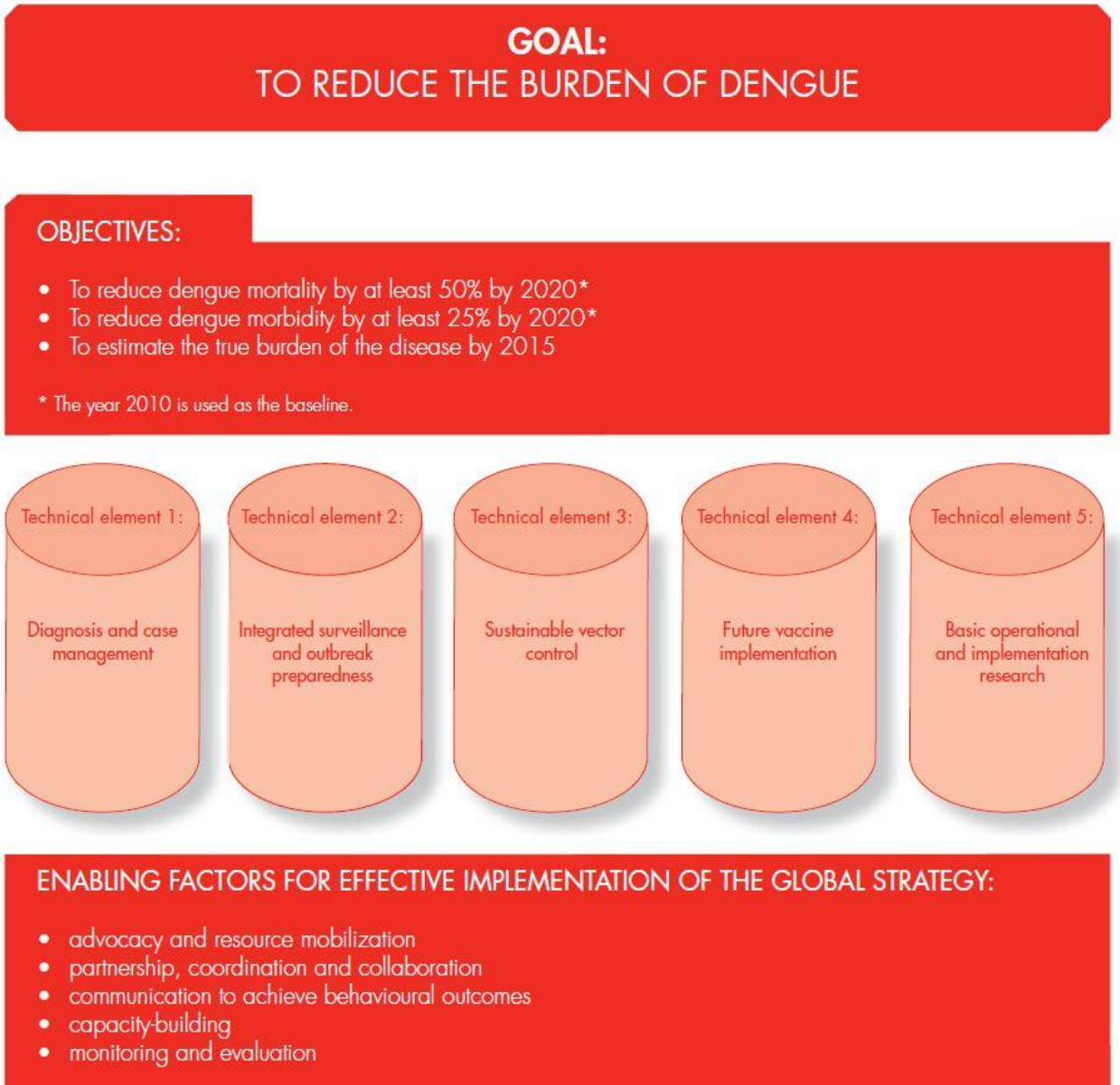
DENGUE: PREVENTION & CONTROL

Professor Usa Thisyakorn, M.D.

Chulalongkorn University

Bangkok, Thailand

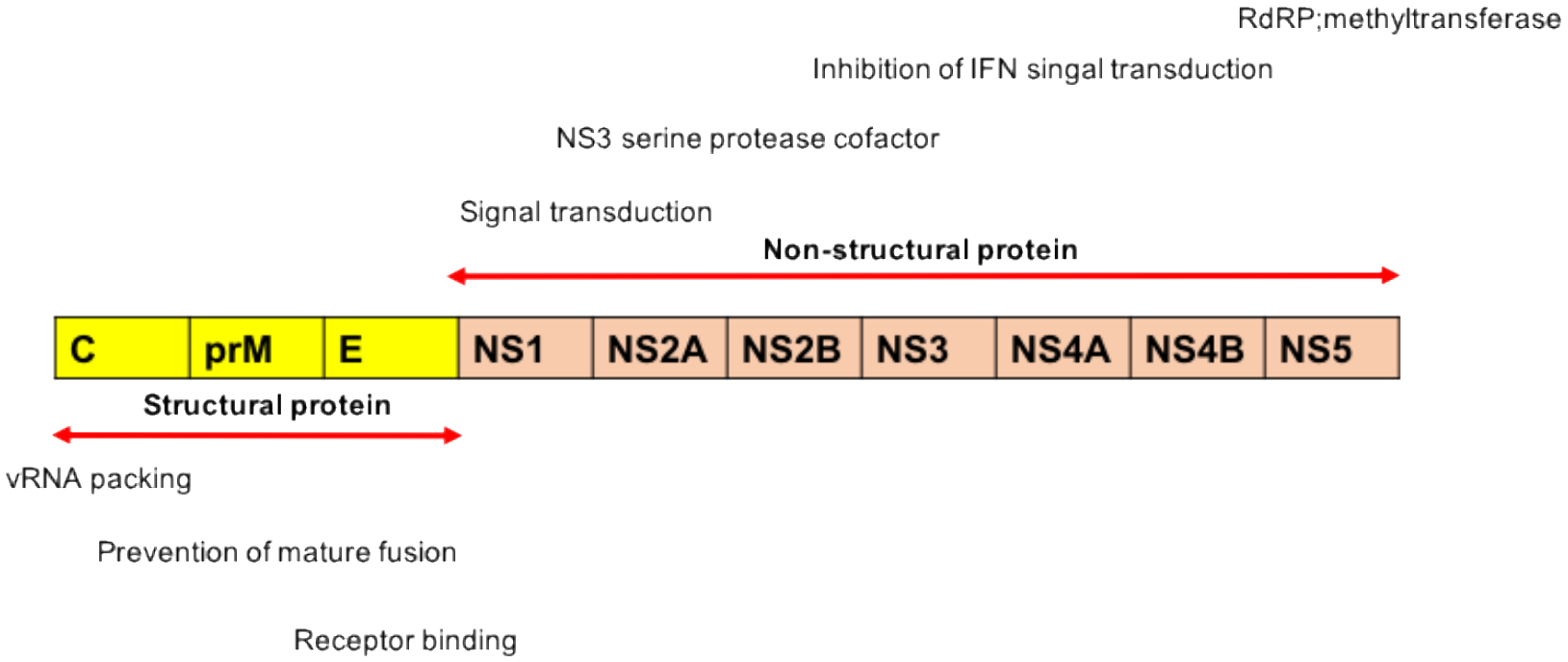
Global strategy for dengue prevention & control, 2012-2020



DENGUE

- Most common global vector-borne viral infection
- Increasing global burden driven by
  - population growth
  - urbanization
  - globalization
  - ecological changes
- An integrated approach to dengue prevention and control is crucial

DENGUE VIRUS

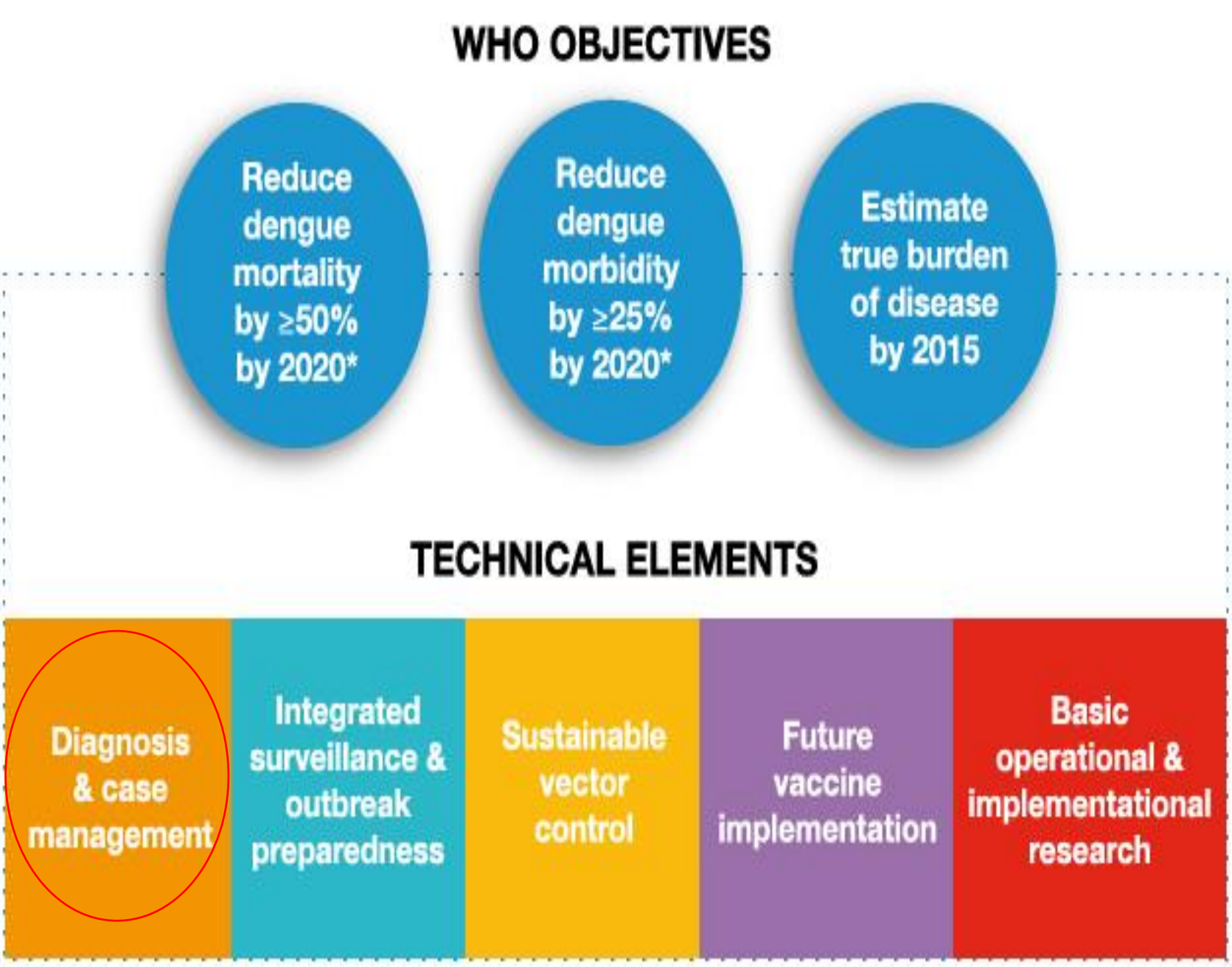


RECEPTORS AND TARGET CELL OF DENGUE

RECEPTORS	TARGET CELLS
Heparin sulfate	Liver cells; VERO; BHK21; C636
Hsp 70/90	Monocyte derived Macrophage; human; Neuroblastoma cells
GRP78/BiP	Liver cells
37/67 Kda high affinity Lamina receptor	Liver cells
CD14	Monocyte derived Macrophage
DC-SIGN	Dendritic cells, Langerhans cells
L-SIGN	Liver cell; LN; Spleen

