DENGUE VACCINE DEVELOPMENT

Results of Phase III Efficacy Studies in Dengue Endemic Regions of the Sanofi Pasteur Candidate Dengue Vaccine

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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

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ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

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

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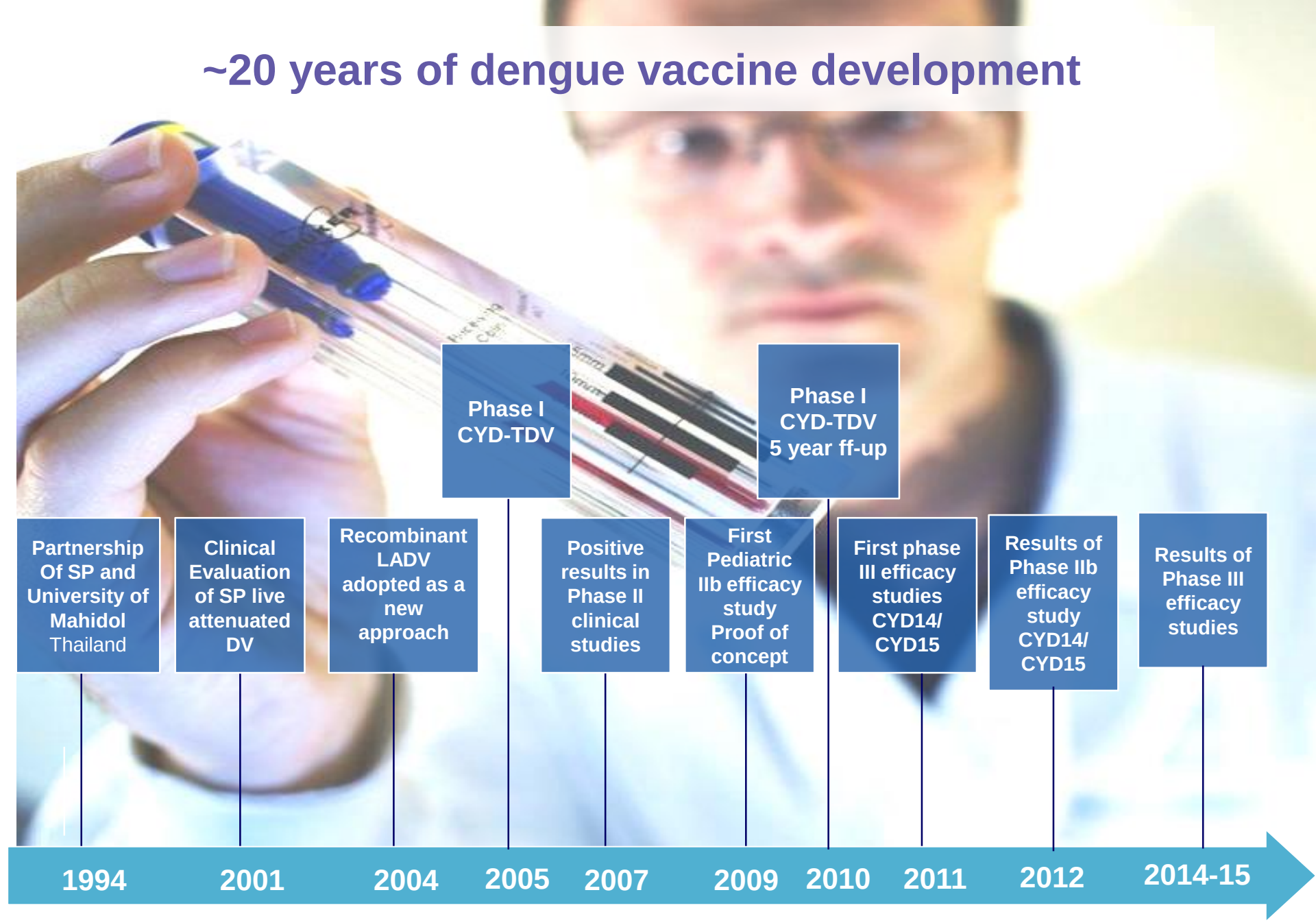
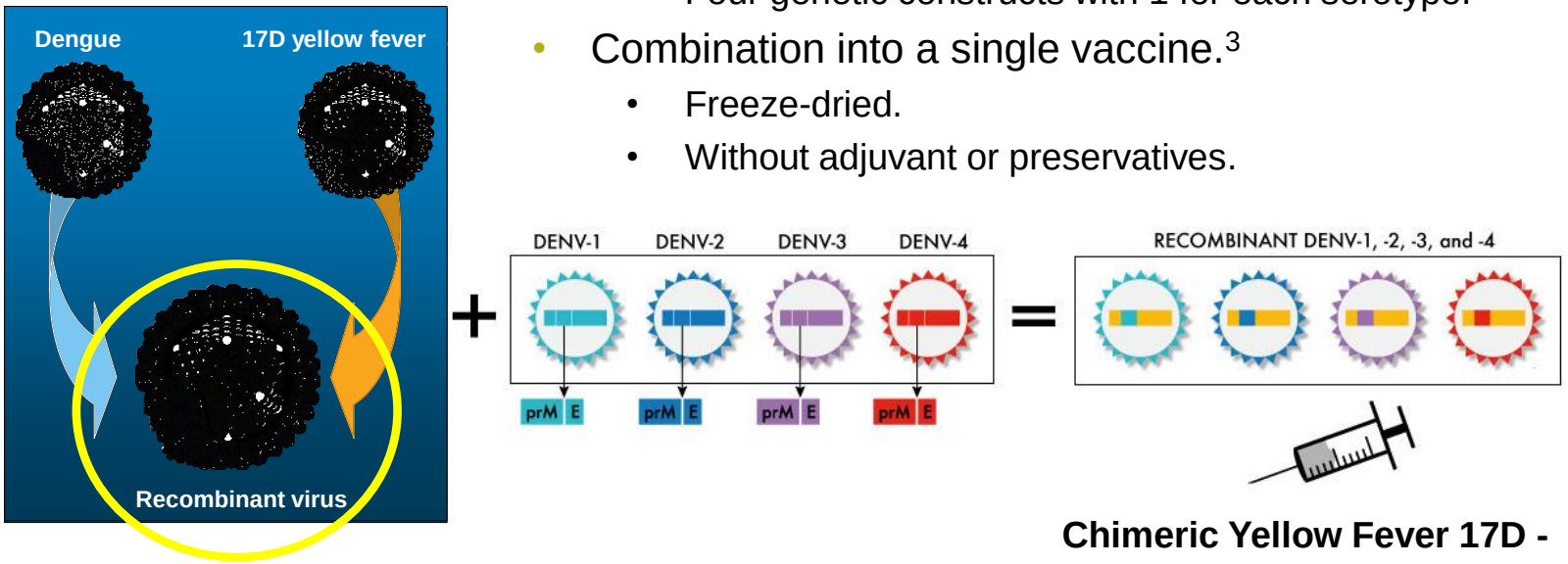
~20 years of dengue vaccine development



