

# sp second generation tetravalent dengue vaccine

## CYD23 Study

Efficacy and Safety of Dengue Vaccine in Healthy  
Children Aged 4 to 10 Years in Thailand

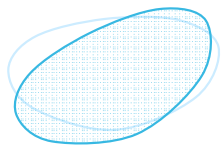
Alain Bouckenooghe, MD, MPH, DTM&H

Clinical R&D, Head Asia/Pacific region

JITMM meeting, Bangkok, Thailand, Oct 2008

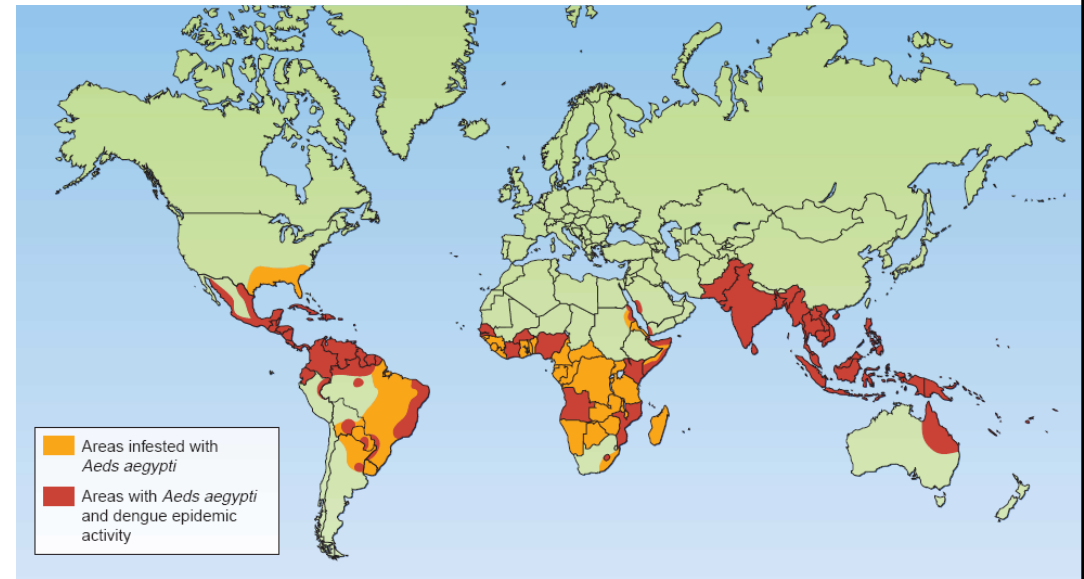
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# Dengue –

- Mosquito-borne flaviviral infection
- Dengue is present in more than 124 countries and territories
- More than 2.5 billion persons live in endemic regions (intertropical areas)
- Every year:
  - ▶ 70 to 100 million infected persons
  - ▶ Estimated over 2 million severe forms (among which 90 % are children)
  - ▶ Approximately 21 000 deaths



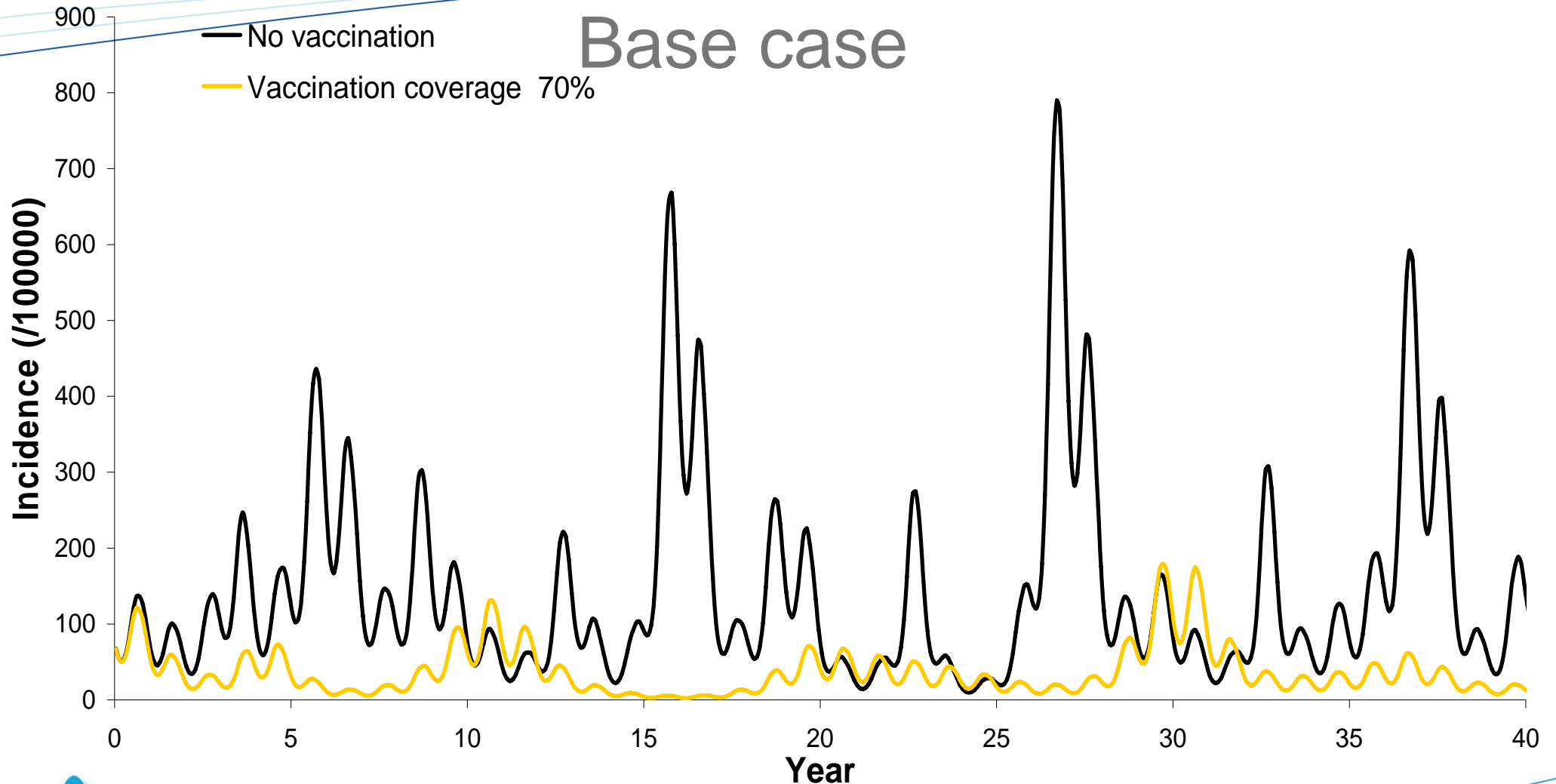
- There is no specific treatment and the care of the disease is based on symptomatic treatment

