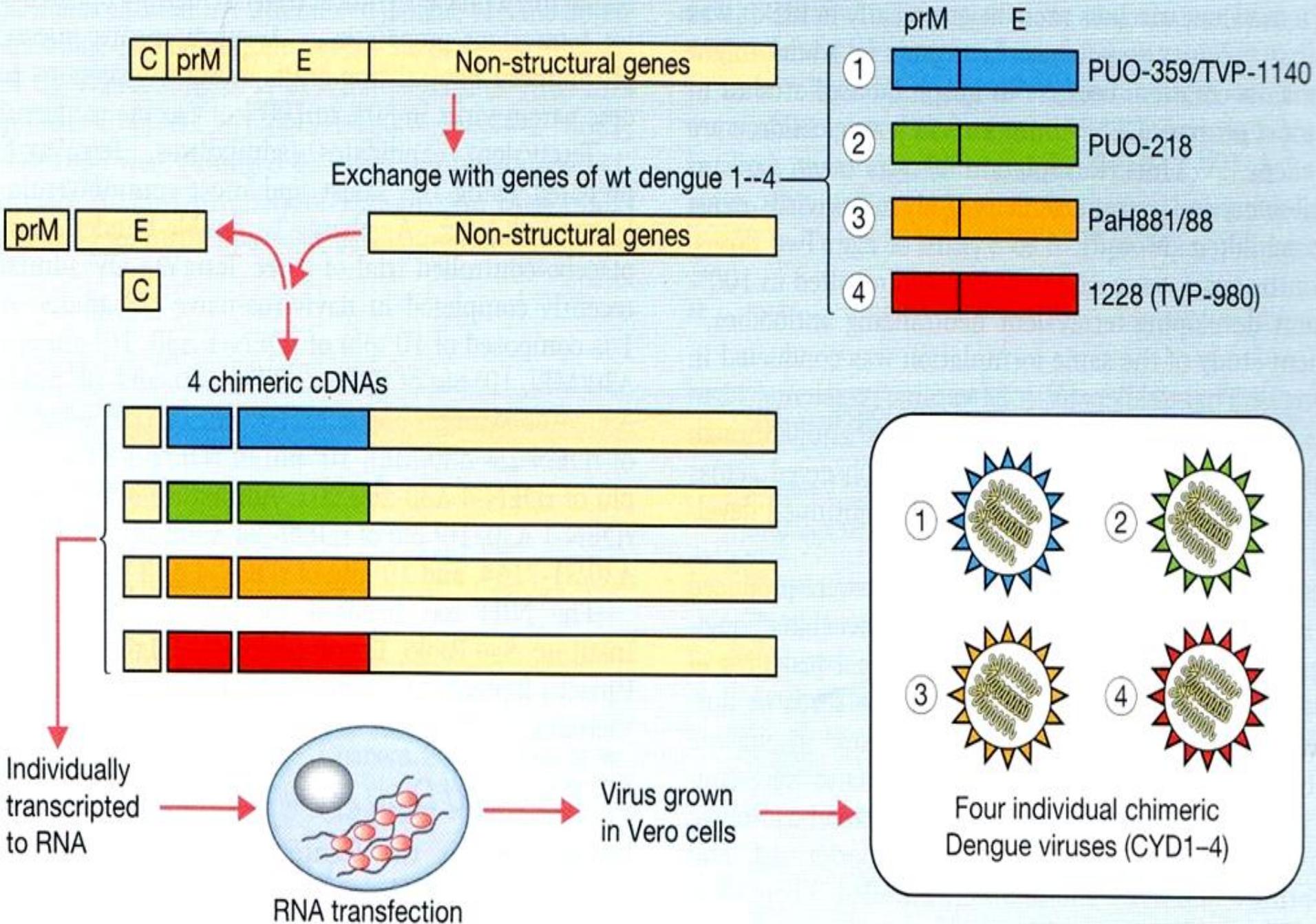
Latest Developments and Future Directions

- **Live attenuated virus**
- **Chimeric virus**
- **Inactivated virus**
- **Subunit**
- **DNA**
- **Vectored**
- **Recombinant E proteins**
- **VLP based**