PATHOGENESIS OF DENGUE DISEASES

- Dengue NS1 protein
- Dengue virus genome
- Antibody-Dependent Enhancement
- T cell
- Endothelial cell
- Dendritic cell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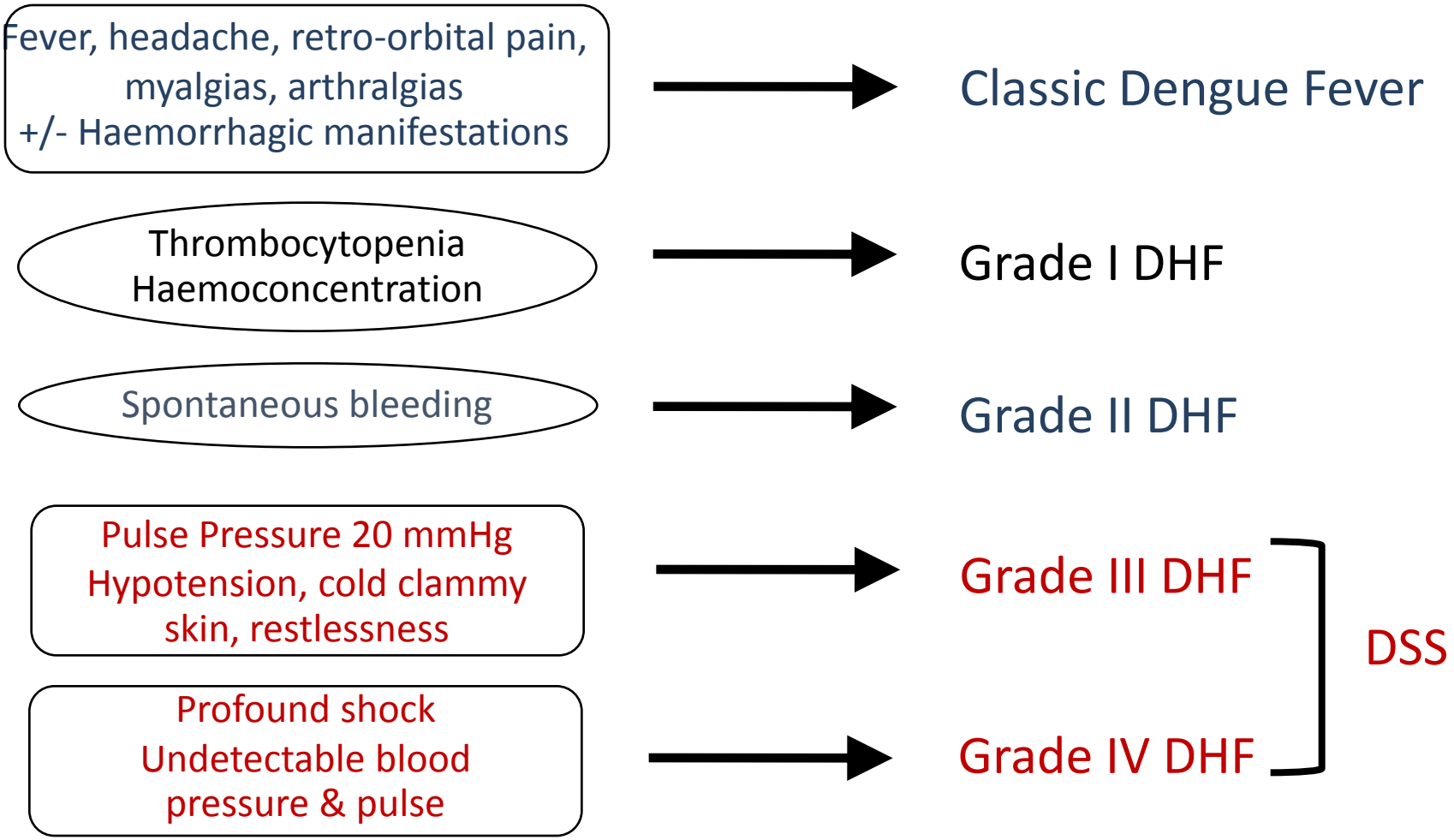
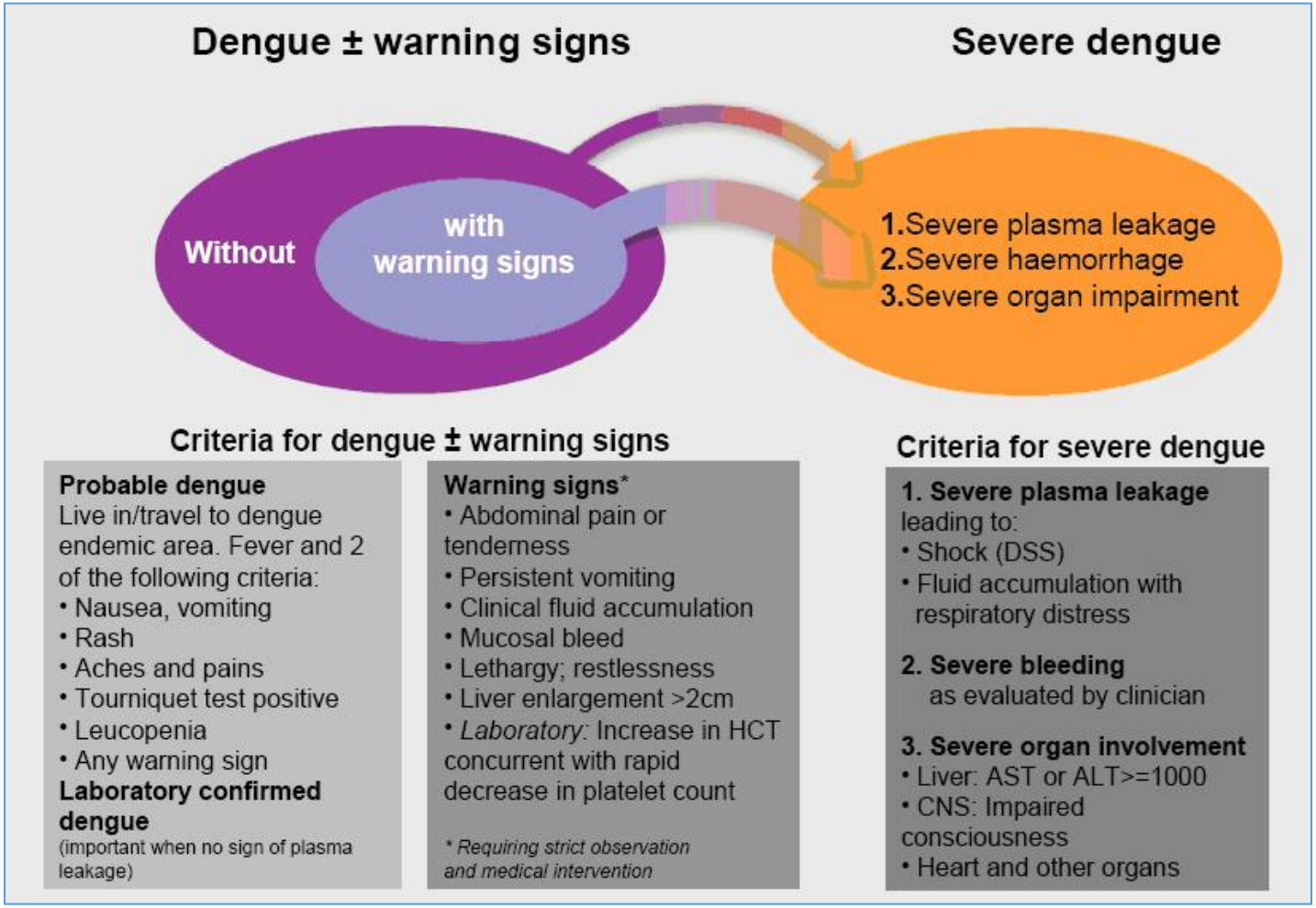
Reduce dengue mortality by ≥50% by 2020*
Reduce dengue morbidity by ≥25% by 2020*
Estimate true burden of disease by 2015
TECHNICAL ELEMENTS
Diagnosis & case management
Integrated surveillance & outbreak preparedness
Sustainable vector control
Future vaccine implementation
Basic operational & implementational research

1997 WHO dengue classification



2009 WHO revised dengue classification by severity

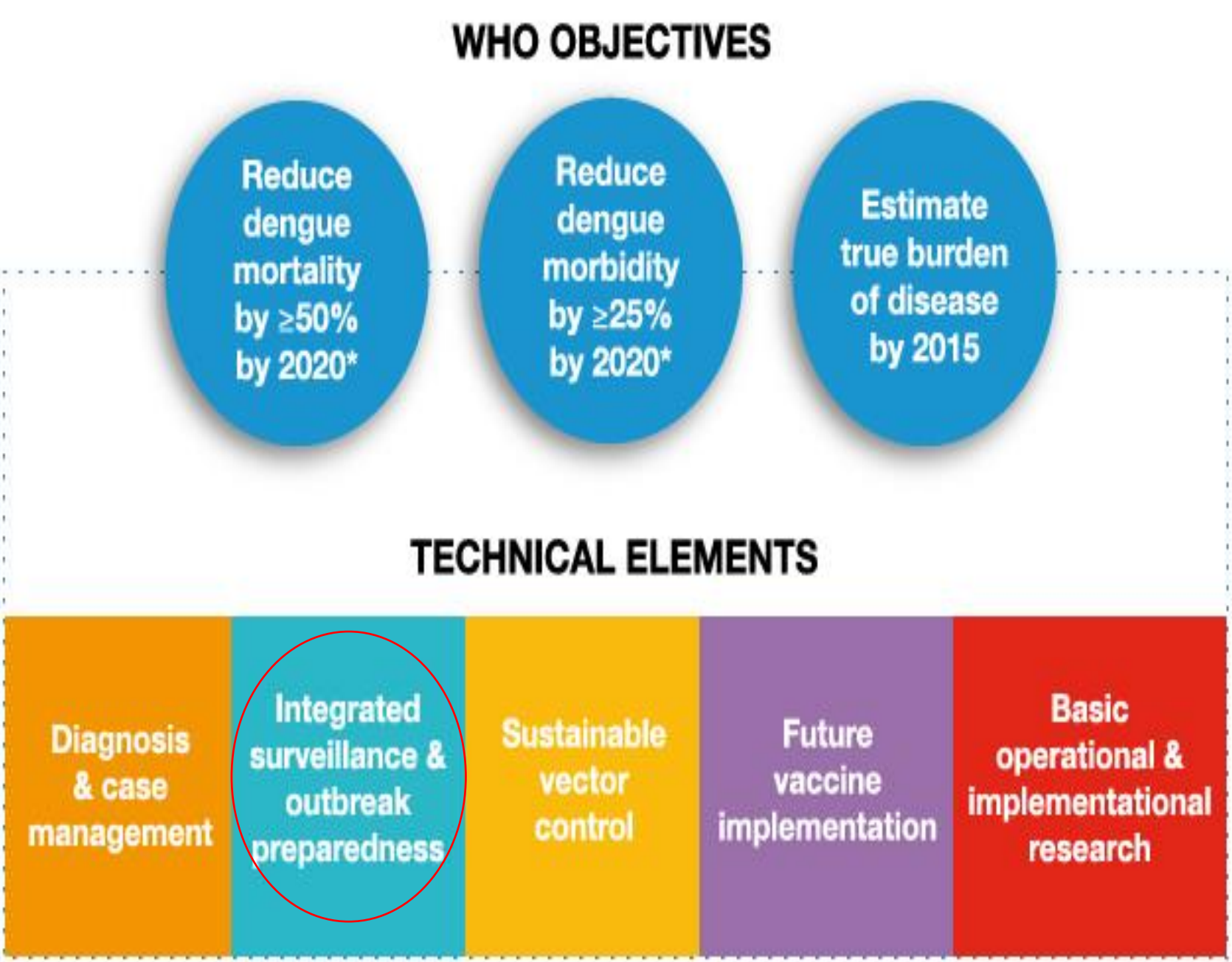


Dengue Guidelines for diagnosis, treatment, prevention and control, New edn. Geneva: WHO; 2009

DENGUE: PITFALLS IN DIAGNOSIS AND MANAGEMENT

- Communications to parents and caregivers
- Diagnostic tests
- Medications
- DDx with other acute febrile illnesses
- Fluid therapy
- Bleeding tendency
- Organopathy

Thisyakorn & Thisyakorn. Southeast Asian J Trop Med Public Health 2017; 48 (Supplement 1): 112-6.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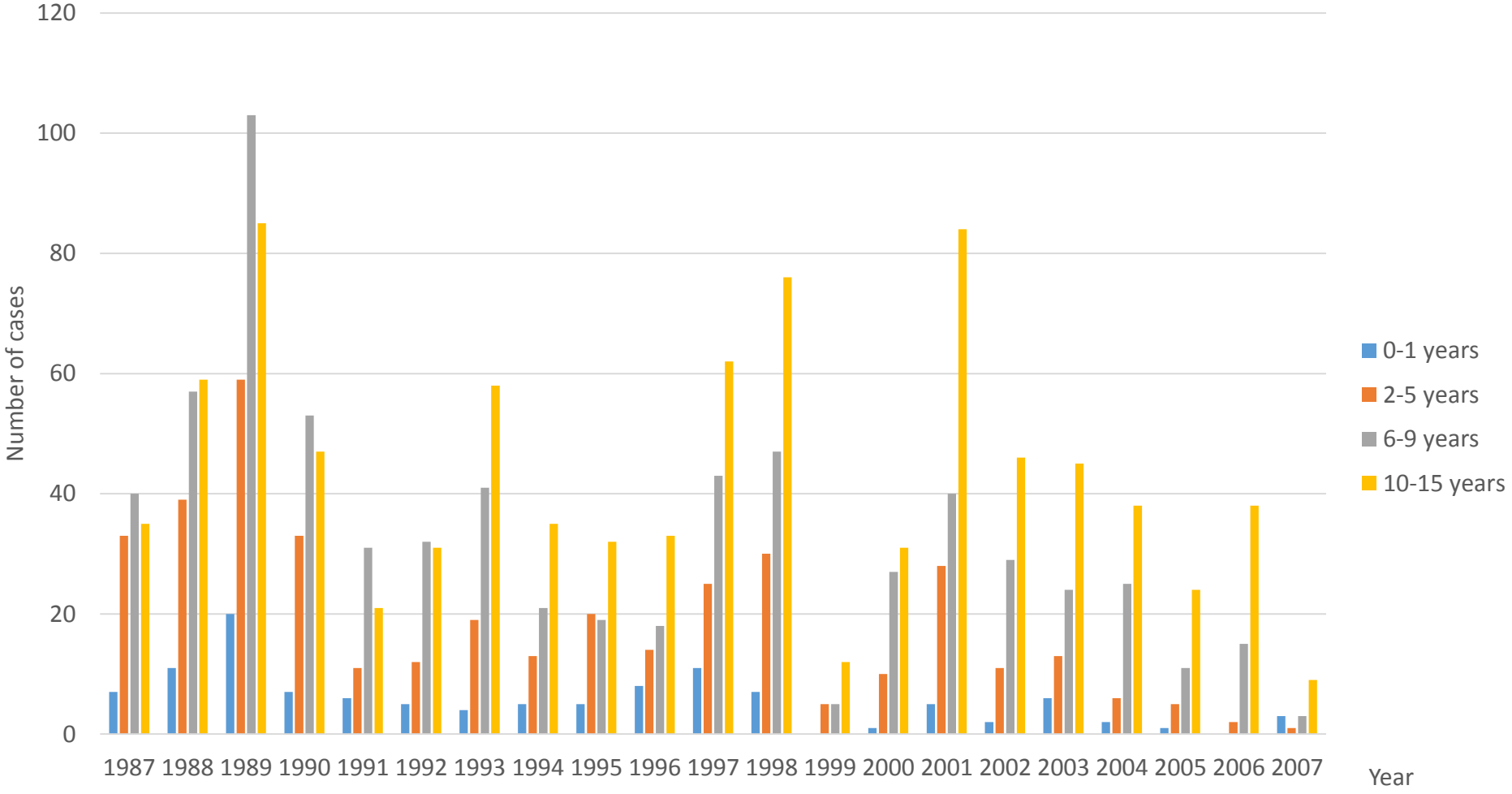
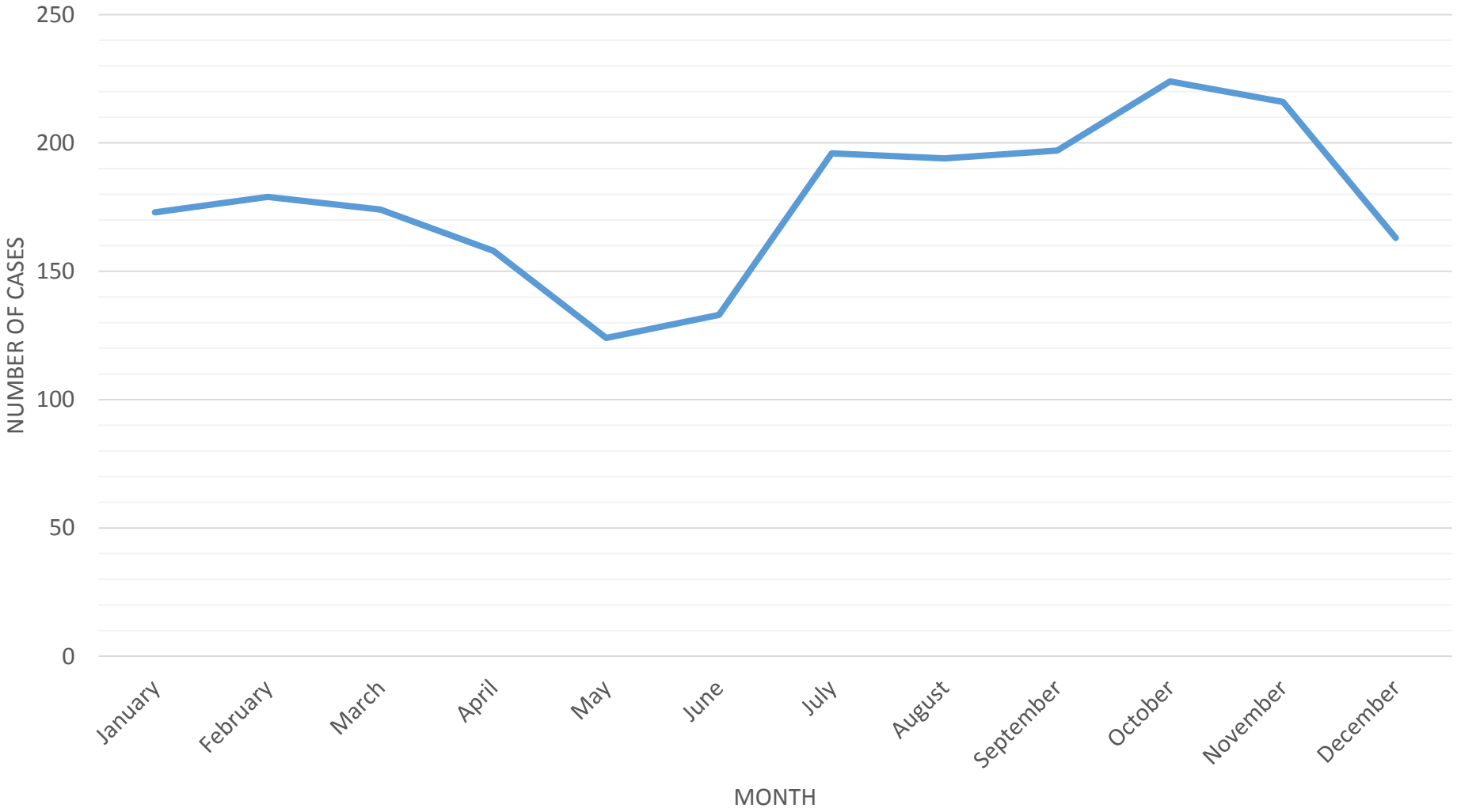
Age distribution of dengue patients in King Chulalongkorn Memorial Hospital between 1987- 2007