**A Dengue vaccine represents a Public Health priority**

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# Impact of vaccination coverage on incidence of DHF/DSS cases

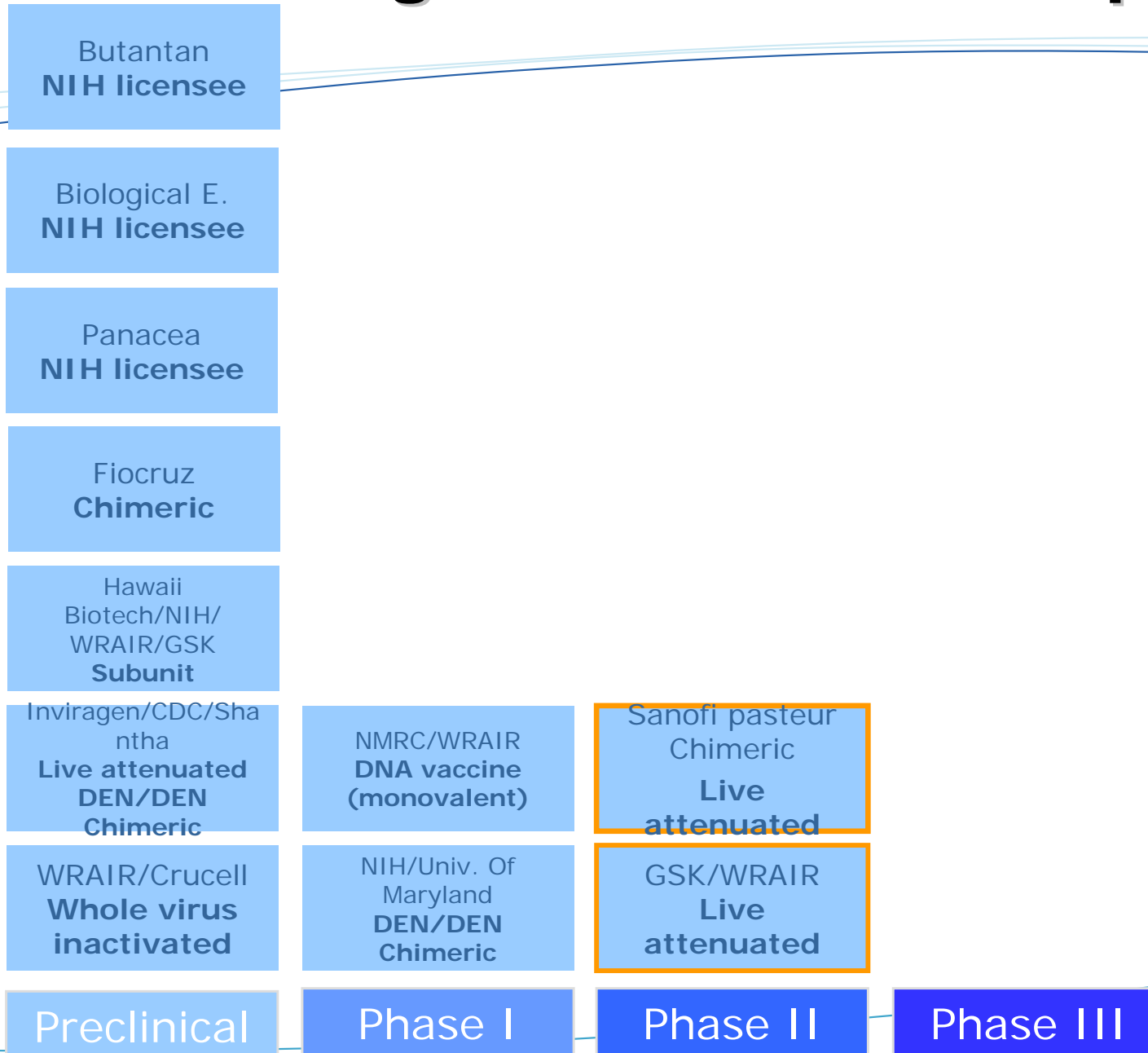


Vaccination alters disease dynamics by reducing the frequency and intensity of years with peak dengue incidence

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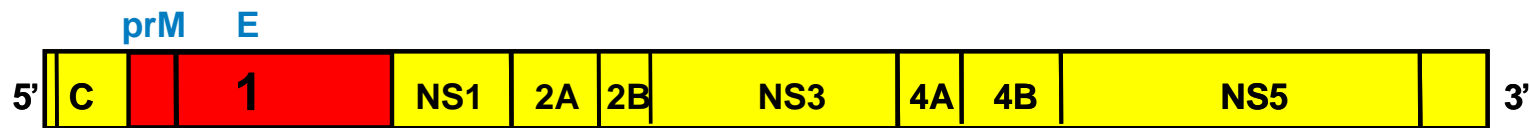
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# Current Dengue Vaccine Developments

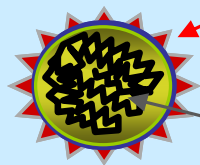


# sanofi pasteur second generation Tetravalent dengue vaccine candidate

Live attenuated dengue vaccines expressing the pre-membrane (prM) and envelope (E) proteins of each dengue serotype, which genes have been inserted in place of the corresponding genes of the YF 17D vaccine



The surface phenotype of these vaccines is thus no longer a YF-17D one, and their tropism is first linked to their dengue envelope



**Envelope is the immunizing Ag from an heterologous virus**

**RNA replication engine is from YF17D**

# Three phase II observer-blind randomized controlled trials

Study:	USA	Philippines	Mexico
Population	66 Adults 18-40yr	18 Adults 18-45yr 36 Adolescents 12-17yr 72 Children 2-11yr	18 Adults 18-45yr 36 Adolescents 12-17yr 72 Children 2-11yr
FV Immune status at baseline**	3%	80%	8%
Protocol	-----3 injections DV or control: Months 0, 3-4, 12-----		
Group 1:	DV*, DV, DV	DV, DV, DV	DV, DV, DV
Group 2:	Placebo, DV, DV	TyphimVi®, DV, DV	Stamaril®, DV, DV
Objective	To describe: safety, viremia and humoral immune responses, after each vaccine injection		