Tetravalent Dengue Vaccines in Clinical Trial Pipeline



Yellow fever V 17D cDNA



DENGUE VACCINE TRIAL SITE

- **Supportive epidemiology**
- **Supportive medical infrastructure**
- **Extensive clinical trials experience**
- **Technical capabilities**
- **Supportive logistic capabilities**
- **Regulatory and Ethical review framework**

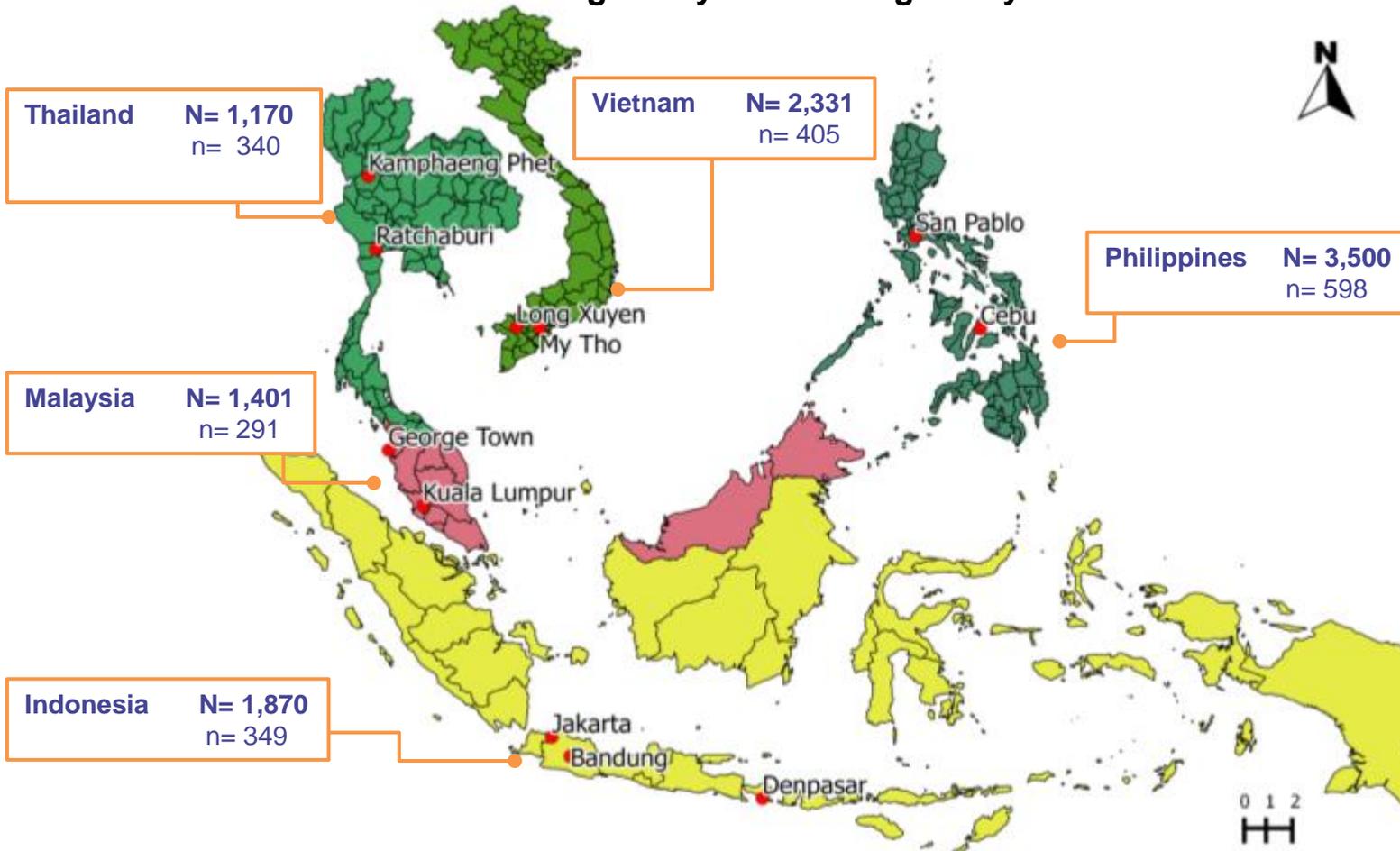
CYD34 STUDY RESULTS

Dengue and other common causes of acute febrile illness in Asia: an active surveillance study in children.