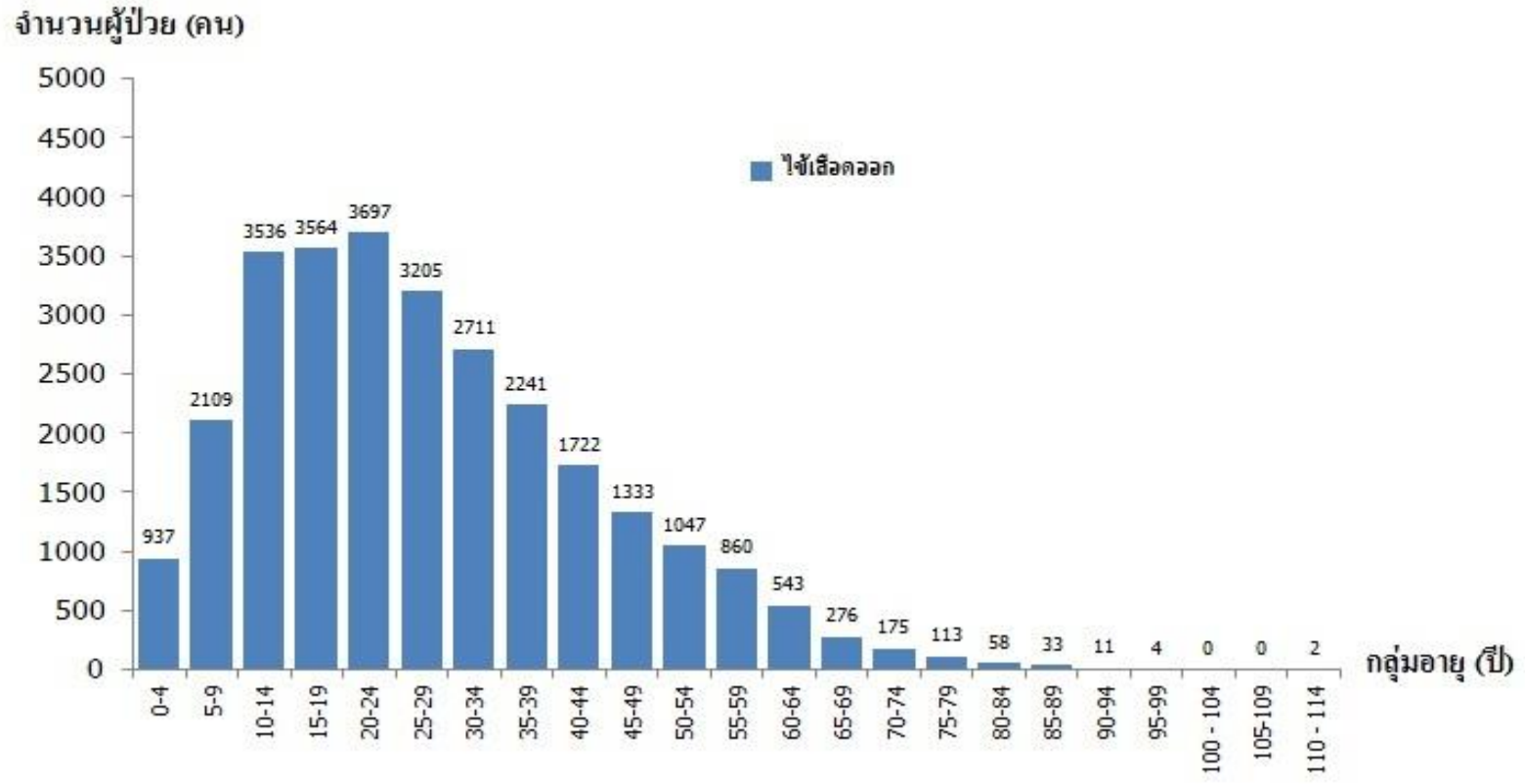
Thisyakorn & Thisyakorn. Southeast Asian J Trop Med Public Health 2017; 48 (Supplement 1): 106-11.

Seasonal distribution of dengue patients in King Chulalongkorn Memorial Hospital between 1987- 2007

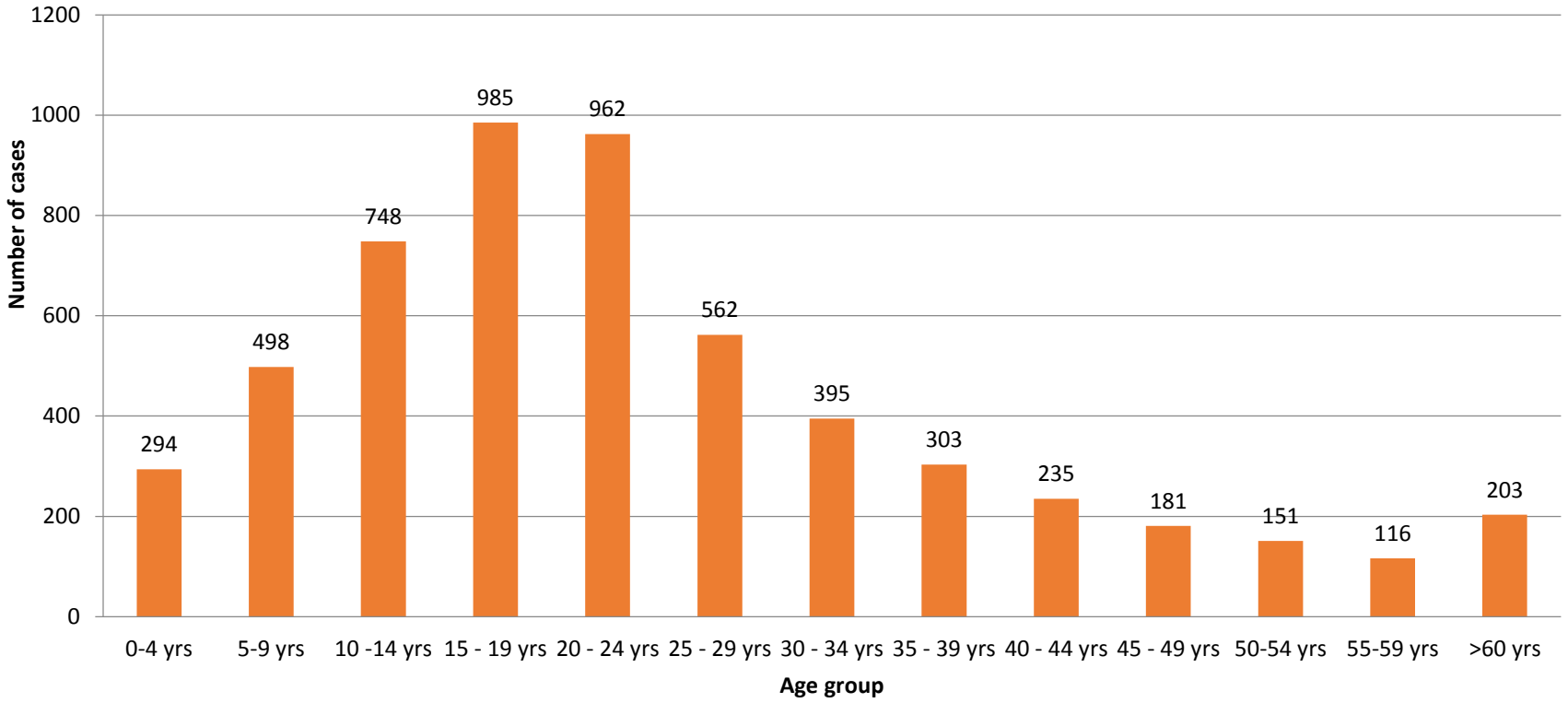


Thisyakorn & Thisyakorn. Southeast Asian J Trop Med Public Health 2017; 48 (Supplement 1): 106-11.

Dengue in Bangkok 2015

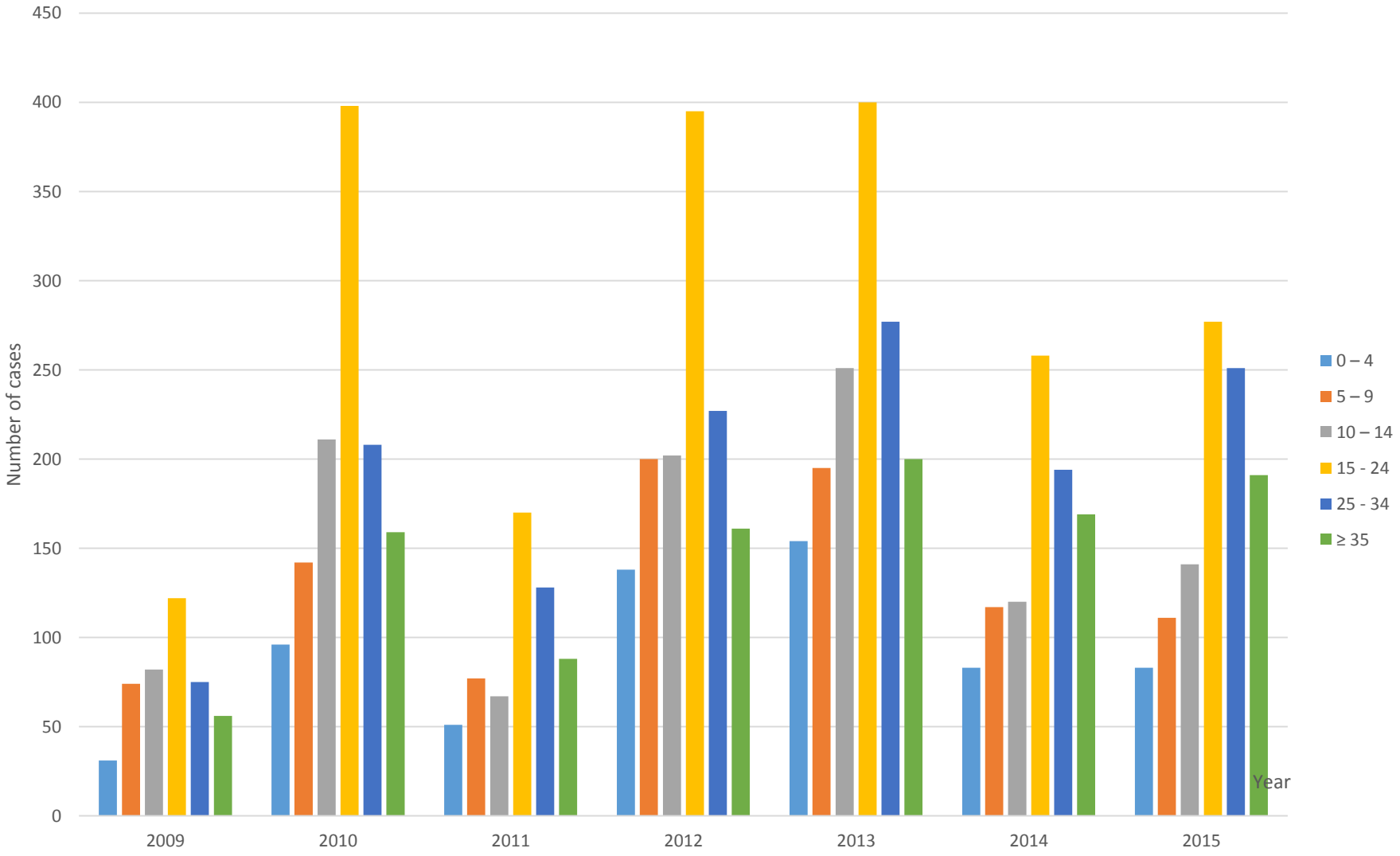


DENGUE AT THAMMASAT UNIVERSITY 2006 - 2015



Tangsathapornpong A, et al. Southeast Asian J Trop Med Public Health 2017; 48 (Suppl1): 39-46.

DENGUE AT VACHIRA PHUKET HOSPITAL 2009 - 2015



Lawtongkum W, et al. Southeast Asian J Trop Med Public Health 2017; 48 (Suppl1): 47-51.

CHANGING EPIDEMIOLOGY OF DENGUE PATIENTS IN RATCHABURI, THAILAND

Usa Thisyakorn* Krisana Pengsaa Suwat Tanayapong** Chule Thisyakorn***

* Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

** Department of Tropical Pediatrics, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand *** Banpong Hospital, Ratchaburi, Thailand

Introduction

Dengue, one of the most devastating mosquito-borne viral diseases in humans, is now a significant problem globally. The disease, caused by the four dengue virus serotypes, ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF) and severe dengue hemorrhagic fever (DHF) with or without shock. In Thailand, dengue patient was first seen in Bangkok in 1958 and then appeared to other part of the country.