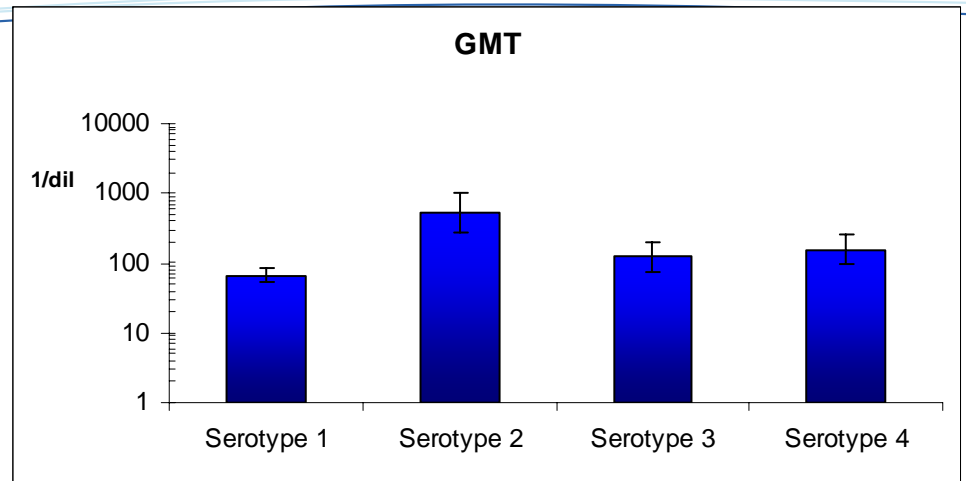
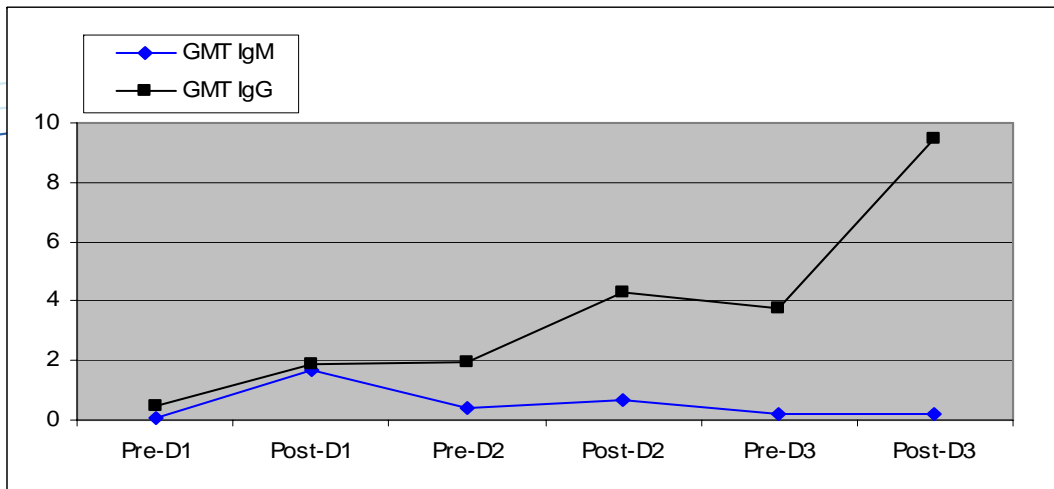
\*DV= Dengue Vaccine

\*\*based on neut antibodies (dengue and JE for the Philippines)

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# Recent Proof of concept established in flavivirus-naive adult US subjects with this tetravalent vaccine

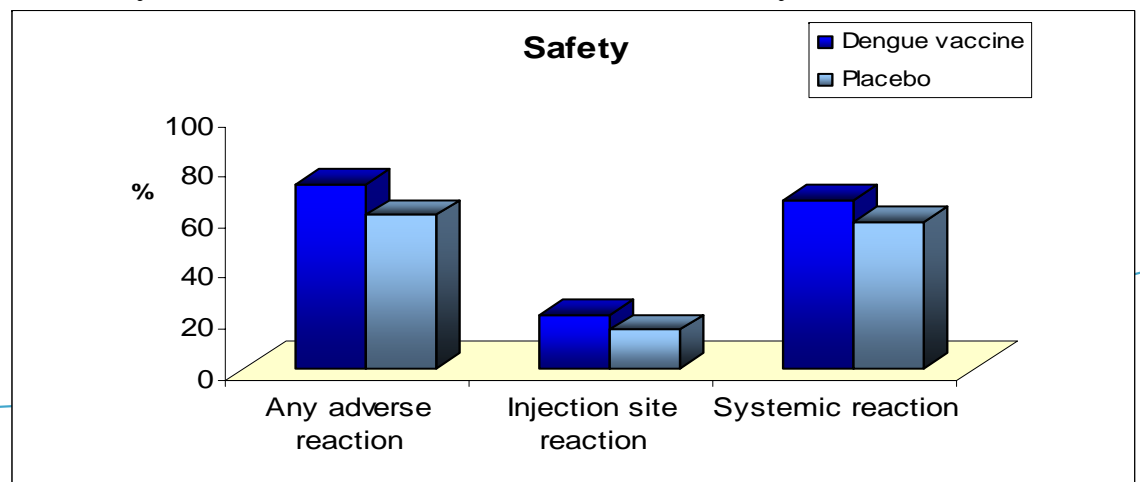
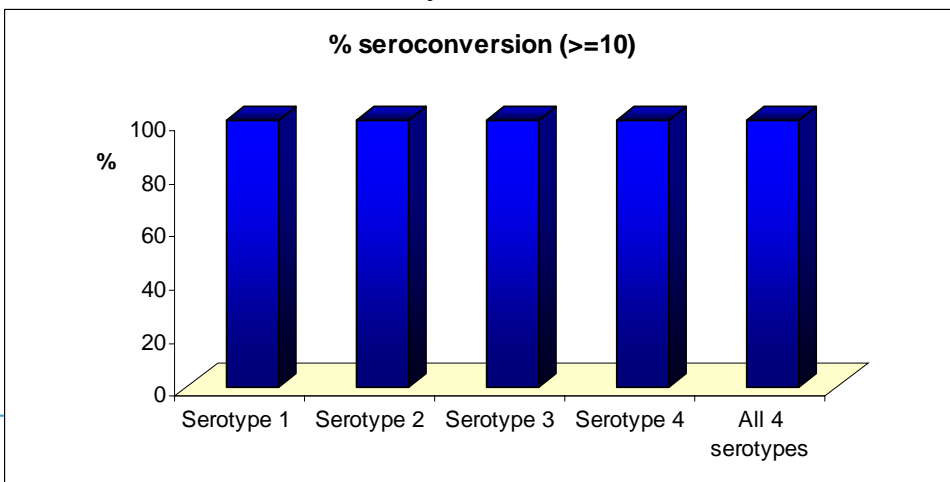