During the study period, the most common identified causes of pediatric acute febrile illness among the seven tested for (dengue, chikungunya, hepatitis A, influenza A, leptospirosis, rickettsia, and *S. typhi*) were chikungunya, *S. typhi* and dengue. Not all dengue cases were clinically diagnosed; laboratory confirmation is essential to refine disease burden estimates.

CYD14 STUDY CONDUCTED ACROSS 5 COUNTRIES IN SOUTH-EAST ASIA

**N=10272 subjects from 2 to 14 yo receiving at least one injection;
n = 1983 immunogenicity and reactivity subset**



THE LANCET

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

*María Rosario Capeding, Ngoc Hvu Tran, Sri Rezeki S Hadinegoro, Hussain Imam Hj Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group**

www.thelancet.com Published online July 11, 2014 [http://dx.doi.org/10.1016/S0140-6736\(14\)61060-6](http://dx.doi.org/10.1016/S0140-6736(14)61060-6)

CYD 15 STUDY



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ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D. for the CYD15 Study Group

November 3, 2014 | DOI: 10.1056/NEJMoa1411037

9 OF TOP 10 COUNTRIES REPORTING CASES WERE STUDY SITES IN CYD14 & CYD15 PHASE III TRIALS

Cases Reported to WHO, 2004–2010

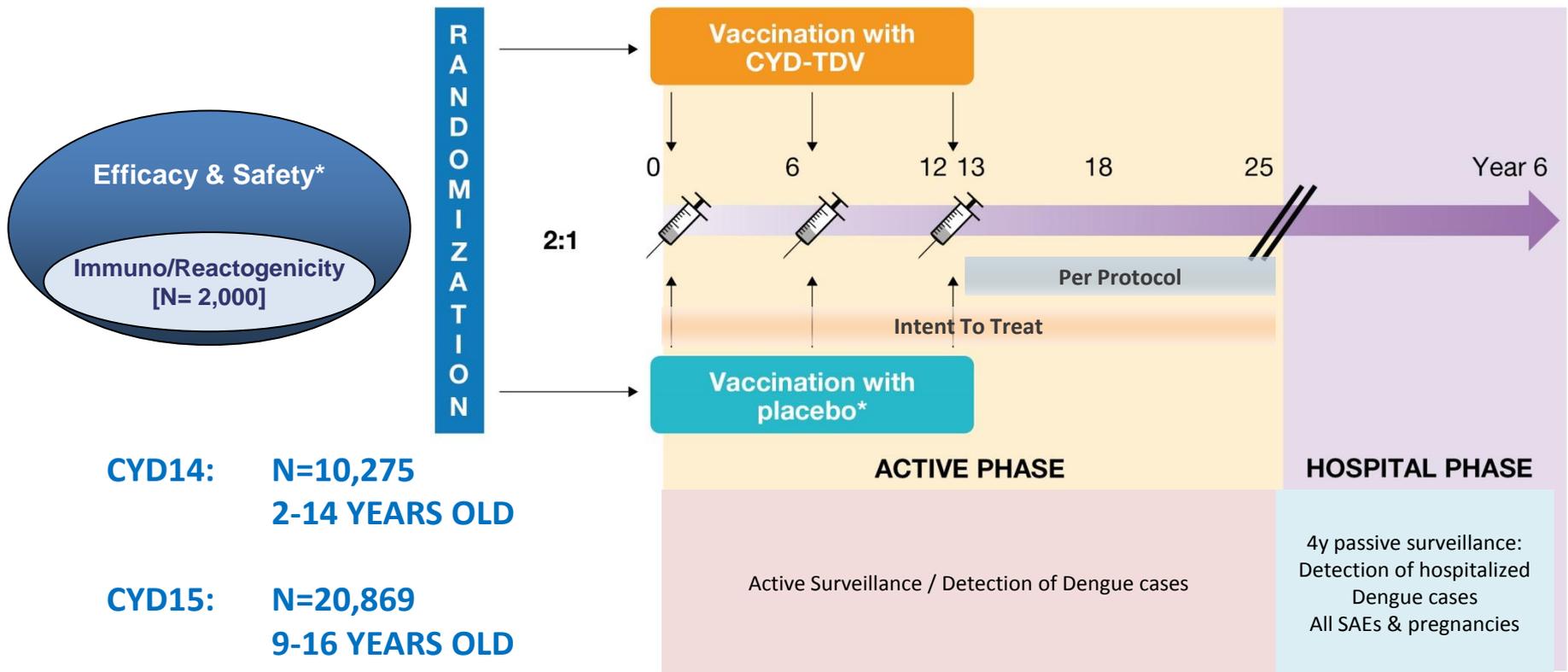
Country	Average Number of Cases
Brazil	447,466
Indonesia	129,435
Vietnam	91,321
Mexico	75,353
Venezuela	61,612
Thailand	60,205
Philippines	54,639
Colombia	53,303
Malaysia	42,568
Honduras	25,972