1 Science 1945;101(2634):640-642
2 AJTMH 2003;69(Suppl 6):5-11

THE FIRST DENGUE VACCINE WITH A SIGNIFICANT TECHNOLOGICAL ADVANCE*

- A 4-serotype, recombinant, live, attenuated vaccine.[1,2]
  - Genes encoding prM/E structural proteins from each dengue serotype combined with the genes encoding capsid (C) and non-structural (NS) proteins from YFV 17D vaccine strain.
  - Four genetic constructs with 1 for each serotype.
- Combination into a single vaccine.[3]
  - Freeze-dried.
  - Without adjuvant or preservatives.



Chimeric Yellow Fever 17D - Tetravalent Dengue Vaccine (CYD-TDV)

C=capsid; DENV=dengue virus; E=envelope; NS=nonstructural; prM=precursor membrane; YFV 17D=yellow fever vaccine 17D.

1. Guirakhoo, 2001, J Virol.
2. Guirakhoo, 2000, J Virol.
3. Guy, 2011, Vaccine.

COUNTRIES IN PHASE III EFFICACY STUDIES

CYD14 efficacy study in Asia
N=10,275

CYD15 efficacy study
in Latin America and the Caribbean
N=20,869

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

STUDY DESIGN: RANDOMIZED, OBSERVER-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PHASE III TRIALS[1,2,3]

Inclusion criteria

- **Children**
  - ✓**2-14 years – CYD14**
  - ✓**9-16 years – CYD15**
- **Good health**
- **No plans to leave study area**

Exclusion criteria

- **Febrile illness (until resolution)**
- **Receiving other vaccines (until 4 weeks after vaccination)**
- **Congenital or acquired immunodeficiency**

Randomization

2:1

N=10,275 ***CYD14***

N=20,869 ***CYD15***

Vaccination with CYD-TDV

Vaccination with placebo*

Months 0 6 12 13 18 25 Year 6

Active phase

Detection of symptomatic dengue cases through active surveillance

- Weekly contact with subjects or subject parents
- School absenteeism surveillance