Objective

This study describes the changes in the epidemiological pattern of dengue patients in Ratchaburi, Thailand.

Materials and Methods

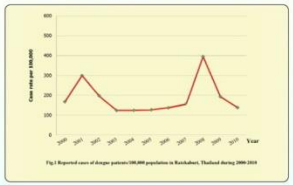
Analysis of dengue patients data reported to Ratchaburi provincial health office, Ministry of Public Health from 2000 to 2010 was done. The diagnosis of dengue patients adhered to-clinical and laboratory criteria for the diagnosis of dengue patients as established by the World Health Organization.

Conclusion

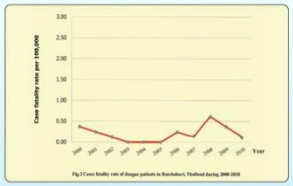
Dengue is a significant problem in Ratchaburi, Thailand. The trend of increasing age in dengue patients has been evident.

Results

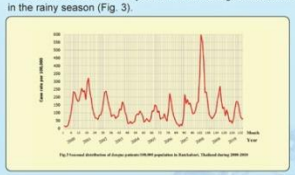
During the year 2000 to 2010, the rate of dengue patients in Ratchaburi varied from 123.45 per 100,000 population in 2003 to 394.25 per 100,000 population in 2008 (Fig. 1).



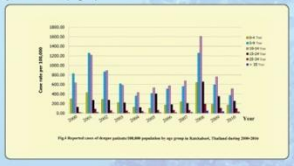
The case fatality rate varied from 0-0.62% (Fig. 2).



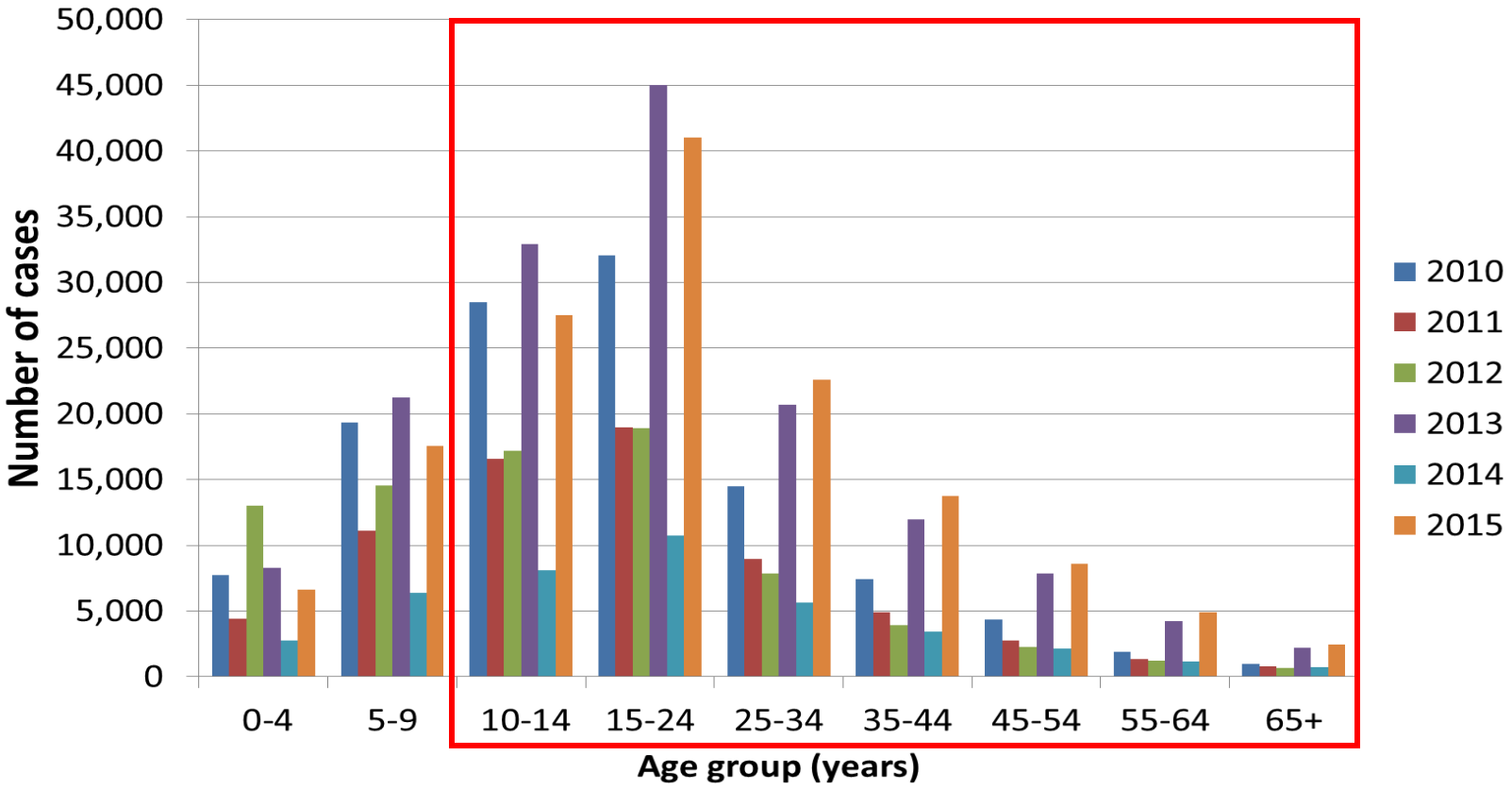
The disease was seen all year round with a higher incidence in the rainy season (Fig. 3).



The incidence by age group has shown that rates in older children and adults have dramatically increased during the past decade (Fig. 4).



Thailand, number of dengue cases per age group from 2010 to 2015



Bureau of Epidemiology, D. o. D. C., MoPH, Thailand (2016). "Bureau of Epidemiology, Department of Disease Control." Annual Epidemiology Surveillance Report (2010 to 2014), Report 506 (2015), Retrieved 12/02/2016, 2016, from http://203.157.15.110/boe/home.php.

Changing epidemiology of dengue in South-East Asia

Shift in affected age groups

and

expansion to rural areas

are evident

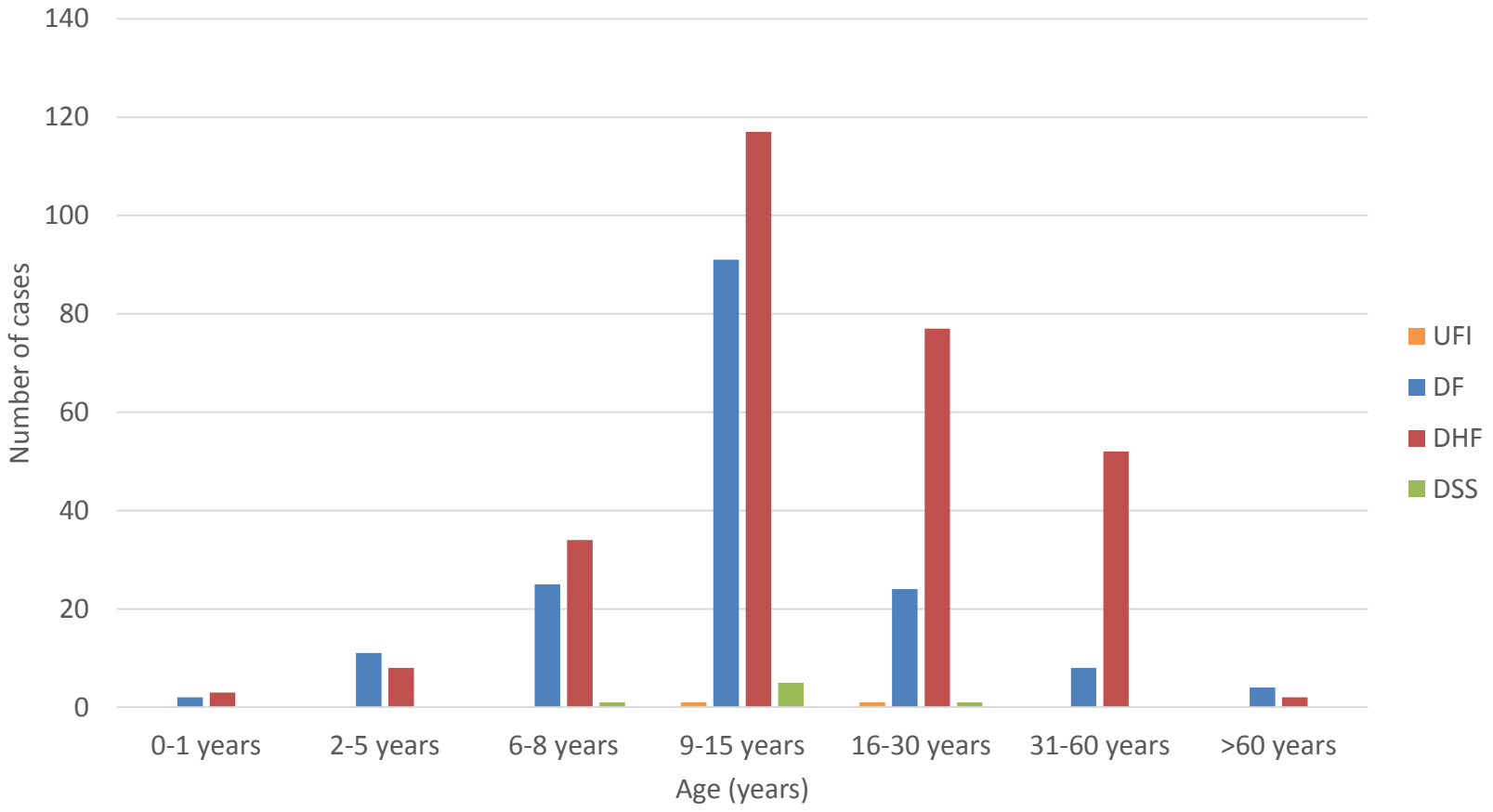
WHO South-East Asia Journal of Public Health | January-March 2013 | 2(1)

DENGUE IN BANGKOK

- **First outbreak: 1958**
- **Rate of patients: 27.99-292.24 per 100,000 population**
- **Case fatality rate: 0-0.21%**
- **Serotype: all 4 serotypes circulate continuously with predominant serotype emerging as the cause of each epidemic**
- **Changing epidemiology: a trend towards higher ages**

Liulak W, et al. Southeast Asian J Trop Med Public Health 2017; 48 (Supplement 1): 33-8.

Age distribution VS dengue severity in Bangkok 2015-2016



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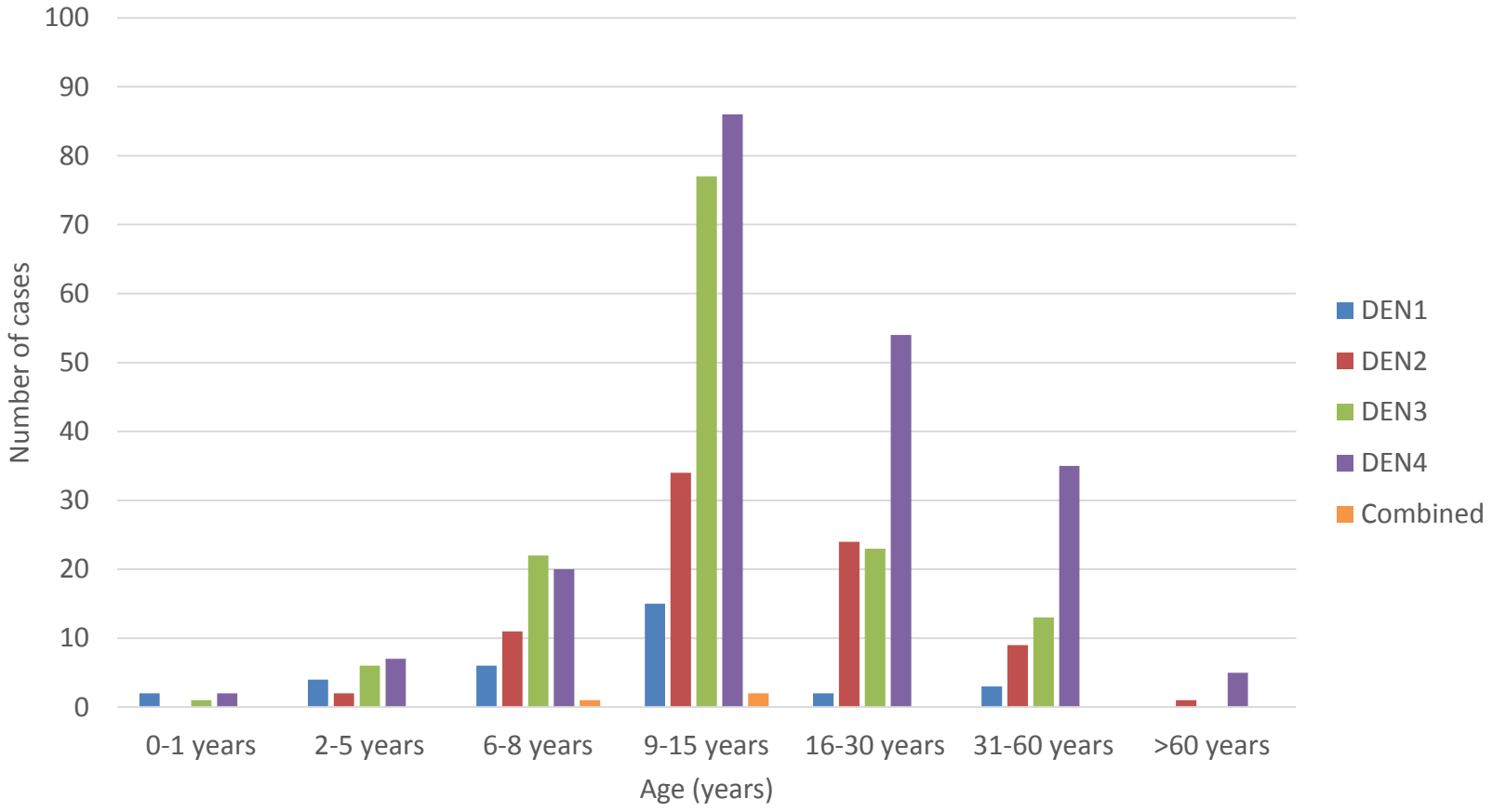
Age distribution VS DEN serotype in Bangkok 2015-2016