World Health Organization (WHO), 2012, Global Strategy for Dengue Prevention and Control.

CYD14 & 15 STUDY DESIGN

- Randomized, observer-blind, placebo-controlled, multi-centre, Phase III trial
- Randomization stratified by age group & study site



* Safety on overall population consists of detection of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI)

** Participants who received placebo were designated as the control group.

Key Results of CYD14 & CYD15

Vaccine Efficacy	CYD 14	CYD 15
Overall efficacy against virologically-confirmed dengue, any serotype (PP)	56.5% (95% CI, 43.8; 66.4)	60.8% (95% CI: 52.0; 68.0)
Preventing DHF (ITT) according to 1997 WHO classification	80.0% (95% CI: 52.7; 92.4)	95.0% (95% CI: 64.9; 99.9)
Preventing hospitalization (ITT)	67.2% (95% CI: 50.3; 78.6)	80.3% (95% CI 64.7; 89.5)
If dengue seropositive at baseline (ITT)	74.3% (95% CI: 53.2; 86.3)	83.7% (95% CI: 62.2; 93.7)
If dengue seronegative at baseline (ITT)	35.5% (95% CI: -26.8; 66.7)	43.2% (95% CI: -61.5; 80.0)

† ITT=intent-to-treat. PP = Per protocol. CI=confidence interval

THE FIRST TETRAVALENT DENGUE VACCINE IS POISED TO COMBAT DENGUE

- **A safe, effective dengue vaccine is on the horizon**
- **Critically important achievement in the fight against dengue**
- **How to implement this new tool effectively**

Thisyakorn U, et al. Dengue Bulletin 2014; 38: 108-12.



1st ADVASC Meeting Report

The ASEAN Dengue Vaccination Advocacy Steering Committee (ADVASC) is a newly formed scientific forum dedicated to dengue vaccine advocacy. The committee consists of medical experts including virologists, paediatricians, physicians and experts in the fields of infectious disease, tropical medicine and immunisation. The first meeting of ADVASC was held on 16 December 2011 and served to define the objectives of ADVASC in relation to the introduction of a dengue vaccine in South-east Asia.

The mosquito-borne dengue virus is a potential threat to almost half of the world's population, with an estimated 50 million people infected annually. Around 500,000 of those infected each year develop dengue haemorrhagic fever (DHF), a severe form of the disease that can lead to dengue shock syndrome and death.¹ DHF is a leading cause of hospitalisation and places a large economic burden on affected countries. South-east Asia and the Western Pacific carry the majority of the global burden, with over 75% of the population at risk of dengue infection living in those regions. The incidence of dengue fever has been rising dramatically, facilitated by increased urbanisation and travel.

Current efforts to halt the spread of dengue focus on mosquito control and reducing virus transmission; however, such efforts alone are not sufficiently effective. A vaccine that protects against the virus would therefore be of tremendous benefit in the fight against dengue. Vaccines against dengue are in development, with the lead candidate currently undergoing Phase III clinical trials. Estimates suggest that the vaccine will be available for the global market by 2015.² Early preparation for vaccine introduction is essential to maximise the benefits of the vaccine.

ADVASC aims to assist the introduction of the dengue vaccine in South-east Asia. This initial meeting provided an opportunity to develop and clarify the group's identity, objectives and activities. In the first session of the meeting, nine presentations were given by the attendees to provide country-specific background information on the current dengue situation across South-east Asia, as detailed in the following table.