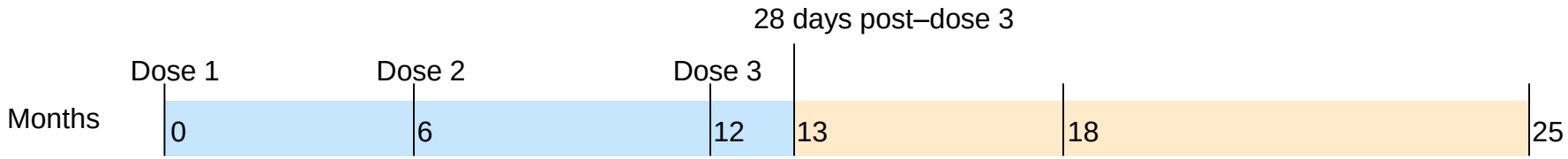
Hospital phase

Detection of symptomatic hospitalized dengue cases

- Self reporting
- Routine verification in network hospitals
- Contact with subjects/subject parents every 3 months

1 Capeding, 2014, Lancet.
ClinicalTrials.gov, 2014, NCT01374516.
2 Villar, 2014, N Engl J Med.
3 Villar, 2014, N Engl J Med (Suppl Appendix)

THE PRIMARY OUTCOME IN CYD 14[1] AND CYD15[2,3] WAS VACCINE EFFICACY AGAINST SYMPTOMATIC VCD[4]



Primary outcome efficacy

Vaccine efficacy against symptomatic VCD, irrespective of disease severity or serotype, occurring >28 days post–dose 3 (per-protocol analysis)

Symptomatic VCD defined as:

- **Acute febrile illness (temp ≥38°C on ≥2 consecutive days)**
- **Virologically confirmed PCR and/or dengue NS1 Ag ELISA**
- **Occuring 28 days post dose 3 (13-25 months)**

The trial followed the WHO guidelines for end points and case definitions for quality, safety, and efficacy.

1 Capeding, 2014, Lancet
2 Villar, 2014, N Engl J Med.
3 Villar, 2014, N Engl J Med (Suppl Appendix).
4 WHO, 2011, Guidelines on the Quality,
Safety and Efficacy of Dengue TetravalentVaccines (live, attenuated).

RESULTS

HIGH PROTOCOL COMPLIANCE AND OPERATIONAL INTEGRITY

- 98.8% of subjects completed the full immunization schedule.
- 98.4% of dengue cases had an acute sample collected within the first 5 days after the onset of fever
- <1% dropout rate in the 5th year of the study

IN CYD14[1], BASELINE CHARACTERISTICS ARE SIMILAR BETWEEN VACCINE CANDIDATE AND CONTROL GROUPS

	Vaccine Group	Control Group
Safety analysis, n	**6,848**	**3,424**
Mean age, years (SD)	8.8 (3.5)	8.8 (3.4)
Males, n (%)	3,324 (49)	1,657 (48)
Per-protocol analysis for efficacy, n 2–5 years, n (%) 6–11 years, n (%) 12–14 years, n (%)	**6,710** 1,615 (24) 3,567 (53) 1,528 (23)	**3,350** 795 (24) 1,793 (54) 762 (23)
Mean age, years (SD)	8.8 (3.4)	8.8 (3.4)
Males, n (%)	3,253 (48.5)	1,623 (48.4)
Immunogenicity subset, intent-to-treat , * n Dengue seropositive at baseline, n (%) JEV, n (%) FV, n (%)	**1,323** 896 (68) 702 (53) 1,042 (79)	**660** 444 (67) 341 (52) 509 (77)
Mean age, years (SD)	8.6 (3.8)	8.6 (3.8)
Males, n (%)	652 (49)	310 (47)

*Anti-dengue and anti-Japanese encephalitis seroprevalence defined as the percentage of participants with a $PRNT_{50}$ titer of ≥10.

DENV=dengue virus; FV=flavivirus; JEV=Japanese encephalitis; PRNT=plaque reduction neutralization test; SD=standard deviation.