## Dengue Vaccine Tetravalent evaluation in US Flavivirus negative Adults

➔ 100 Seroconversion\* for 4 types, with robust titers after 3 doses

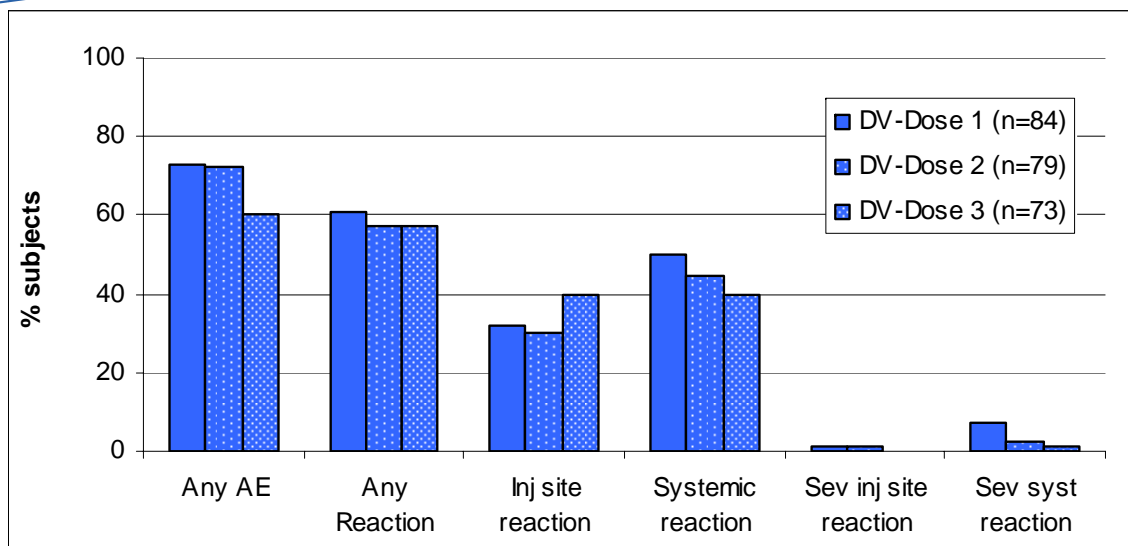
➔ Satisfactory safety profile

\*Dengue 50% Plaque reduction neutralization titer (seropositivity > 1:10) for each of the four serotypes for two different laboratory strains - data from the WHO Laboratory Reference Center, Mahidol University Thailand