Attendees at the 1st ADVASC Meeting in Bangkok, L-R (back row) Jeremy Brett, Dr Suttie Sriwan, Dr Zukliff Ramli, Dr Daniel Goh, Professor Tompong Tantiwachin, front row Dr Maria Rosario Capeding, Professor Usa Thaisyakorn, Anil Warial* (hon)

Table 1: ADVASC Meeting Presentations

Professor Usa Thaisyakorn	<i>Dengue in the Asia-Pacific region</i> 75% of global burden is in Asia-Pacific region. Need preparation in advance of vaccine release to ensure rapid introduction.
Professor Usa Thaisyakorn	<i>Dengue surveillance in Thailand</i> Dengue surveillance system in place since 1958, reporting mandatory, usually within 24 hours. Reports are public.
Dr Maria Rosario Capeding	<i>The Global Dengue v2V Initiative</i> v2V aims to establish and document burden of dengue, raise awareness of vaccination benefits, provide guidance in relation to introduction and advocate for funding.
Dr Maria Rosario Capeding	<i>Dengue and vaccination programmes in the Philippines</i> Safety and immunogenicity of tetravalent vaccine in subjects aged 2-45 years, including follow-up. Immunogenicity and safety in healthy toddlers 12-15 months. Efficacy and safety in healthy children 2-14 years. First scientific symposium 12 Aug 2011, positive media response.
Dr Daniel Goh	<i>Dengue in Singapore</i> High success rate for immunisation for childhood diseases. Good vaccine acceptance and coverage. Infrastructure for implementation in place, but some concerns over new vaccine. National Environment Agency (NEA) currently undertakes mosquito control.



OBJECTIVES

- **Identifying & making practical recommendations on:**
 - Improved surveillance and case diagnostics
 - Select initial groups for vaccination
 - Address program feasibility
 - Prepare and implement risk management plan
- **Communicating recommendations to all stakeholders**
- **Collaborating with other relevant dengue initiatives**



Letter to the Editor

ADVASC—New regional initiative supporting transition from dengue vaccine to vaccination in Southeast Asia**Keywords:**

Advocacy
 ASEAN
 Dengue
 Vaccination

Dear Editor,

I am pleased to announce the formation of a new scientific forum dedicated to dengue vaccine advocacy in Southeast Asia. The ASEAN Member States Dengue Vaccination Advocacy Steering Committee (ADVASC) aims to disseminate information and make recommendations on dengue vaccine introduction strategies in Southeast Asia.

ADVASC members (Table 1) include virologists, paediatricians, physicians and experts across the fields of infectious disease, tropical medicine and immunisation. Countries represented include Indonesia, the Philippines, Malaysia, Singapore and Thailand. ADVASC recognises the value of partnerships with other groups working on dengue and vaccine introduction in the region, and intends to work wherever possible with the World Health Organization (WHO), the Dengue Vaccine Initiative (DVI) and the Dengue Vaccine to Vaccination initiative (Dengue v2V) [1].

The objectives of ADVASC were agreed at the inaugural Steering Committee meeting held in Bangkok on 16 December 2011 (Box 1). Presentations at the meeting addressed topics of dengue epidemiology – documenting the increasing prevalence of the disease across the ASEAN region and at the individual country level – and dengue infection in adults, which is often misdiagnosed due to the perception of dengue as a paediatric disease.

Dengue is a mosquito-borne viral disease found throughout equatorial regions and is a potential threat to almost half of the world's population [2]. Many factors have contributed to a recent dramatic rise in dengue fever cases, including increased urbanisation and travel [3]. Recent studies estimate that 50–100 million people are infected per year, of whom about 500,000 develop dengue haemorrhagic fever (DHF) – a severe form of the disease – and 22,000 die [4].

More than 70% of the population at risk for dengue worldwide (around 1.8 billion people) live in the regions of Southeast Asia and the Western Pacific that bear nearly 75% of the current global dengue burden [5].

There is currently no specific antiviral treatment for dengue and preventing the disease through vector control methods alone is problematic. Vaccines for dengue are in development, with the lead candidate currently in Phase III clinical trials and estimated to be available by 2015 [6].