1 Capeding, 2014, Lancet.
Sanofi Pasteur, 2014, data on file.

IN CYD15[1], BASELINE CHARACTERISTICS ARE SIMILAR BETWEEN VACCINE CANDIDATE AND CONTROL GROUPS

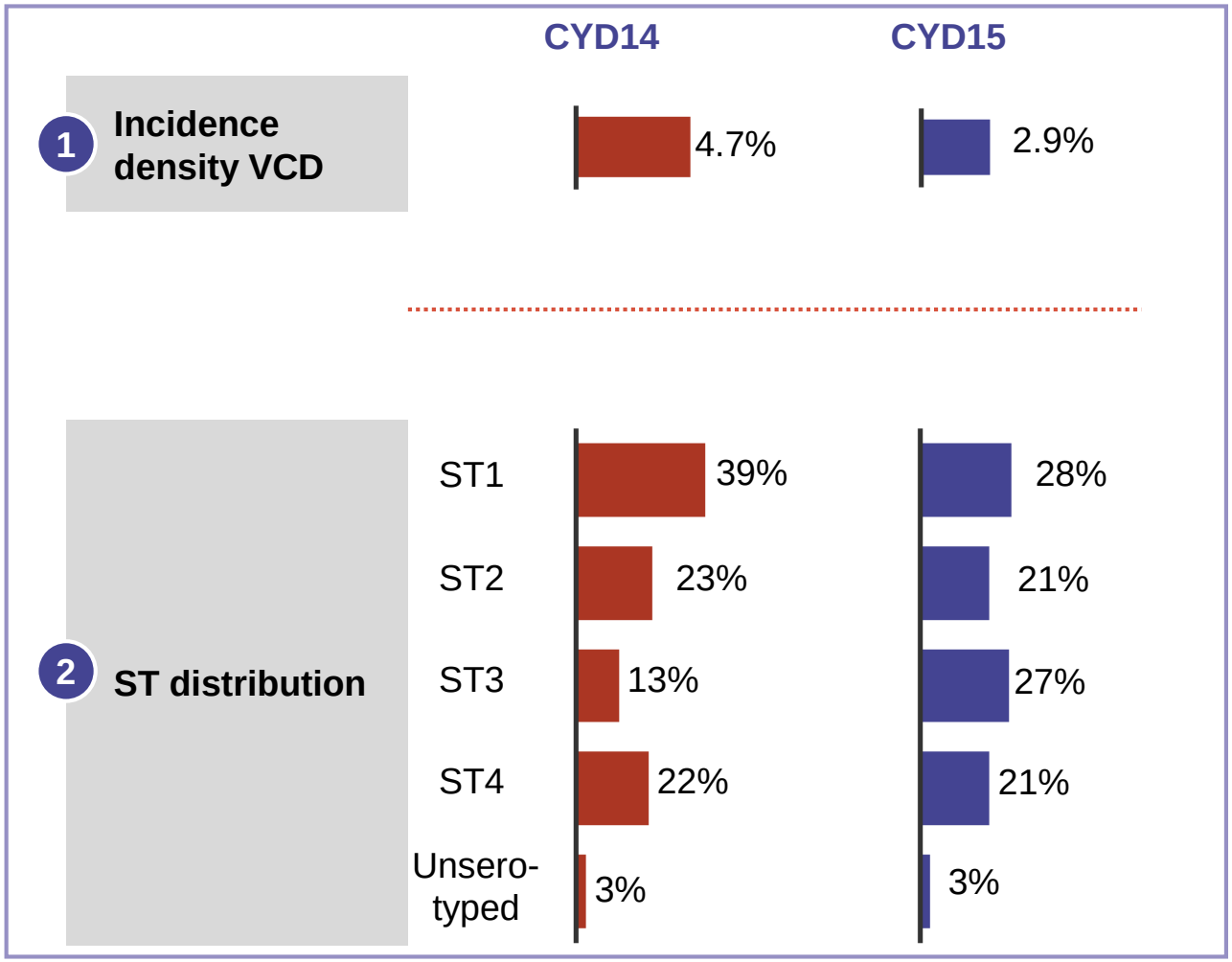
	Vaccine group	Control group
Safety analysis, n	**13,915**	**6,939**
Mean age, years (SD)	12.5 (2.1)	12.5 (2.1)
Males, n (%)	6,878 (49.4)	3,411 (49.2)
Per-protocol analysis for efficacy, n	**12,574**	**6,261**
Mean age, years (SD)	12.4 (2.1)	12.4 (2.1)
Males, n (%)	6,254 (49.7)	3,105 (49.6)
Immunogenicity subset, intent-to-treat , n	**1,301**	**643**
Dengue seropositive at baseline,* % (95% CI)	80.6 (78.3–82.7)	77.0 (73.5–80.2)
Mean age, years (SD)	12.3 (2.1)	12.4 (2.1)
Males, n (%)	631 (48.5)	339 (52.7)

*Antidengue seroprevalence is defined as the percentage of participants with a $PRNT_{50}$ titer of ≥10.

PRNT=plaque reduction neutralization test; SD=standard deviation.

1 Villar, 2014, N Engl J Med.

EFFICACY TRIALS COVER DIFFERENT EPIDEMIOLOGICAL SETTINGS OF ENDEMIC COUNTRIES WITH ALL 4 DENGUE SEROTYPES CIRCULATING [1, 2, 3]