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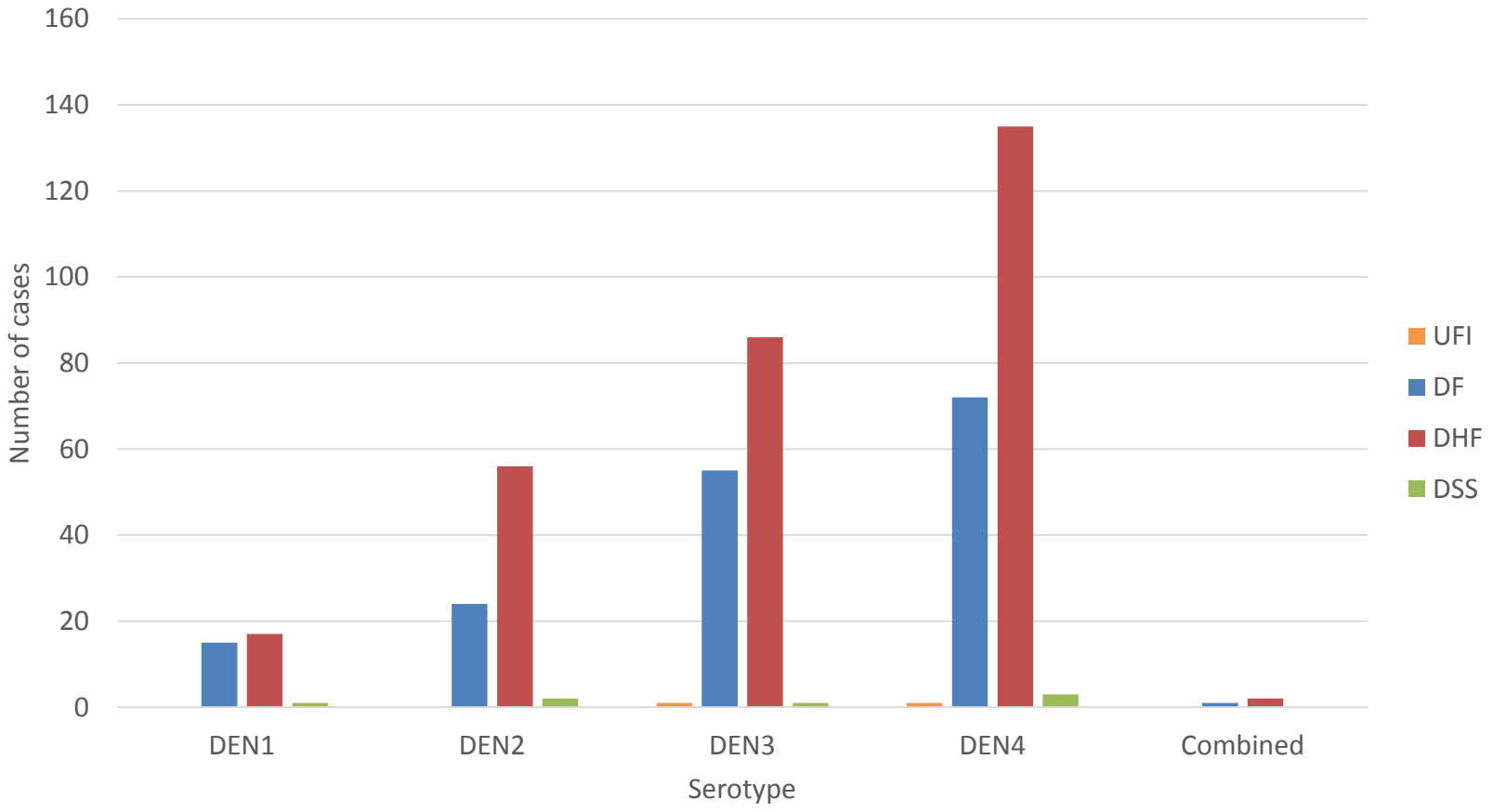

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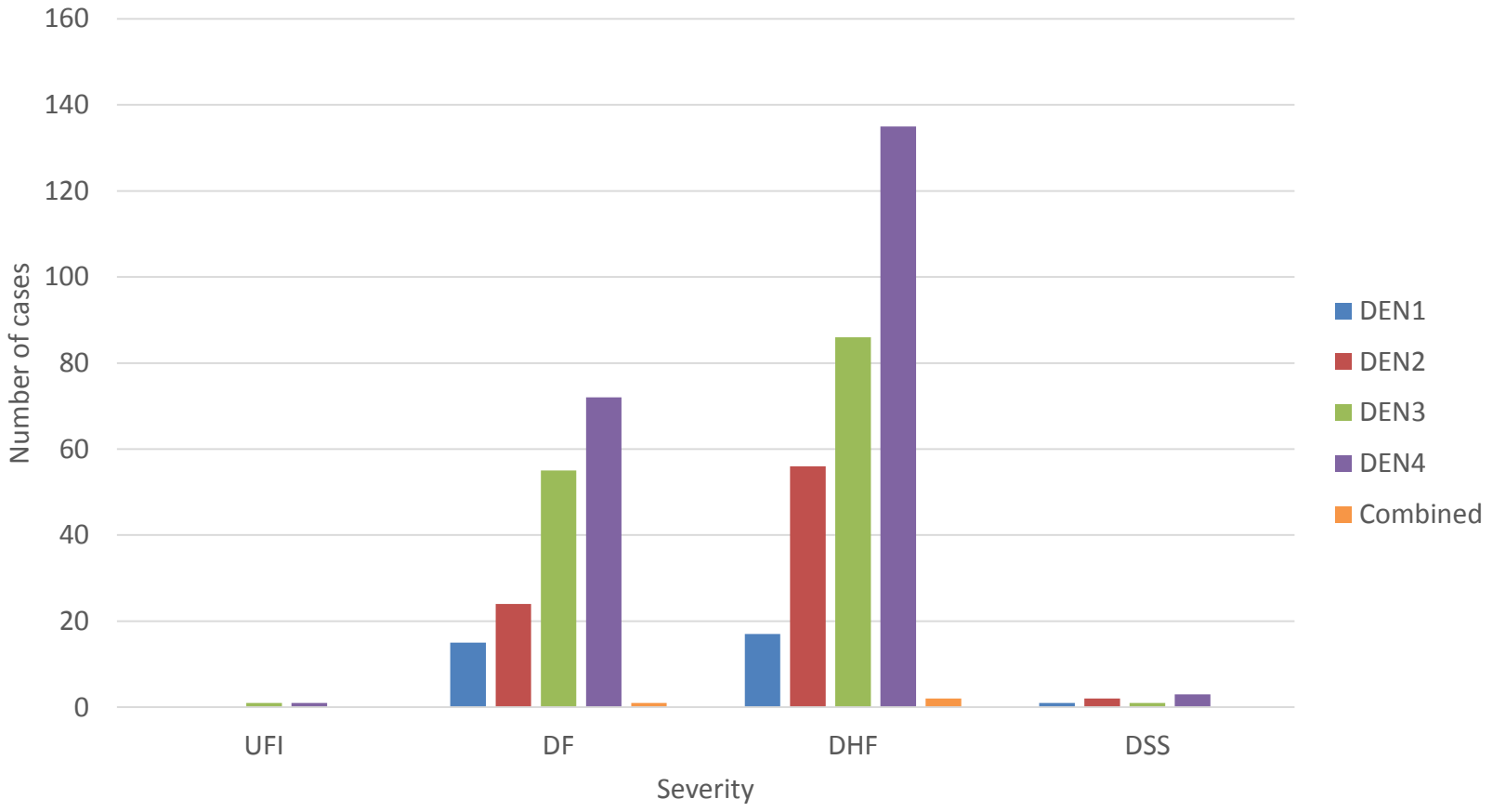

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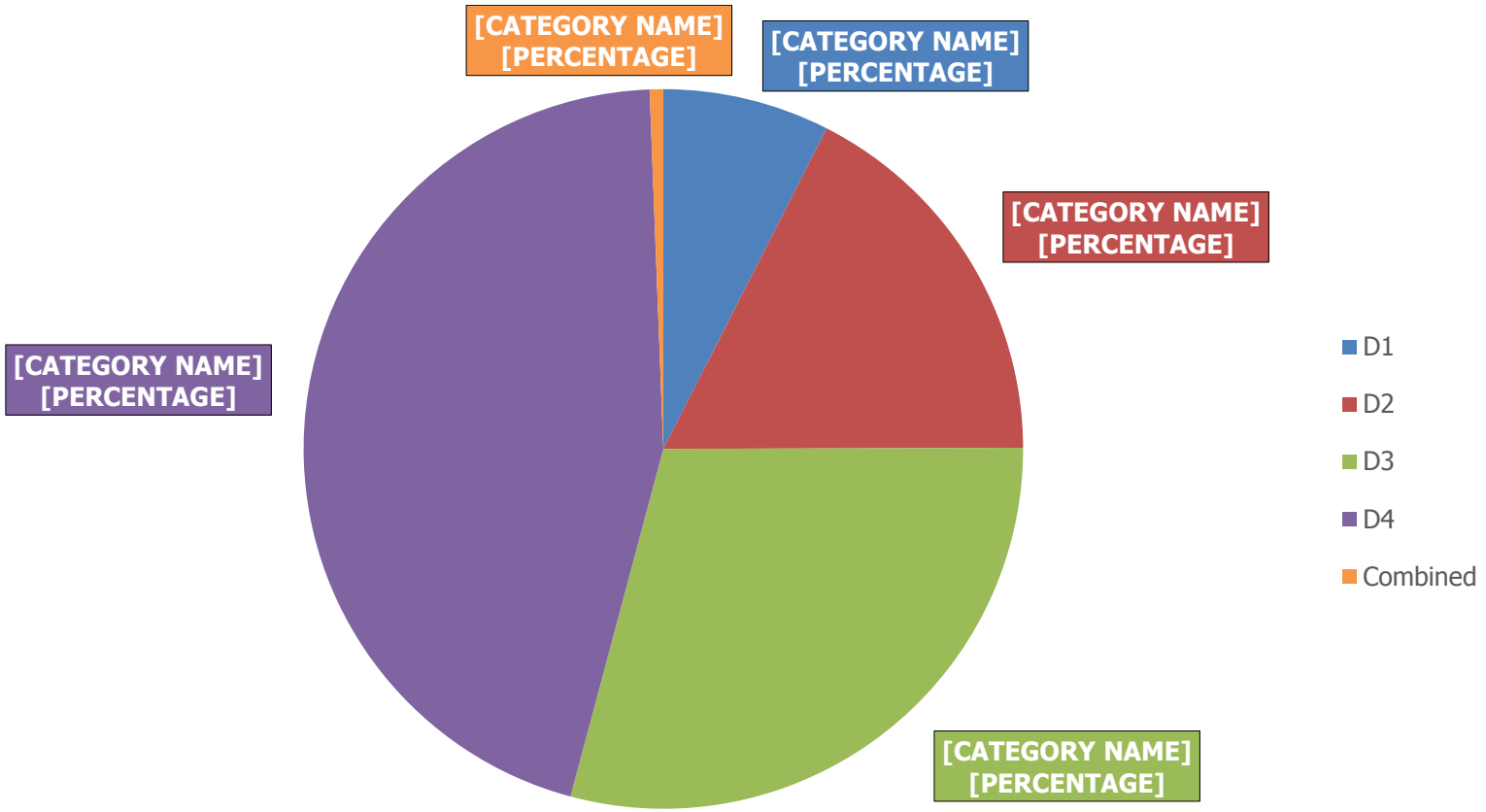

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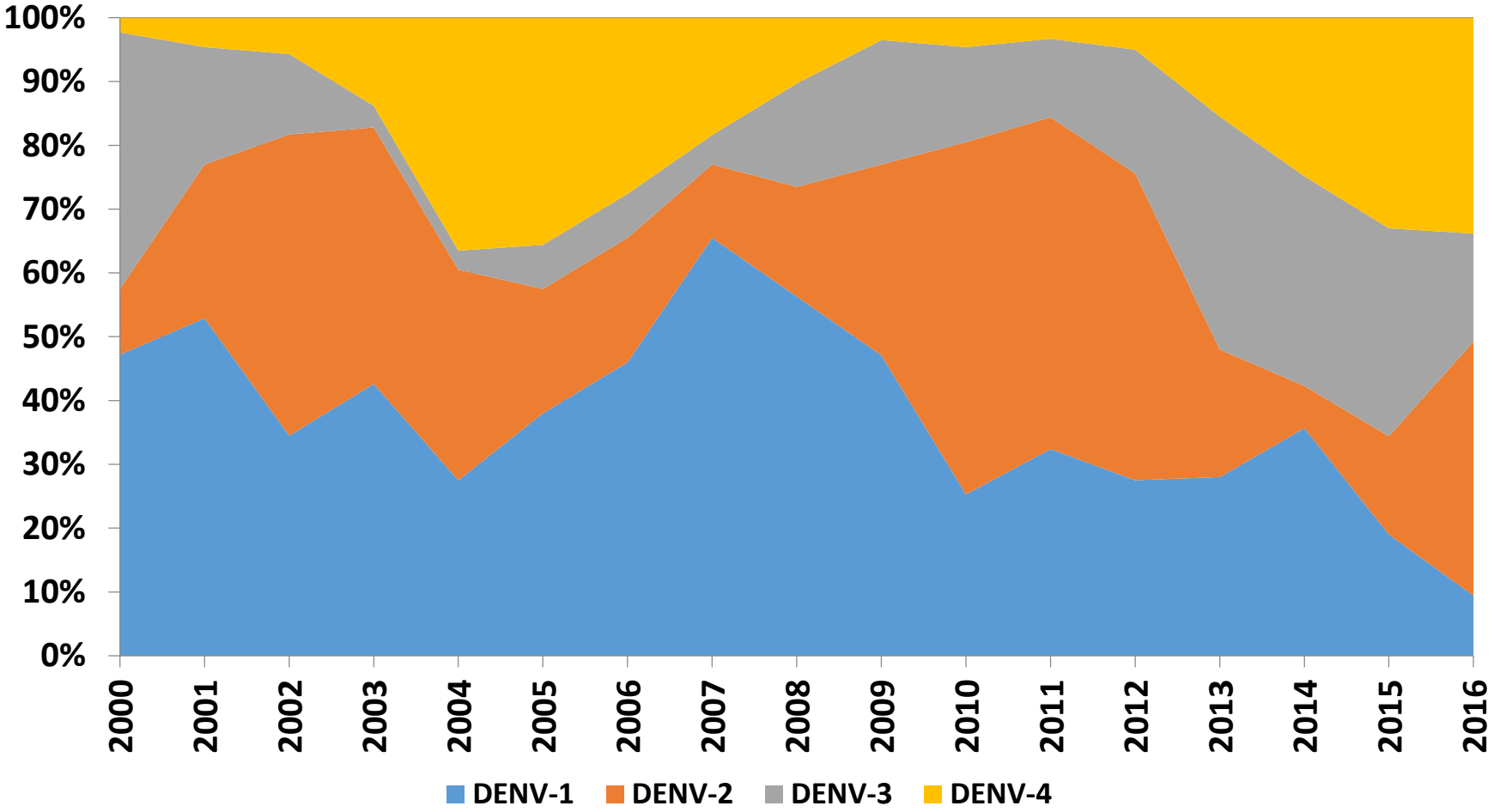
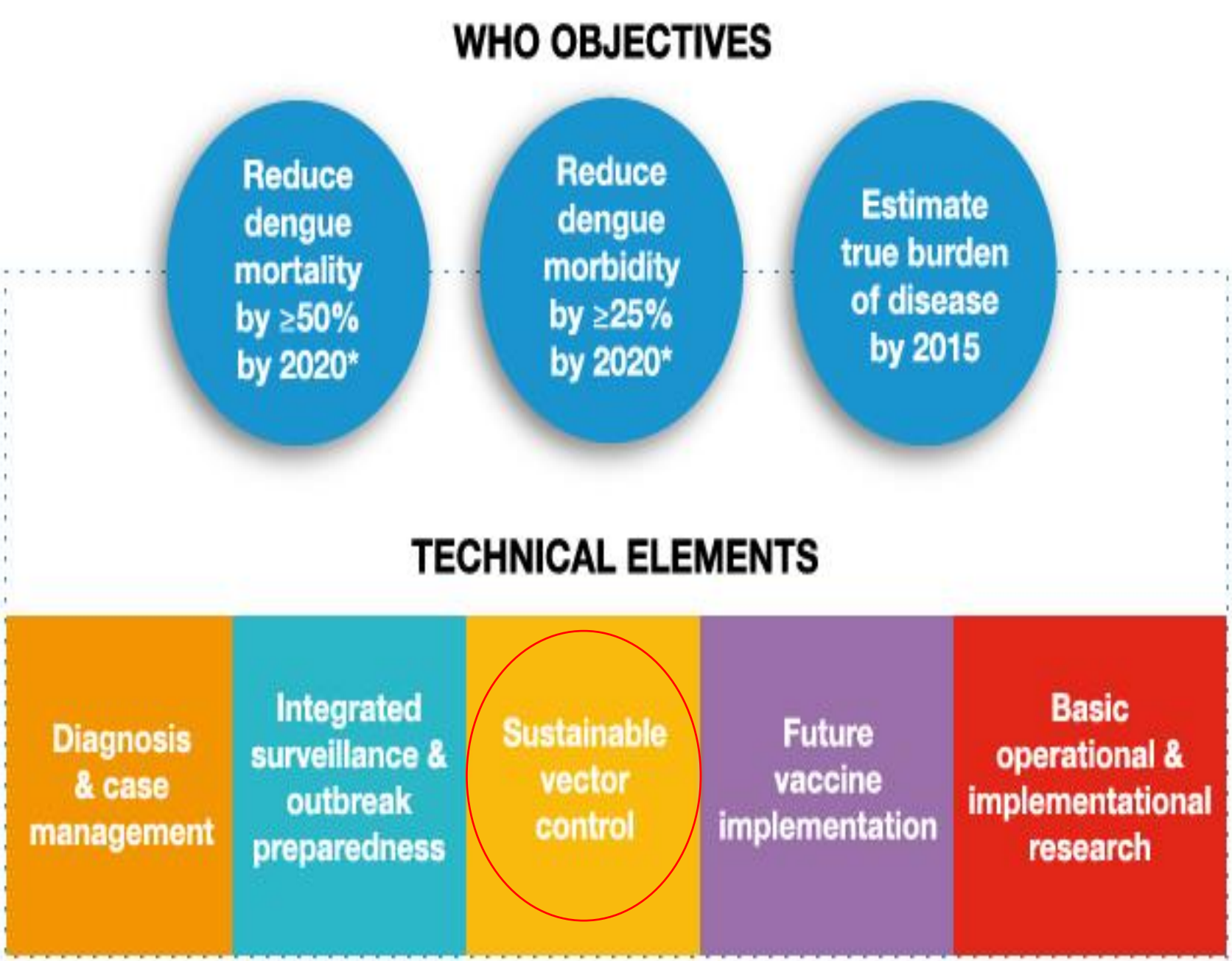
Dengue serotype in Thailand from 2000-2016