Box 1: Objectives of ADVASC

1. Identifying opportunities and making practical recommendations about how to:
 - a. Improve surveillance and laboratory capacity for dengue disease confirmation, including:
 - i. Documenting and standardising existing systems and coverage
 - ii. Standardising case confirmation and diagnostics
 - b. Select initial target groups for vaccination
 - c. Address programme feasibility by improving existing infrastructure (cold chain, pharmacovigilance, vaccination compliance monitoring, and vaccine supply and distribution logistics)
 - d. Prepare and implement a risk management plan
2. Communicating recommendations to:
 - a. National and local government bodies
 - b. International, regional, and local medical and academic societies
 - c. Other stakeholders including WHO (Southeast Asia and Western Pacific Regional Offices)
 - d. The public/media
3. Collaborating with other relevant dengue initiatives including v2V and DVI

Table 1
 ADVASC members.

Professor Usa Thisyakorn (Chair)	Chulalongkorn University, Thailand
Dr Maria Rosario Capeding	Research Institute for Tropical Medicine, the Philippines
Dr Daniel Goh	Yong Loo Lin School of Medicine, Singapore
Dr Zulikifli Ismail	KPJ Selangor Specialist Hospital, Malaysia
Professor Terapong Tantawichien	Chulalongkorn University, Thailand
Dr Sutee Yoksan	Mahidol University, Thailand
Professor Sri Rzeki Hadinegoro	Dr Cipto Mangunkusumo Hospital, Indonesia

Early preparation for vaccine introduction will ensure that the vaccine can reach those who need it as early as possible. In 2012, ADVASC intends to focus on understanding dengue surveillance systems in Southeast Asia, making recommendations on regional standardisation and identifying gaps in diagnostic capabilities and case classification. Robust surveillance of dengue will allow valid assessment of vaccine impact and aid control of the disease.

Financial disclosure

ADVASC is supported by an unrestricted educational grant from Sanofi Pasteur.



Ist ADVA Workshop

Bangkok
Thailand
22-23 September 2012



Ist ADVA Workshop

Bangkok
Thailand
22-23 September 2012

Recommendations from 1st ADVA

**Standardizing
the monitoring &
reporting of dengue
in the ASEAN region**



2nd ADVA Workshop

4th and 5th March 2014, Kuala Lumpur, Malaysia



Recommendations from 2nd ADVA

- Collaborations and regional data sharing networks**
- Informed decisions about dengue control**