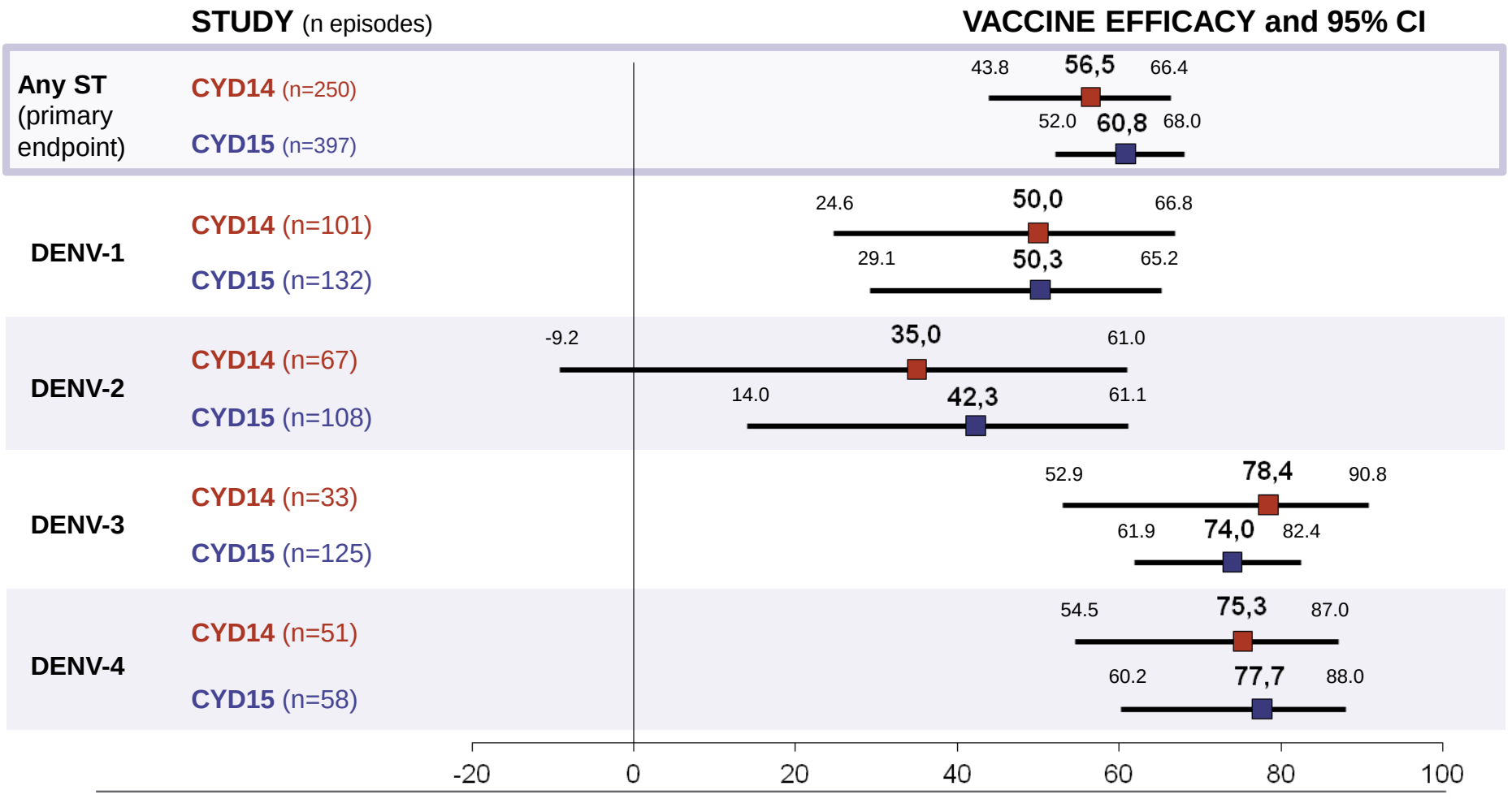


*Case stands for subject who reported at least 1 VCD during the 25-month duration of the follow-up.

1 Capeding, 2014, Lancet.
2 Villar, 2014, N Engl J Med.
3 Villar, 2014, N Engl J Med (Suppl Appendix).

SEROTYPE SPECIFIC VACCINE EFFICACY AGAINST VCD (ANY SEVERITY) PP POPULATION

12 m follow-up from months 13 – 25 [1, 2]



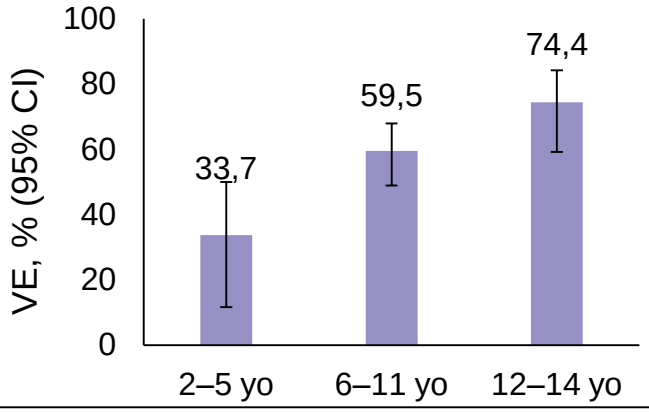
1. Capeding, 2014, Lancet.
2. Villar, 2014, N Engl J Med.