Source: NIH, MOPH, 2000-2016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TECHNICAL ELEMENTS
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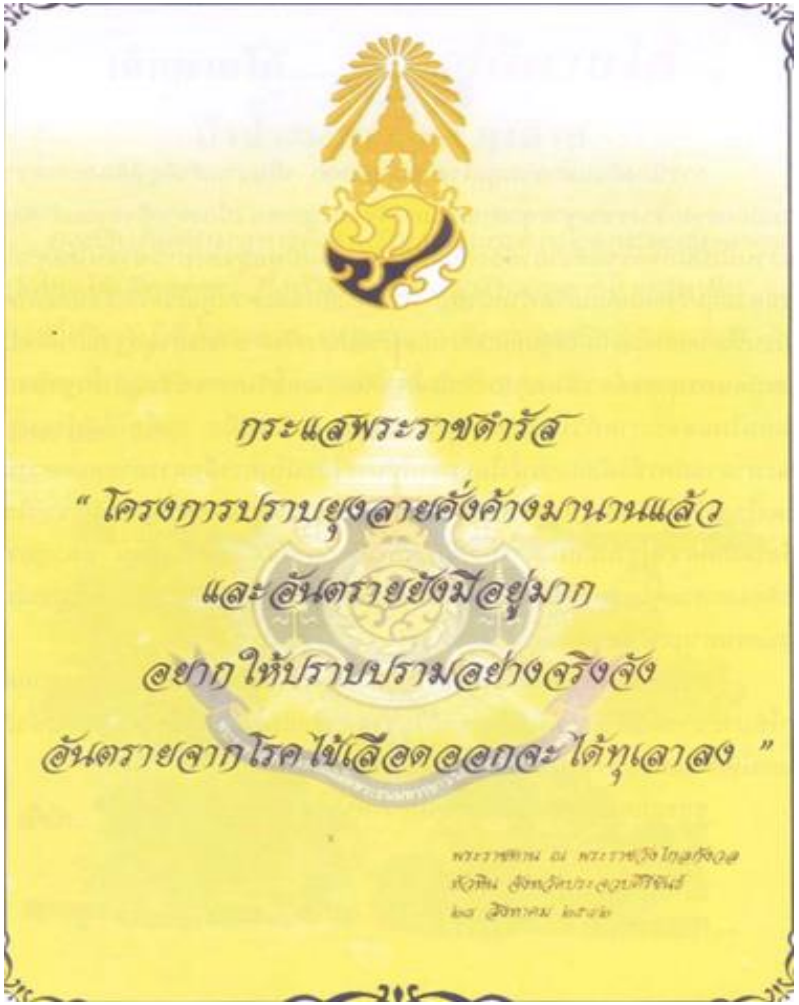
Integrated surveillance & outbreak preparedness
Sustainable vector control
Future vaccine implementation
Basic operational & implementational research


DONT
MAKE DE
USA
WORRY!

The King's announcement about the prioritization of dengue in 1999



- **Major impact on the surveillance for dengue and increased in number of DF reports seen from 2003 to 2011, after the electronic system was in place.**

- **In 1999, MOPH initiated a dengue prevention and control program**
  - **Aim is to reduce incidence of dengue to < 50 cases per 100,000 population**
  - ***A. aegypti* larval source reduction through an integrated, community-based approach**

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**

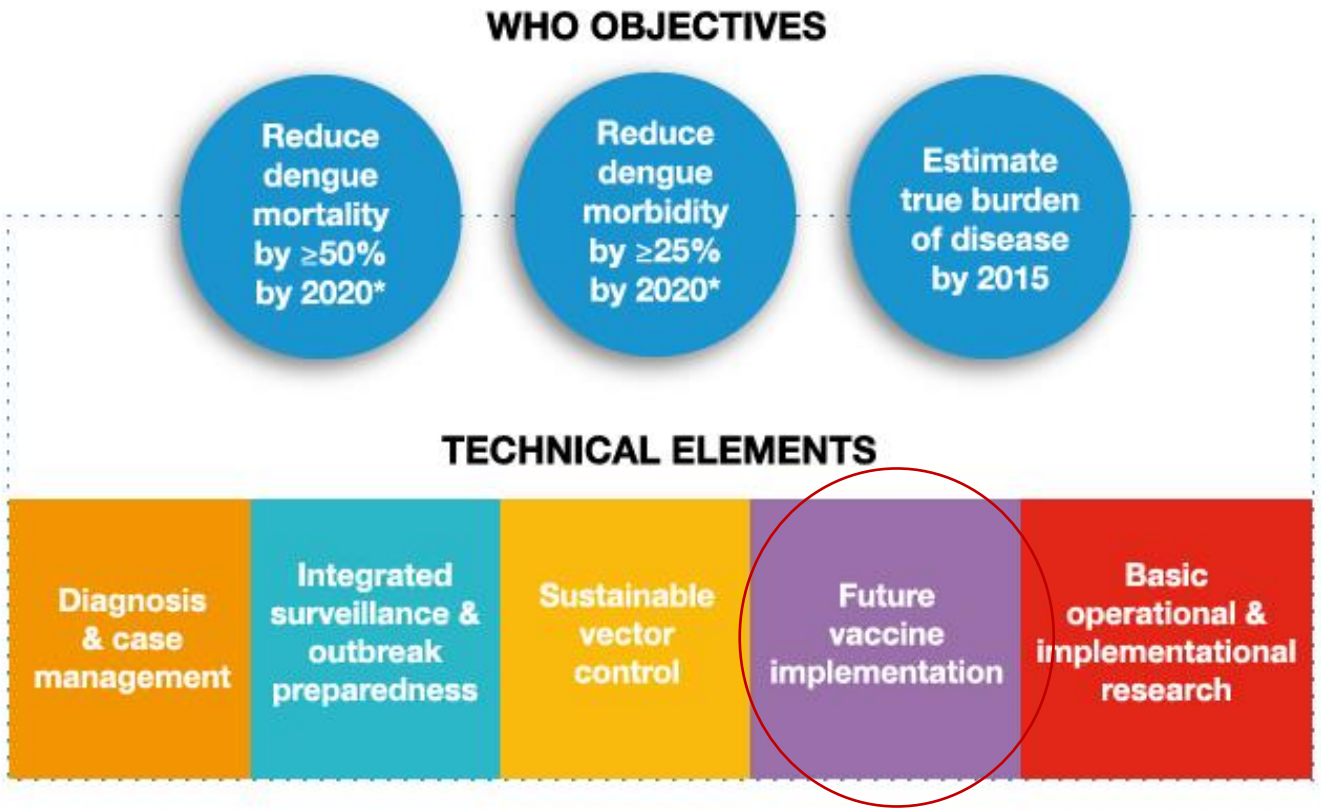
Accessible at http://apps.who.int/tdr/svc/publications/training-guideline publications/dengue-diagnosis-treatment; 2009 [accessed 04.07.11].

DENGUE VECTOR CONTROL: ASSESSING WHAT WORKS?

- **Vector control can be effective, implementation remains an issue**
- **Single interventions are probably not useful, efficacy varies, with little sustainability**
- **Combinations of interventions have mixed results**
- **Interventions are often applied in outbreaks with questionable effectiveness**
- **Key elements for more effective vector control: timely alerts of outbreaks followed by immediate vector control and health promotional campaigns**
- **Careful implementation may be most important**

Horstick O, et al. Southeast Asian J Trop Med Public Health2017; 48 (Supplement 1): 181-95.

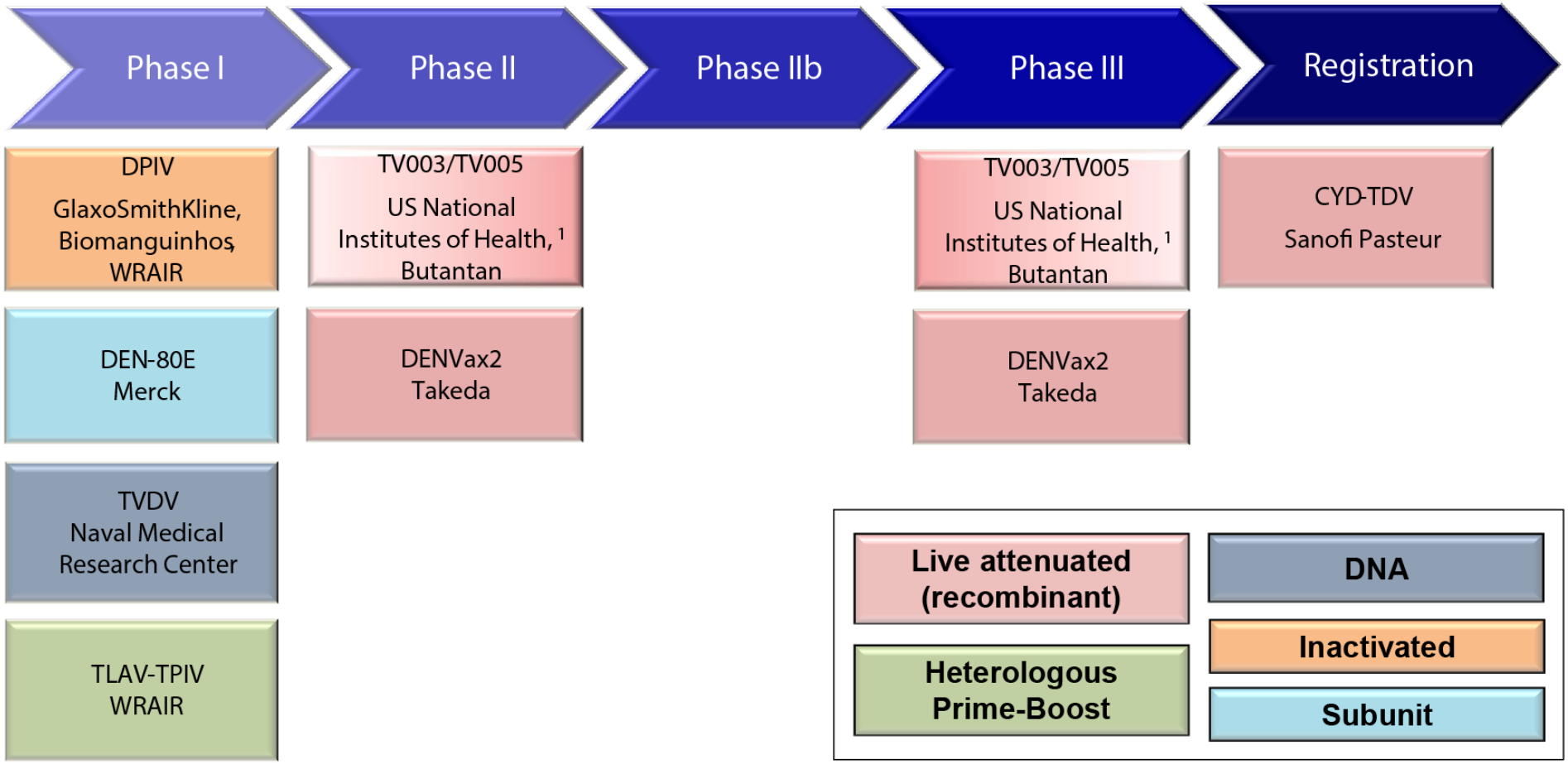
The candidates dengue vaccine could help meet WHO objectives of decreasing dengue-related mortality by ≥50% and morbidity by ≥25% by 2020.[1]



*The baseline year is 2010.
WHO=World Health Organization.