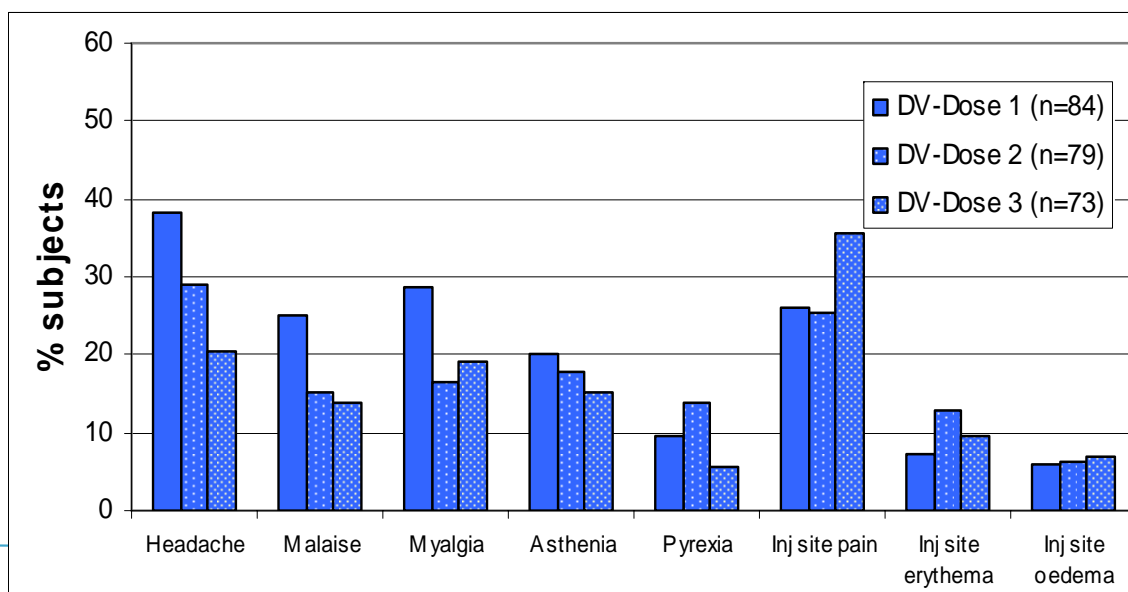


# Mexico (Non Endemic Country) - Reactogenicity after each dose of dengue vaccine in grp 1 (DV - 3 doses) (all subjects)

**No SAE after the 3rd dose**



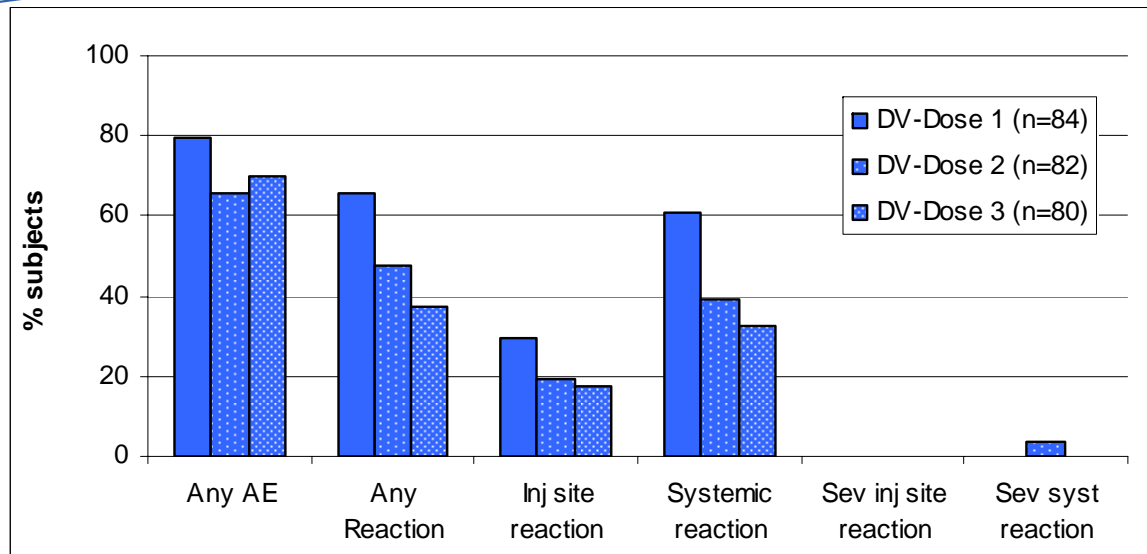
- Trend for a decrease of some systemic reactions after a 2nd and 3rd dose (headache, malaise, myalgia)
- Injection site pain tends to be more frequent after a 3rd dose (especially in adults) but reactions are mild and transient (<=3 days)



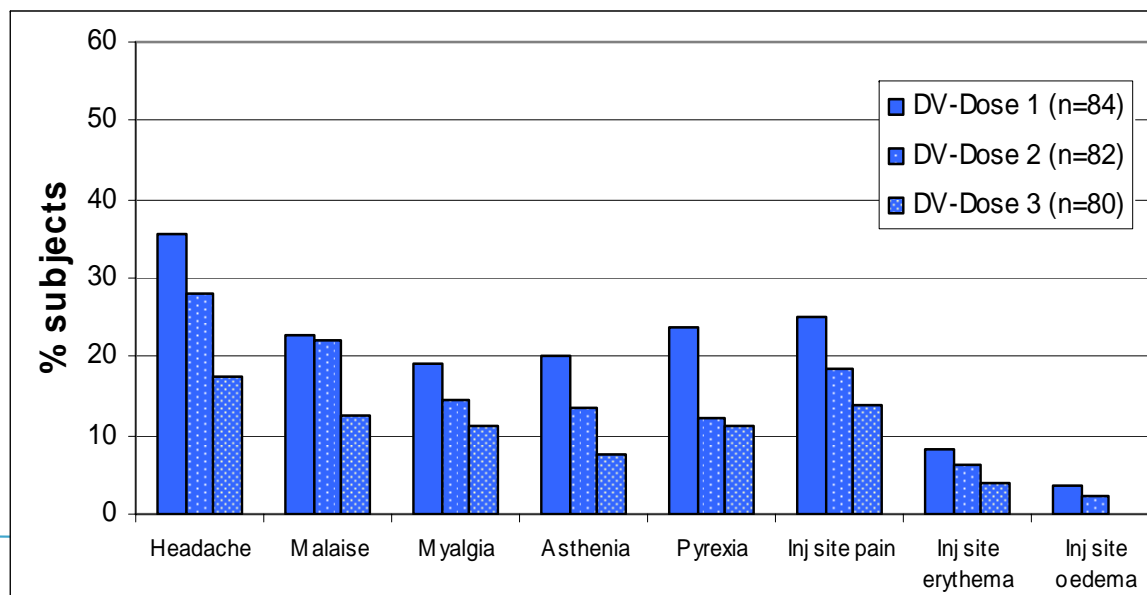


# Philippines (Endemic Country) - Reactogenicity after each dose of dengue vaccine in grp 1 (DV 3 doses) (all subjects)

**No SAE after the 3rd dose**

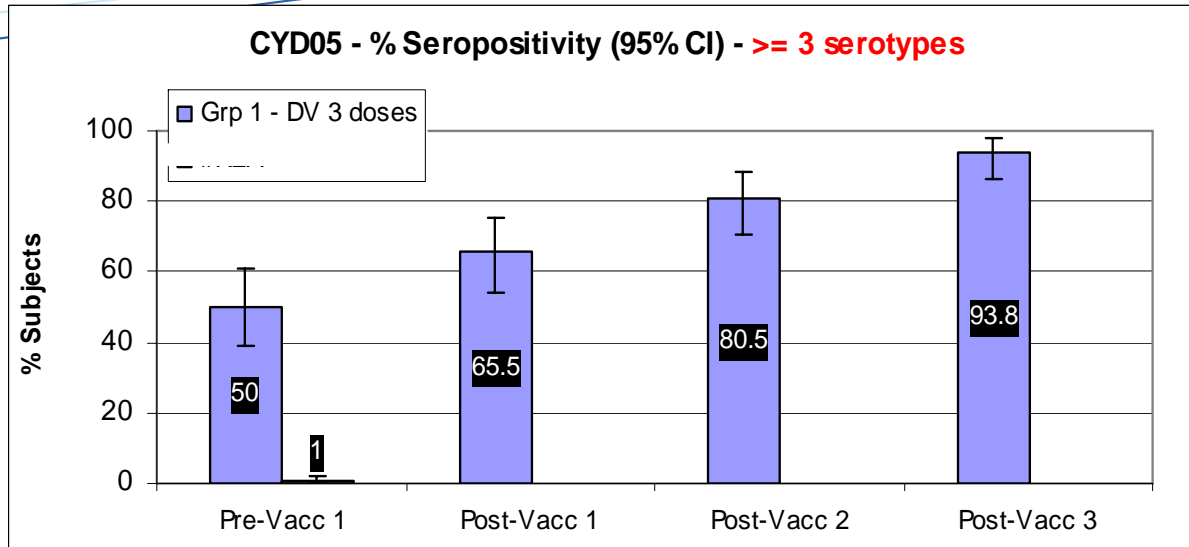


➤ Trend for a decrease of reactions (both injection site & systemic reactions) after a 2<sup>nd</sup> and 3<sup>rd</sup> dose