PP = Per protocol;

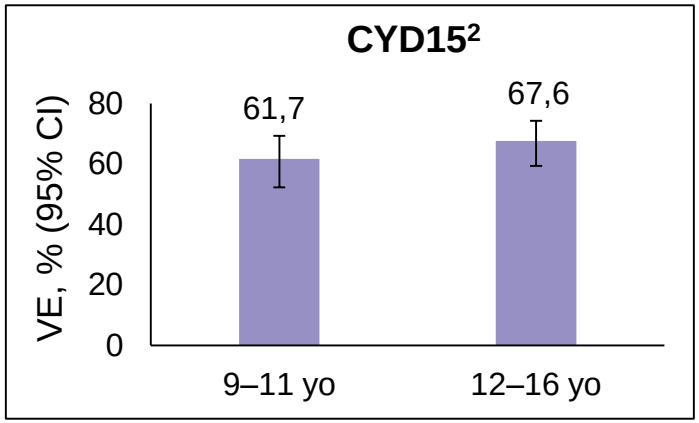
HIGHER VACCINE EFFICACY WITH AGE AND POSITIVE BASELINE SEROSTATUS DURING THE 25-MOS. ACTIVE PHASE

VE Results by Age

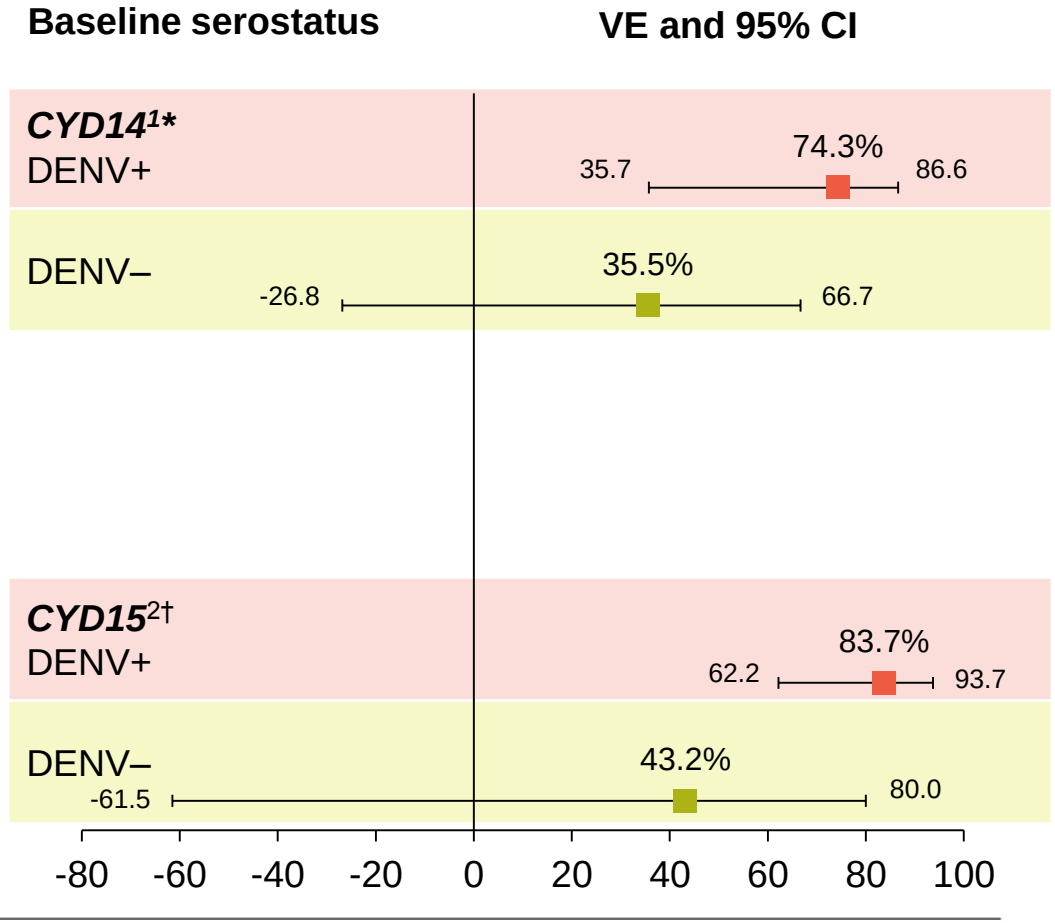
CYD14[1]



CYD15[2]