1. WHO, 2012, Global Strategy for Dengue Prevention and Control.

Clinical Dengue Vaccine Development Pipeline

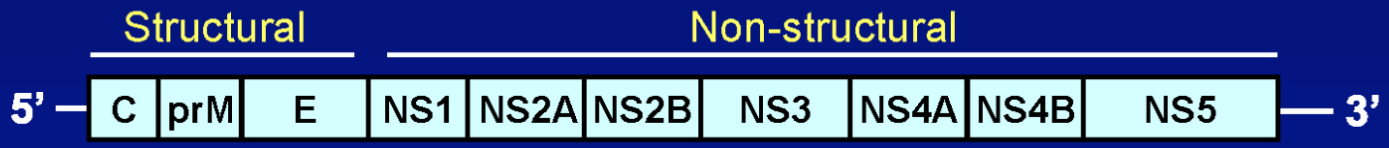


[1]Licensing agreements also with Merck, Panacea, SII, Vabiotech

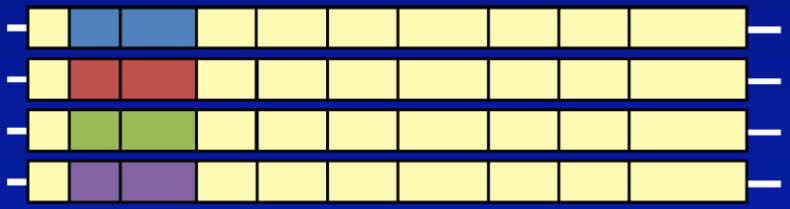
Phase 3 study approved for Butantan

World Health Organization

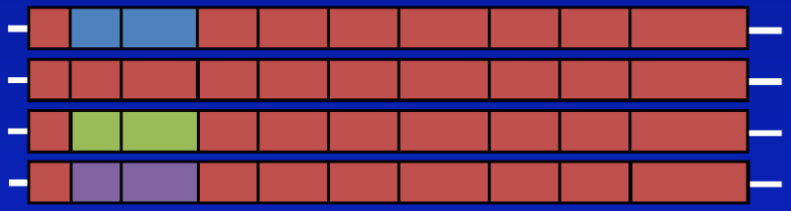
Recombinant live attenuated DENV vaccine strategies



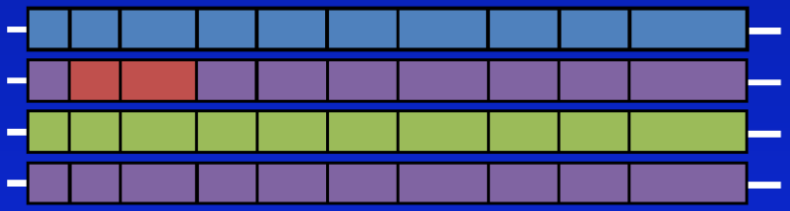
Sanofi-Pasteur

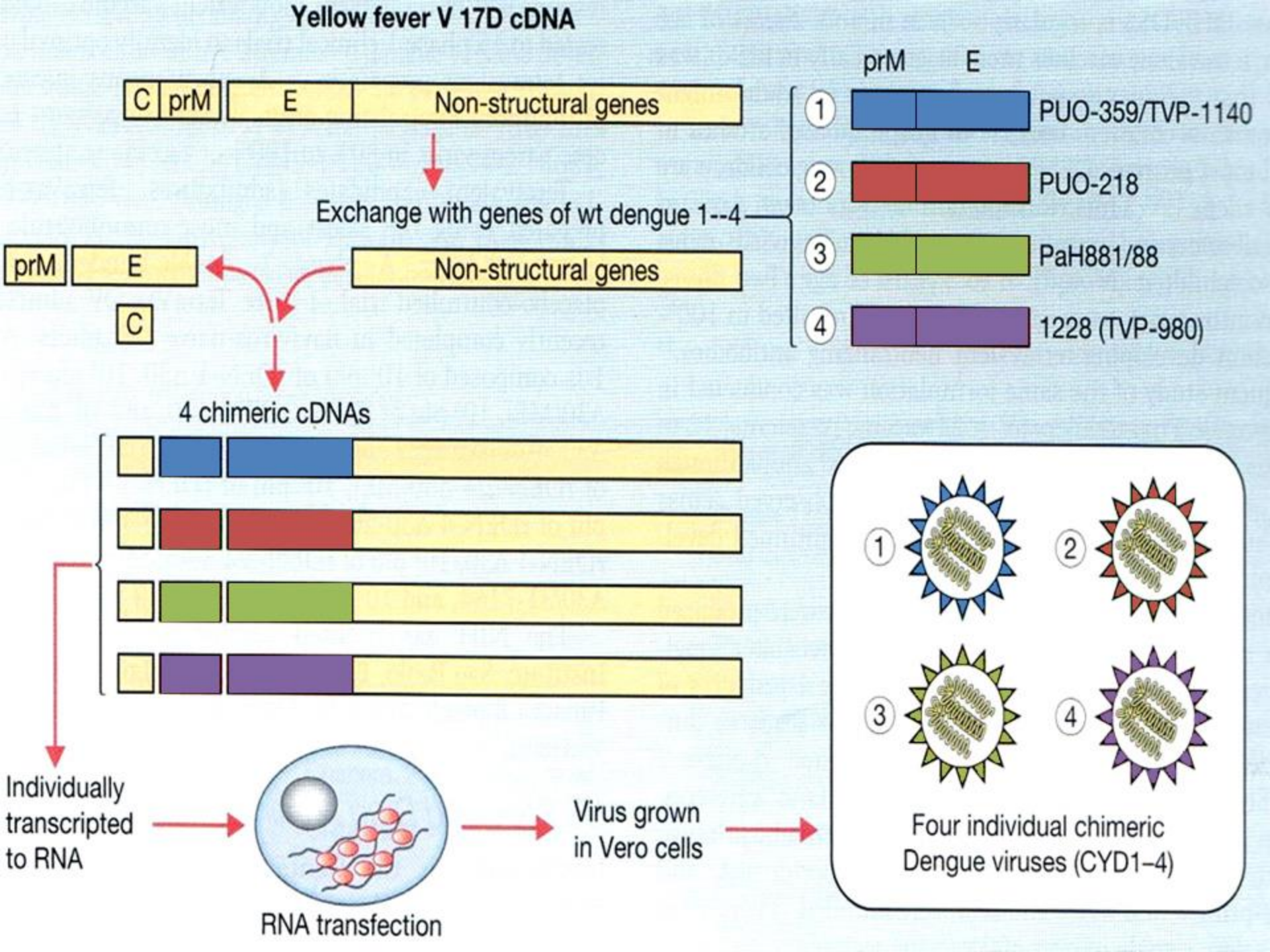


Inviragen



NIAID / LID




Yellow fever V 17D cDNA
C
prM
E
Non-structural genes
Exchange with genes of wt dengue 1--4
prM
E
Non-structural genes
C
4 chimeric cDNAs
prM
E
1
PUO-359/TVP-1140
2
PUO-218
3
PaH881/88
4
1228 (TVP-980)
Individually transcripted to RNA
RNA transfection
Virus grown in Vero cells
1
2
3
4
Four individual chimeric Dengue viruses (CYD1–4)

OBJECTIVE OF THE PUBLICATION: GLOBAL VIEW OF CLINICAL PROFILE OF SANOFI PASTEUR VACCINE CANDIDATE BASED ON EFFICACY AND LTFU INTERIM ANALYSES DATA

CYD14 efficacy study in Asia[1]
2–14 years (N=10,275)


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

http://linkinghub.elsevier.com/retrieve/pii/S0140673614610606

CYD15 efficacy study in Latin America and the Caribbean[2]
9–16 years (N=20,869)


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

http://www.nejm.org/doi/full/10.1056/NEJMoa1411037

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease[3]

www.nejm.org/doi/full/10.1056/NEJMoa1506223

LTFU=long-term follow-up.

1. Capeding, 2014, Lancet.
2. Villar, 2015, N Engl J Med
3. Hadinegoro, 2015, N Engl J Med.

KEY RESULTS OF CYD14 & CYD15

- Variable efficacy for all serotypes
- Increased efficacy in people with prior dengue infection
- High efficacy in protecting against severe dengue
- Good efficacy in decreasing hospitalization
- Prevented asymptomatic dengue infection
- Safe

SAGE & DENGUE VACCINE

- **The WHO SAGE recommends countries consider introduction of CYD-TDV in geographic settings where dengue is highly prevalent.**

- **Integrated vaccination strategy with a communication strategy, vector control, clinical care, surveillance.**

- **Introduction requires careful assessment by each country.**

15 April 2016

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

29 JULY 2016, 91th YEAR / 29 JUILLET 2016, 91e ANNÉE
No 30, 2016, 91, 349–364
http://www.who.int/wer

Contents

Dengue vaccine: WHO position paper – July 2016

Note de synthèse de l'OMS sur le vaccin contre la dengue – juillet 2016

WHO position

Countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease.

In defining populations to be targeted for vaccination, prior infection with dengue virus of any serotype, as measured by seroprevalence, should be approximately 70% or greater in the age group targeted for vaccination in order to maximize public health impact and cost-effectiveness. Vaccination of populations with seroprevalence between 50% and 70% is acceptable but the impact of the vaccination programme may be lower. The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination.

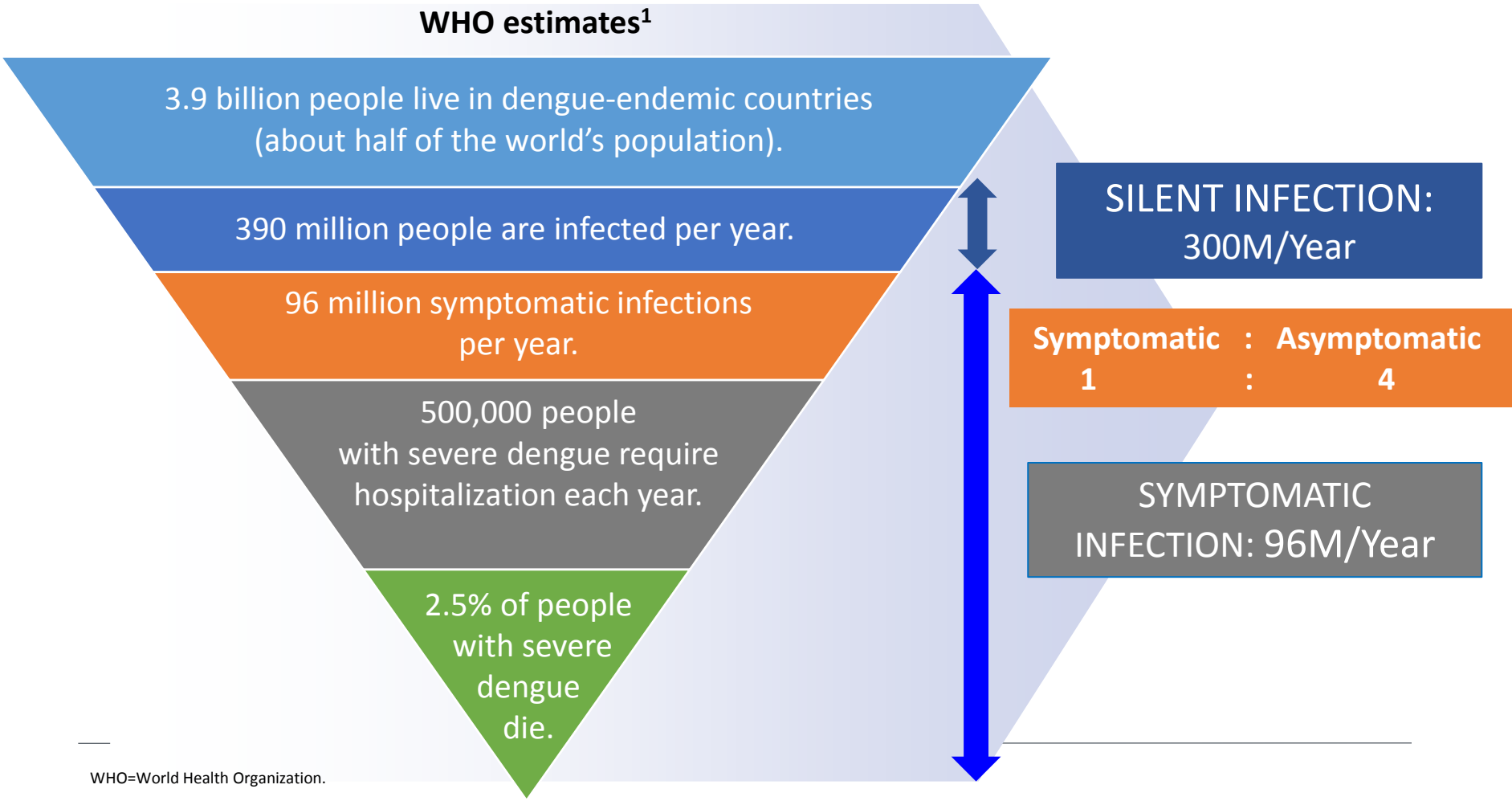
Dengue vaccine introduction should be a part of a comprehensive dengue control strategy, including well-executed and sustained vector control, evidence-based best practices for clinical care for all patients with dengue illness, and strong dengue surveillance. Vaccine introduction must be accompanied by a targeted communication strategy. Decisions about introduction require careful assessment at the country level, including consideration of local priorities, national and subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific inputs, affordability and budget impact. At the time of introduction, countries are encouraged to have a functional pharmacovigilance system with at least minimal capacity to monitor and manage adverse events following immunization.[44] Countries considering vaccination should also have a dengue surveillance system able to detect and report hospitalized and severe dengue cases consistently over time.

DENGUE VACCINE: WHO POSITION PAPER

- **Countries should consider introduction of CYD-TDV in geographic settings where dengue is high burden.**
- **A combination of seroprevalence data, and programmatic factors should define the target population.**
- **Integrated vaccination strategy with vector control, clinical care, surveillance, communication strategy.**
- **Introduction requires careful assessment by each country.**

29 July 2016

ABOUT 400 MILLION PEOPLE INFECTED PER YEAR
300 MILLION OF ASYMPTOMATIC = RESERVOIR FOR DENGUE TRANSMISSION



WHO=World Health Organization.