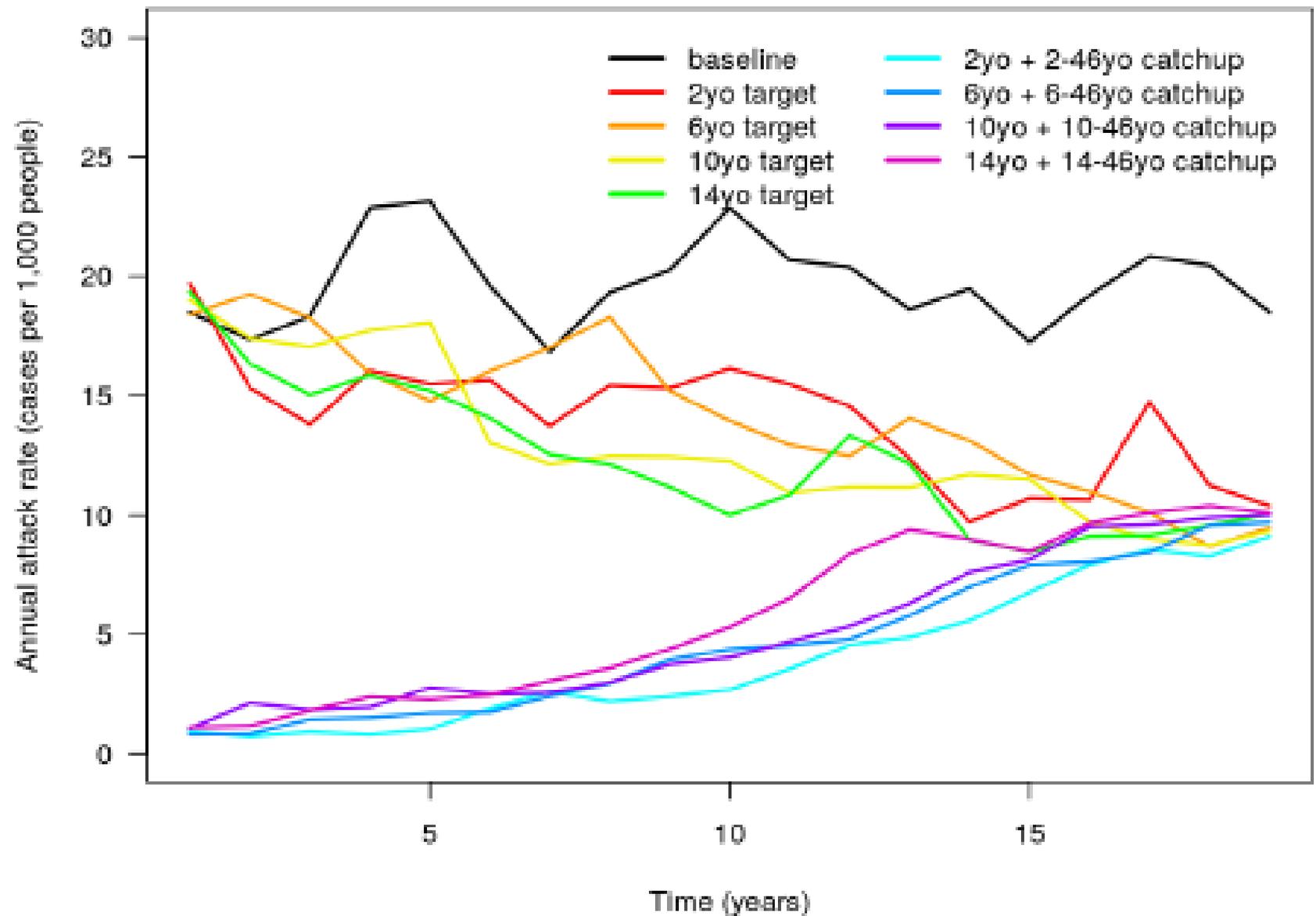
ASEAN Dengue Vaccination Advocacy Workshop
8th – 9th January 2015