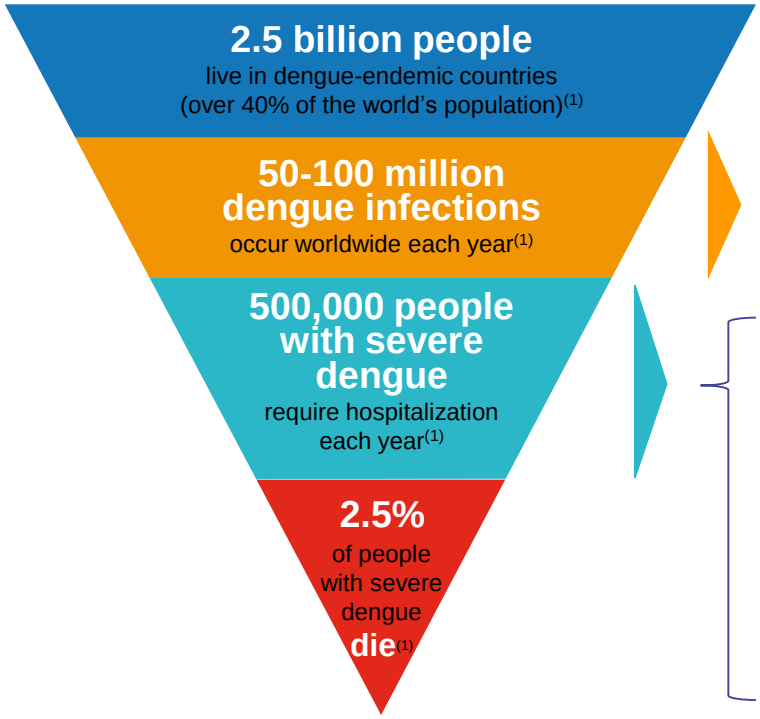
VE Results by Baseline Serostatus



*Comparison made on ITT. RR=relative risk: incidence of VC dengue cases in CYD group vs control group.
†Dengue+: baseline titer for at least 1 DENV serotype is ≥10 1/dil.
DENV=dengue virus; ITT=intent to treat; VCD=virologically confirmed dengue; VE=vaccine efficacy; yo=years old.

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

PHIII EFFICACY STUDIES [2,3] IN ASIA AND LATIN AMERICA DEMONSTRATED A CONSISTENT EFFICACY DURING THE 25 MONTH ACTIVE PHASE



Key Study Results

	CYD 14, Asia[2]	CYD 15, LatAm[3]
	56.5% Reduction in symptomatic dengue[4]	**60.8%** Reduction in symptomatic dengue[4]
	80.0%* Reduction in severe disease[5]	**95.0%†** Reduction in severe disease[5]
	67.2%‡ Reduction in hospitalized cases[6]	**80.3%§** Reduction in hospitalized cases[6]

*95% CI: 52.7-92.4 †95% CI: 64.9-99.9 ‡95% CI: 50.3-78.6 §95% CI: 64.7-89.5

(2) Capeding, 2014, Lancet
(3) Villar and al., 2014, NEJM
(5) DHF, WHO 1997 criteria, intent to treat
(6) Intent To Treat, 25m post dose 1

CONSISTENT EFFICACY PROFILE IN SUBJECTS 9–16 YEARS OF AGE DURING THE EFFICACY PHASE

Key Efficacy Results

25-month active phase* Pooled efficacy analyses‡[1]

Reduction in symptomatic dengue

65.6%

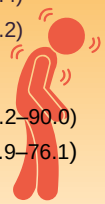
(95% CI: 60.7–69.9)

For each serotype:

- DENV-1: 58.4% (95% CI: 47.7–66.9)
- DENV-2: 47.1% (95% CI: 31.3–59.2)
- DENV-3: 73.6% (95% CI: 64.4–80.4)
- DENV-4: 83.2% (95% CI: 76.2–88.2)

By dengue serostatus:

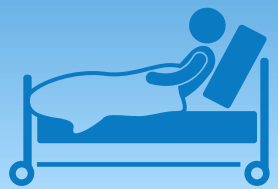
- Seropositive: 81.9% (95% CI: 67.2–90.0)
- Seronegative: 52.5% (95% CI: 5.9–76.1)



Reduction in hospitalized dengue

80.8%

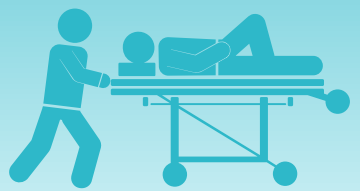
(95% CI: 70.1–87.7)