1. WHO, 2015, Dengue Fact Sheet.
2. WHO, 2012, Global Strategy for Dengue Prevention and Control.

Studies That Assessed Relative Incidence of Asymptomatic Dengue Virus Infection

Reference	Location	Age, y	Subjects, No.	Study Period	Incidence Ratio (Symptomatic:Asymptomatic)
Busch et al [44]	Rio de Janeiro, Brazil	16–67	16 241	2012	1:2.7
Porter et al [45]	West Java, Indonesia	18–66	2536	2000–2002	1:3
Balmaseda et al [24]	Managua, Nicaragua	2–9	3713	2004–2005	1:18
			3689	2005–2006	1:5
			3563	2006–2007	1:16
			3676	2007–2008	1:3
Montoya et al [43]	Managua, Nicaragua	2–14	5541	2004–2011	1:2.6 (2009–2010); 1:20.4 (2006–2007)
Katzelnick et al [34]	Managua, Nicaragua	2–14	7547	2004–2014	1:2.6
Burke et al [27]	Bangkok, Thailand	4–16	1752	1980–2001	1:5.6
Endy et al [42]	Kamphaeng Phet, Thailand	10 (median)	2119	1998–2000	1:0.9
Mammen et al [46]	Kamphaeng Phet, Thailand	0.5–15	556	2004–2005	1:0.9
Present study	32 cities in 10 countries (Asia and Latin America)	2–16	3669	2011–2013	1:3.9

JID 2016:214 (1 October) • Olivera-Botello et al

The Journal of Infectious Diseases

MAJOR ARTICLE

Tetravalent Dengue Vaccine Reduces Symptomatic and Asymptomatic Dengue Virus Infections in Healthy Children and Adolescents Aged 2–16 Years in Asia and Latin America

Gustavo Olivera-Botello,[1] Laurent Coudeville,[1] Karen Fanouillere,[2] Bruno Guy,[1] Laurent Chambonneau,[3] Fernando Noriega,[4] and Nicholas Jackson[3]; for the CYD-TDV Vaccine Trial Group[a]

[1]Sanofi Pasteur, Lyon, [2]Sanofi, Chilly-Mazarin Cedex, and [3]Sanofi Pasteur, Marcy l'Etoile, France; and [4]Sanofi Pasteur, Swiftwater, Pennsylvania

Background. Asymptomatic dengue virus–infected individuals are thought to play a major role in dengue virus transmission. The efficacy of the recently approved quadrivalent CYD-TDV dengue vaccine against asymptomatic dengue virus infection has not been previously assessed.

Methods. We pooled data for 3 736 individuals who received either CYD-TDV or placebo at 0, 6, and 12 months in the immunogenicity subsets of 2 phase 3 trials (clinical trials registration NCT01373281 and NCT01374516). We defined a seroconversion algorithm (ie, a ≥4-fold increase in the neutralizing antibody titer and a titer of ≥40 from month 13 to month 25) as a surrogate marker of asymptomatic infection in the vaccine and placebo groups.

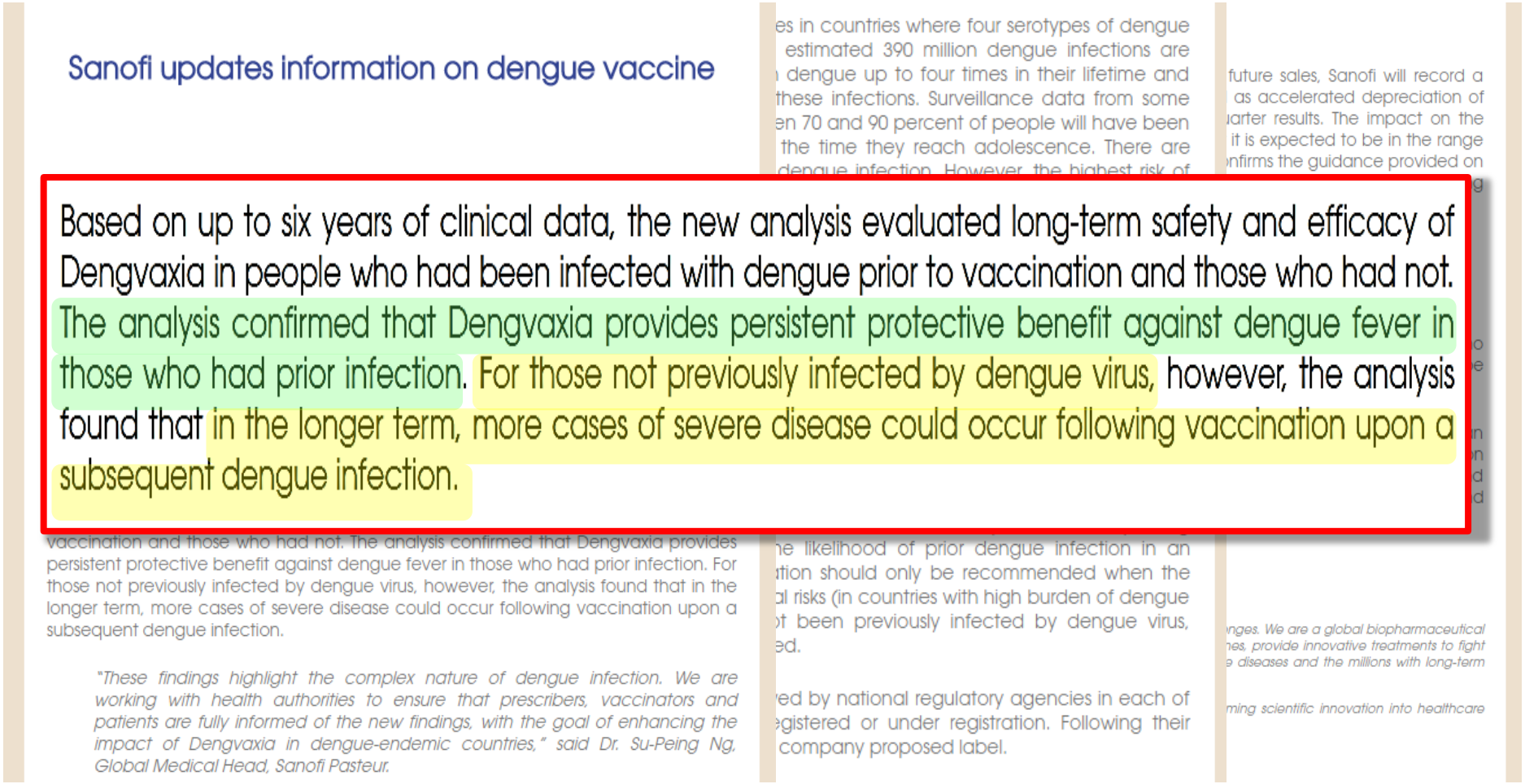
Results. The algorithm detected seroconversion in 94% of individuals with a diagnosis of virologically confirmed dengue between months 13 and 25, validating its discriminatory power. Among those without virologically confirmed dengue (n = 3 669), 219 of 2 485 in the vaccine group and 157 of 1 184 in the placebo group seroconverted between months 13 and 25, giving a vaccine efficacy of 33.5% (95% confidence interval [CI], 17.9%–46.1%) against asymptomatic infection. Vaccine efficacy was marginally higher in subjects aged 9–16 years (38.6%; 95% CI, 22.1%–51.5%). The annual incidence of asymptomatic dengue virus infection in this age group was 14.8%, which was 4.4 times higher than the incidence for symptomatic dengue (3.4%).

Conclusions. The observed vaccine efficacy against asymptomatic dengue virus infections is expected to translate into reduced dengue virus transmission if sufficient individuals are vaccinated in dengue-endemic areas.

New Supplementary Analysis by Anti-Dengue NS1 Lab

Sanofi Press Release on November 29, 2017

Sanofi updates information on dengue vaccine



Sanofi updates information on dengue vaccine

Based on up to six years of clinical data, the new analysis 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.

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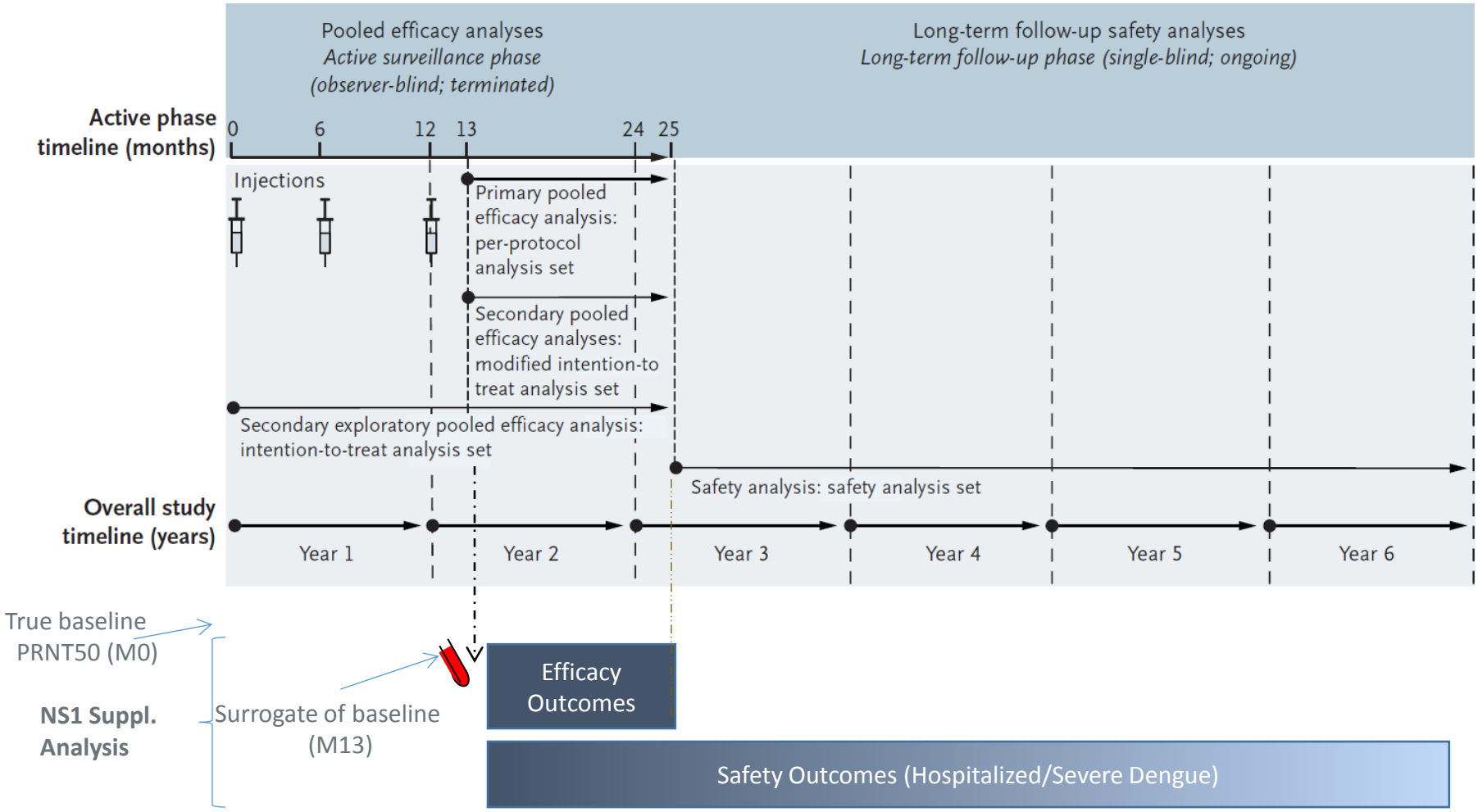
"These findings highlight the complex nature of dengue infection. We are working with health authorities to ensure that prescribers, vaccinators and patients are fully informed of the new findings, with the goal of enhancing the impact of Dengvaxia in dengue-endemic countries," said Dr. Su-Peing Ng, Global Medical Head, Sanofi Pasteur.

http://mediaroom.sanofi.com/sanofi-updates-information-on-dengue-vaccine/ (retrieved on 6 December 2017)

Measuring dengue exposure status: NS1 study initiative

All subjects provided M13 samples – Possible surrogate of baseline for post M13 outcomes*

* Conditional to applying an **assay not meaningfully affected by vaccination**



1.Hadinegoro, 2015, N Engl J Med.

ADVA statement regarding the CYD-TDV (I)

ADVA
Asian Dengue Vaccination Advocacy

1. The results are preliminary and were made by retrospective analysis of blood samples taken a month after the third dose of the vaccine in the original CYD 14 (in Asia) and CYD 15 (in Latin America) studies.

ADVA statement regarding the CYD-TDV (II)

ADVA
Asian Dengue Vaccination Advocacy

2. The test performed is new and had been validated using PRNT as the reference. It indicates past-infection with wild dengue virus only, and excludes vaccine-induced immunity.

ADVA statement regarding the CYD-TDV (III)

ADVA
Asian Dengue Vaccination Advocacy

3. The results showed that seropositive (previously infected) individuals benefited from the vaccine. As many parts of Asia and areas in our own countries have high seropositive rates, the vaccine will have potential benefits across populations in Asia.

ADVA statement regarding the CYD-TDV (IV)

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4. Seronegative subjects (no previous dengue infection) tend to have higher hospitalization rates–Specifically, an additional 5 hospitalisations per 1000 vaccines in five years.

ADVA statement regarding the CYD-TDV (V)

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Asian Dengue Vaccination Advocacy

5. Seronegative subjects were also observed to have more DHF Grades I and II, speficically two extra cases per 1000 vaccinees in five years. There was no shock, bleeding nor mortality in this group.

ADVA statement regarding the CYD-TDV (VI)

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6. Serological pretesting is required, although not practical, but we need to have an appropriate, cheap, readily- and universally- available test. The gold-standard PRNT test is costly and not readily available while the test used by the manufacturer is currently only used on a research basis.

To avoid confusion, a practical approach using the most reliable laboratory testing has to be discussed and implemented.

ADVA statement regarding the CYD-TDV (VII)

ADVA
Asian Dengue Vaccination Advocacy

Summary

This outcome should not cause undue panic among individuals who have already received the dengue vaccine. The severe dengue that occurred in initially seronegative vaccinees were in DHF Grades I and II and did not lead to shock, any bleeding or mortality.

The report also reinforces the fact that seropositive individuals would benefit from receiving the vaccine.

WHO OBJECTIVES

- Reduce dengue mortality by ≥50% by 2020*
- Reduce dengue morbidity by ≥25% by 2020*
- Estimate true burden of disease by 2015

TECHNICAL ELEMENTS

- Diagnosis & case management
- Integrated surveillance & outbreak preparedness
- Sustainable vector control
- Future vaccine implementation
- Basic operational & implementational research

Conclusion

- **Dengue is one disease entity with different clinical manifestations, often with unpredictable clinical evolutions and outcomes**
- **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**

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Professor and Head, Nagasaki University Hospital

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Global Hakata Main Bldg. 7-1-8, Hakataeki-minami, Hakata-ku, Fukuoka, 812-0016, Japan
TEL: +81-92-437-4156 / FAX: +81-92-437-4163 / Email: acpid@c-linkage.co.jp

THANK YOU