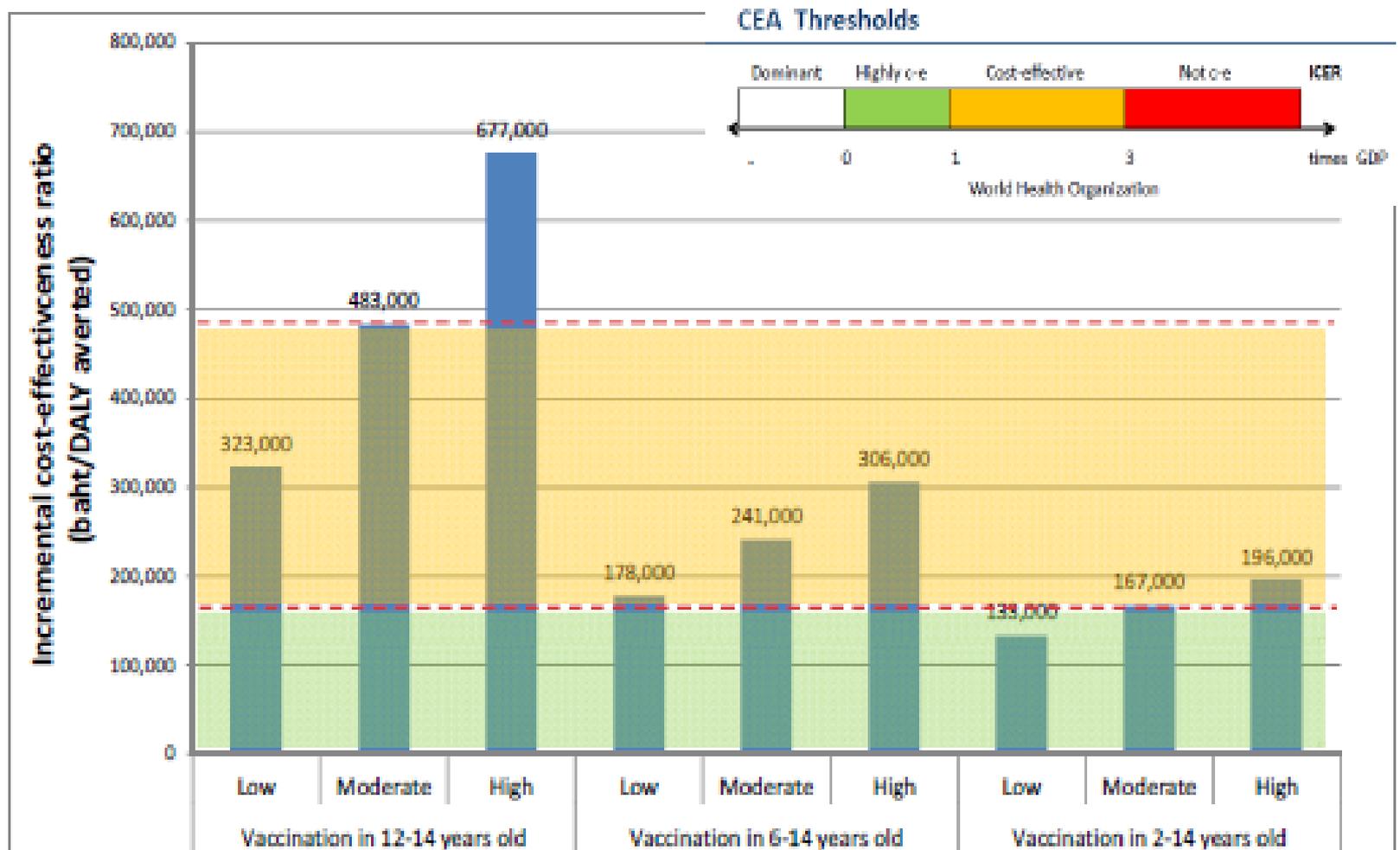
Recommendations from 3rd ADVA

**The use of mathematical
modelling to support rational
decision-making and
strategies for dengue control**

Effect of vaccines on dengue cases (high force of infection)



The effect of transmission intensity (low/moderate/high) on ICER



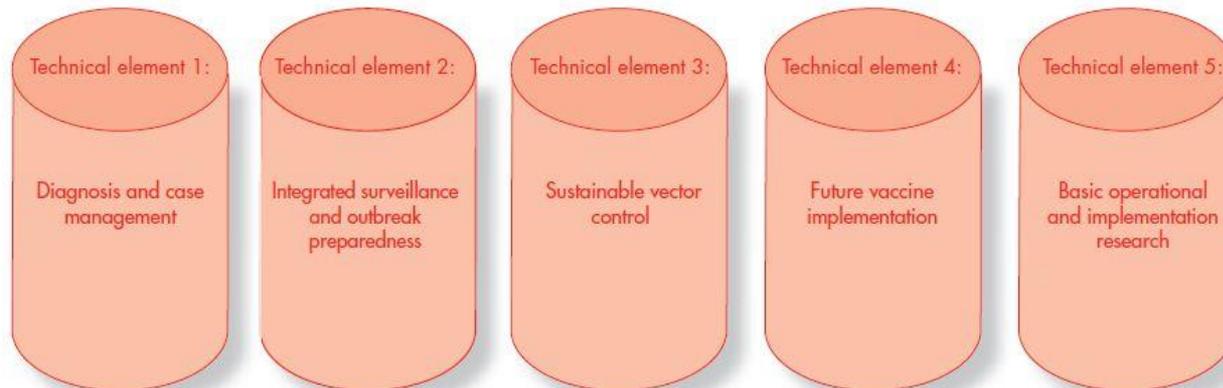
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DENGUE PATIENTS IN DIFFERENT AGE GROUPS

- **Clinical manifestations and severity varied with age**
- **CNS manifestations were more common in infants**
- **DSS were less common in infants**
- **Proper management depends on different age-specific clinical manifestations and severity**

CONCLUSION

- **The human and economic cost of dengue are significant and likely to be even higher than estimated**
- **Disease prevention is a key to public health**

ACPID 2016
Bangkok, Thailand



**8th Asian Congress of
Pediatric Infectious Diseases**
15-18 November, 2016

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