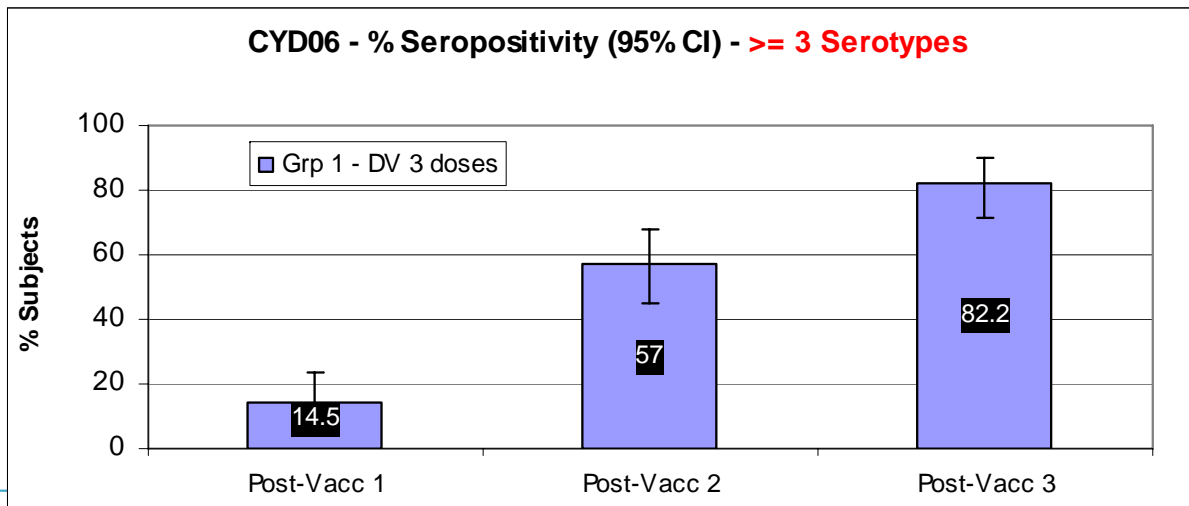


# CYD05(Philippines)/CYD06 Mexico)Trials

– % of seropositive subjects against at least 3 serotypes after each injection –all subjects

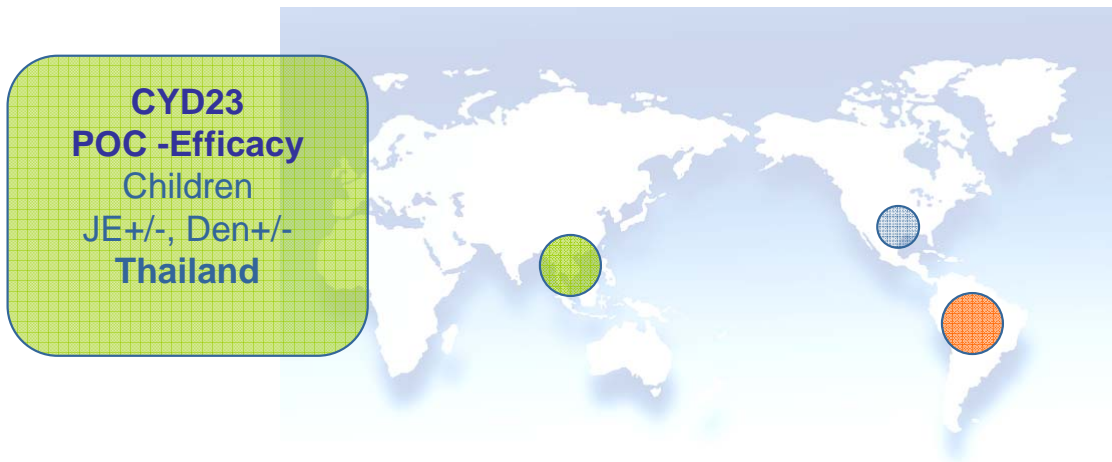
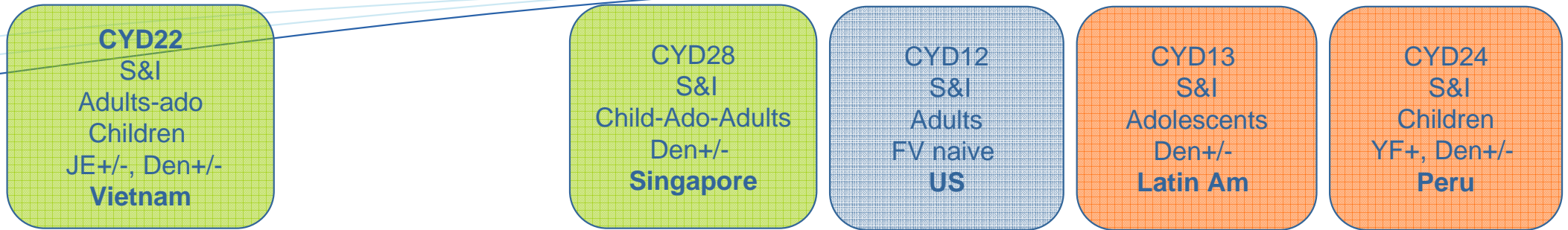


Three doses of DV with the schedule 0, 3, 12 months induce a good immune response in a naïve and non-naïve population

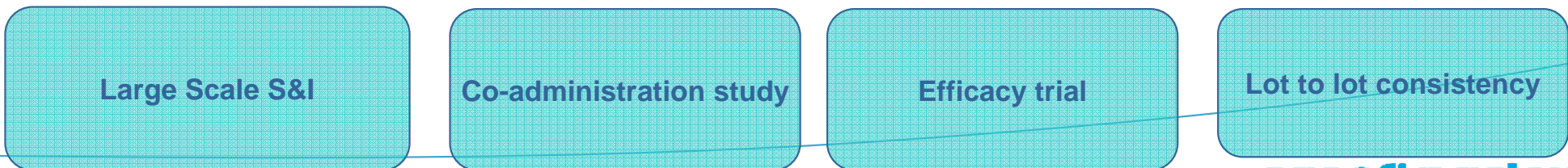


# From phase II trials to phase III trials

## Phase II trials – Safety and Immunogenicity (S&I)



## Phase III trials



# 3 POC efficacy trial (CYD23, Thailand)

## Trial Design

- Choice of Ratchaburi province:
  - **PDVI cohort**
  - **High dengue incidence average: 1.4 % in children**
  - **Long-lasting collaboration with a team at Mahidol University\***
- Observer-blind study
- Principal Investigator : Pr Arunee Sabchareon
- 4002 children from 4 to 11 years old at time of inclusion: 1/3 control vaccine (rabbits vaccine Verorab); 2/3 dengue vaccine
- Vaccination period : 3 sub-cutaneous injections at D0, D0 + 6 months, D0 + 12 months, with a two-step approach for the first vaccination:

\* Faculty of Tropical Medicine and Center for Vaccine Development (Mahidol University)

# Trial Design

<b>Population</b>	<b>Group 1 (Dengue Vaccine Group)</b>	<b>Group 2 (Control Group Verorab)</b>	<b>TOTAL</b>
<b>Children: 4-10 years</b>	<b>2668</b>	<b>1334</b>	<b>4002</b>

# Objectives: Primary

- To assess the efficacy of dengue vaccine after three injections in preventing symptomatic virologically\* confirmed dengue cases, regardless of the severity, due to any of the four serotypes in children aged 4 to 10 years at the time of inclusion

*\* According to WHO Guidelines for the evaluation of dengue vaccines in populations exposed to natural infection.  
TDR/IVR/DEN/01*

# Objectives: Secondary (All subjects)

## *Efficacy*

- ▶ To assess the efficacy of dengue vaccine in children aged 4 to 10 years at the time of inclusion in:
  - 【 Preventing severe virologically-confirmed dengue cases due to any of the four serotypes
  - 【 Preventing symptomatic dengue cases, either virologically-confirmed or probable based on serological criteria, due to any of the four serotypes

These evaluations will be performed in subjects

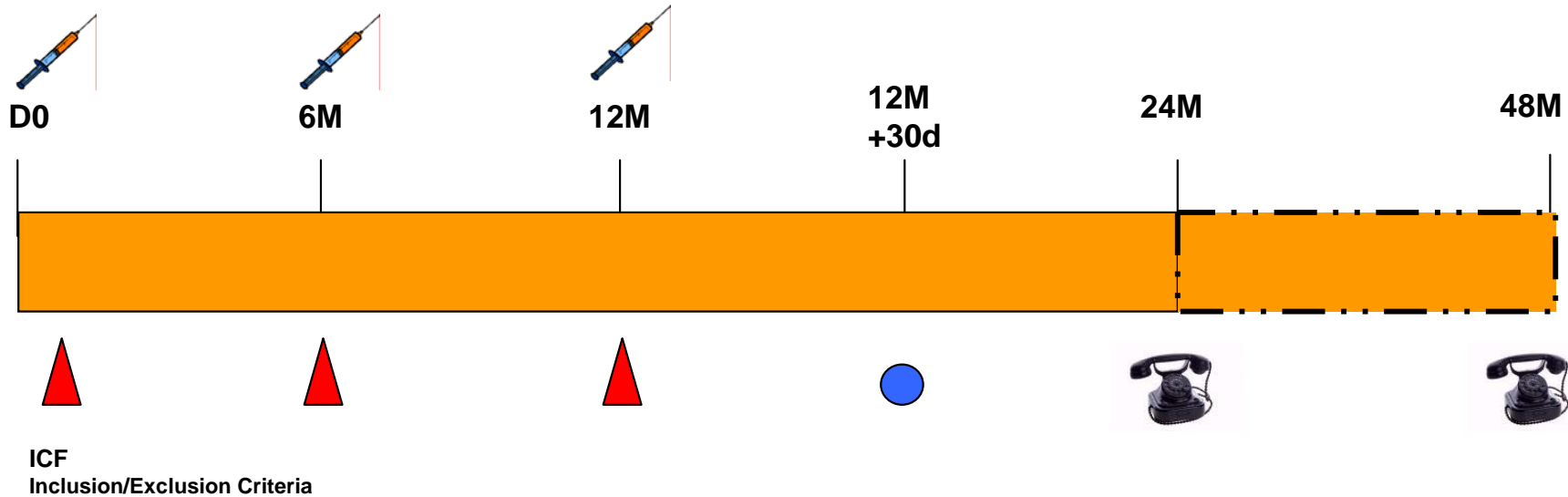
- 【 having received at least two injections
- 【 having received three injections of dengue vaccine

## *Safety*


- ▶ To evaluate the occurrence of SAEs in all subjects throughout the trial period

# Flow Chart (All subjects)

## Efficacy Evaluation



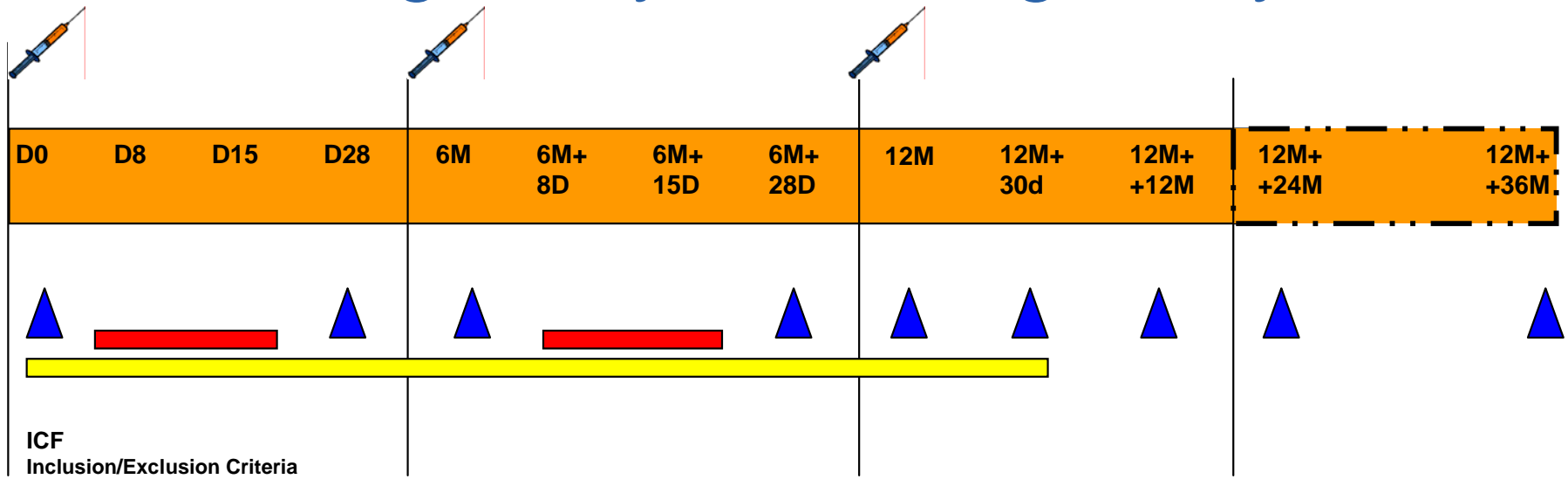
 30 Minute observation period

 Blood sample / Efficacy Evaluation



# Flow Chart (Subgroup)

## Reactogenicity, Immunogenicity, Viremia

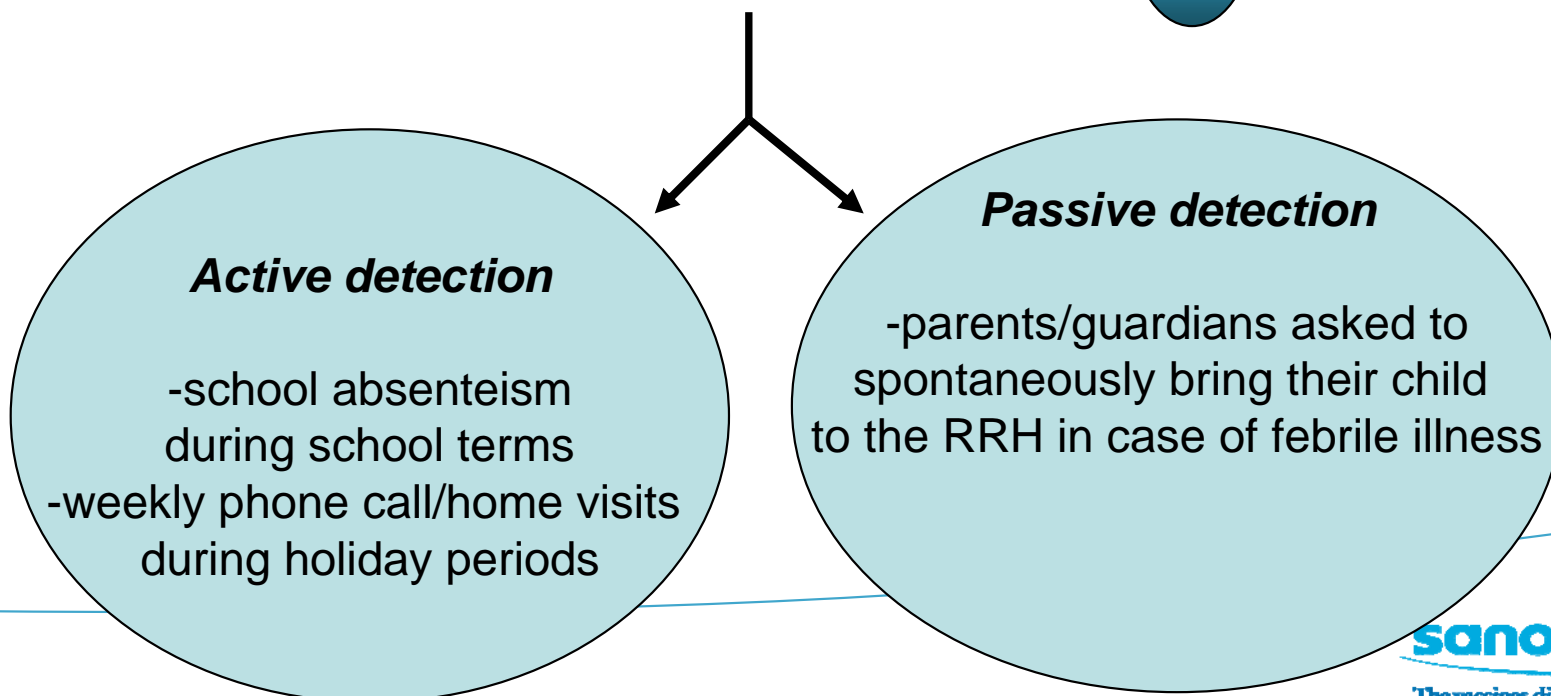
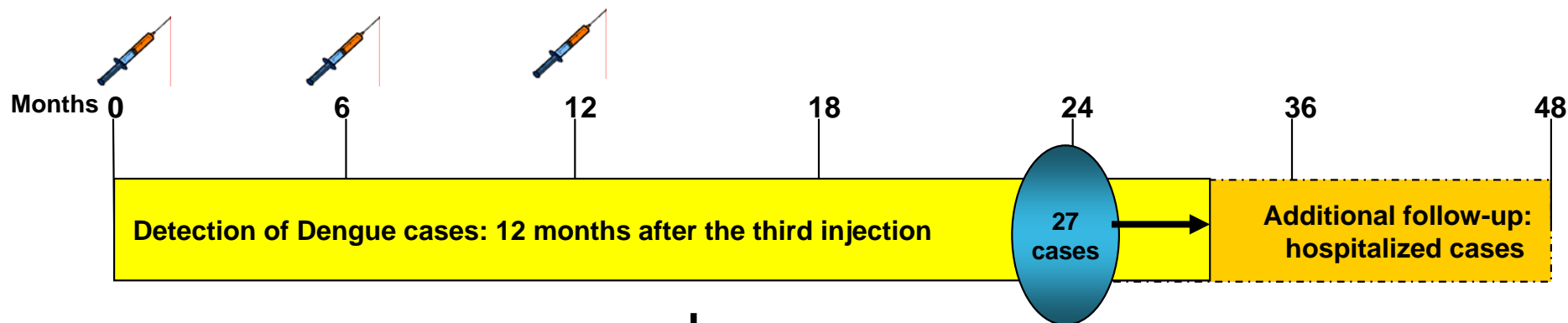


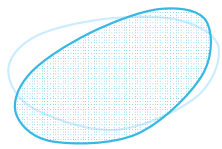
ICF  
Inclusion/Exclusion Criteria

- Reactogenicity: 1050 subjects
- ▲ Immunogenicity: 300 subjects
- Viremia / Biological safety: 100 subjects

# Trial Design

## Follow-up of dengue cases





# Dengue Asia IDMC members

- ▶ Pr. Kim Mulholland (Chairman)
- ▶ Pr. Siripen Kalayanaroj
- ▶ Dr. Tran Tinh Hien
- ▶ Pr. Quak Seng Hock
- ▶ Pr. Peter Smith
- ▶ Mr Jukka Jokinen, PhD (Expert statistician)