Reduction in severe dengue †

93.2%

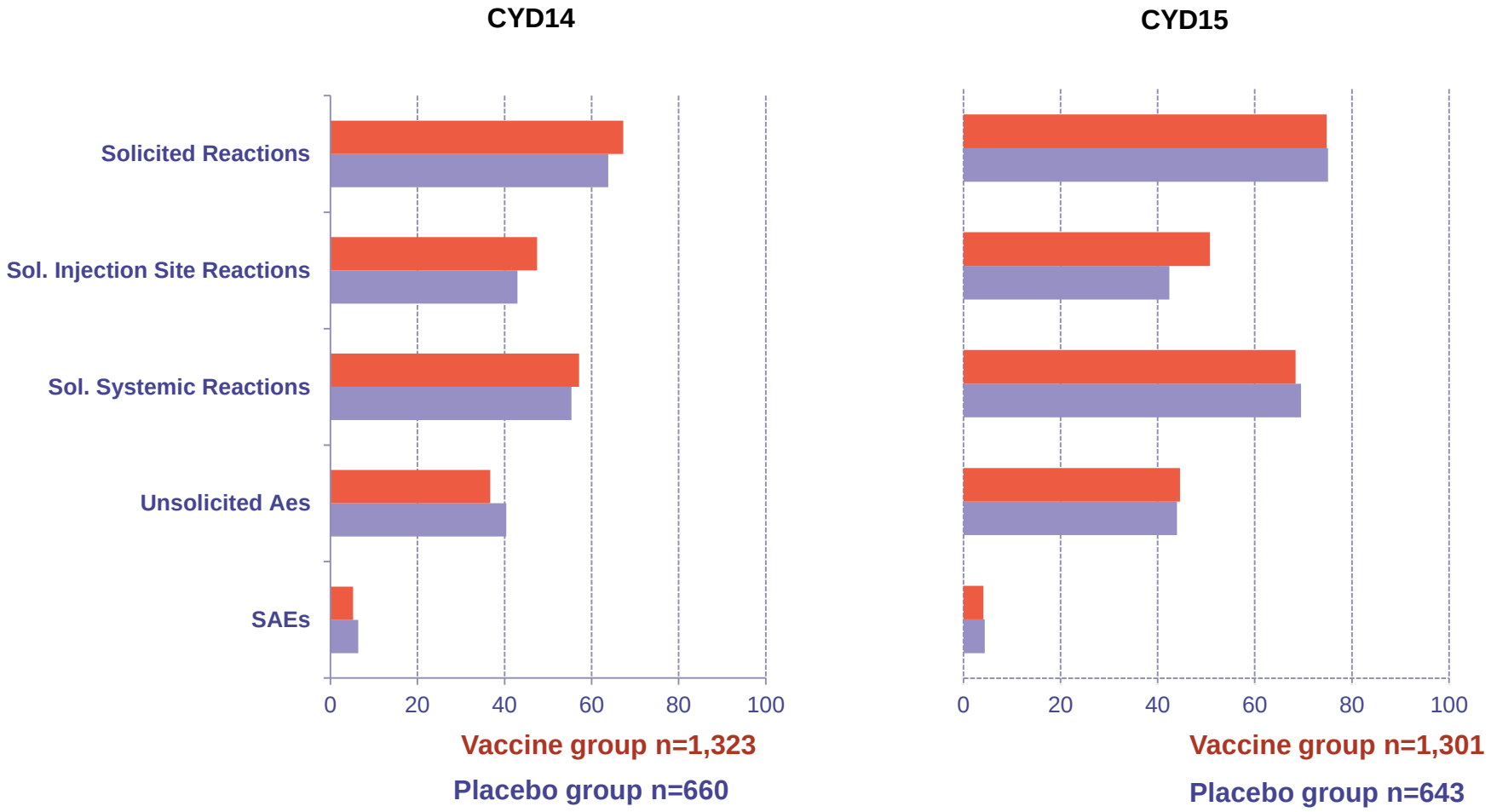
(95% CI: 77.3–98.0)



*Data come from the 2 pivotal, phase III, large-scale efficacy trials CYD14 and CYD15, which were designed to fully assess efficacy; postdose 1; [1]*Full Analysis Set for Efficacy (FASE): all* subjects who received at least one injection. †dengue hemorrhagic fever, World Health Organization 1997 criteria. CI=confidence interval; DENV=dengue virus.

1.Hadinegoro, 2015, N Engl J Med.

SIMILAR SAFETY PROFILE OBSERVED BETWEEN STUDIES AND COMPARED TO PLACEBO DURING THE 25-MONTH OF THE STUDIES [1,2] (ACTIVE PHASE)



(1) Capeding, 2014, Lancet
(2) Villar and al., 2014, NEJM

CONSISTENT SAFETY PROFILE IN SUBJECTS 9–16 YEARS OF AGE DURING THE EFFICACY AND LONG-TERM FOLLOW-UP (LTFU) PHASES[1-3]

- **Similar AE reporting rates between vaccine and control groups**
- **SAEs consistent with medical disorders in the age group**
- **No evidence of sensitization.**

AE=adverse event; LTFU=long-term follow-up; RR=relative risk; SAE=serious adverse event; VCD=virologically confirmed dengue.

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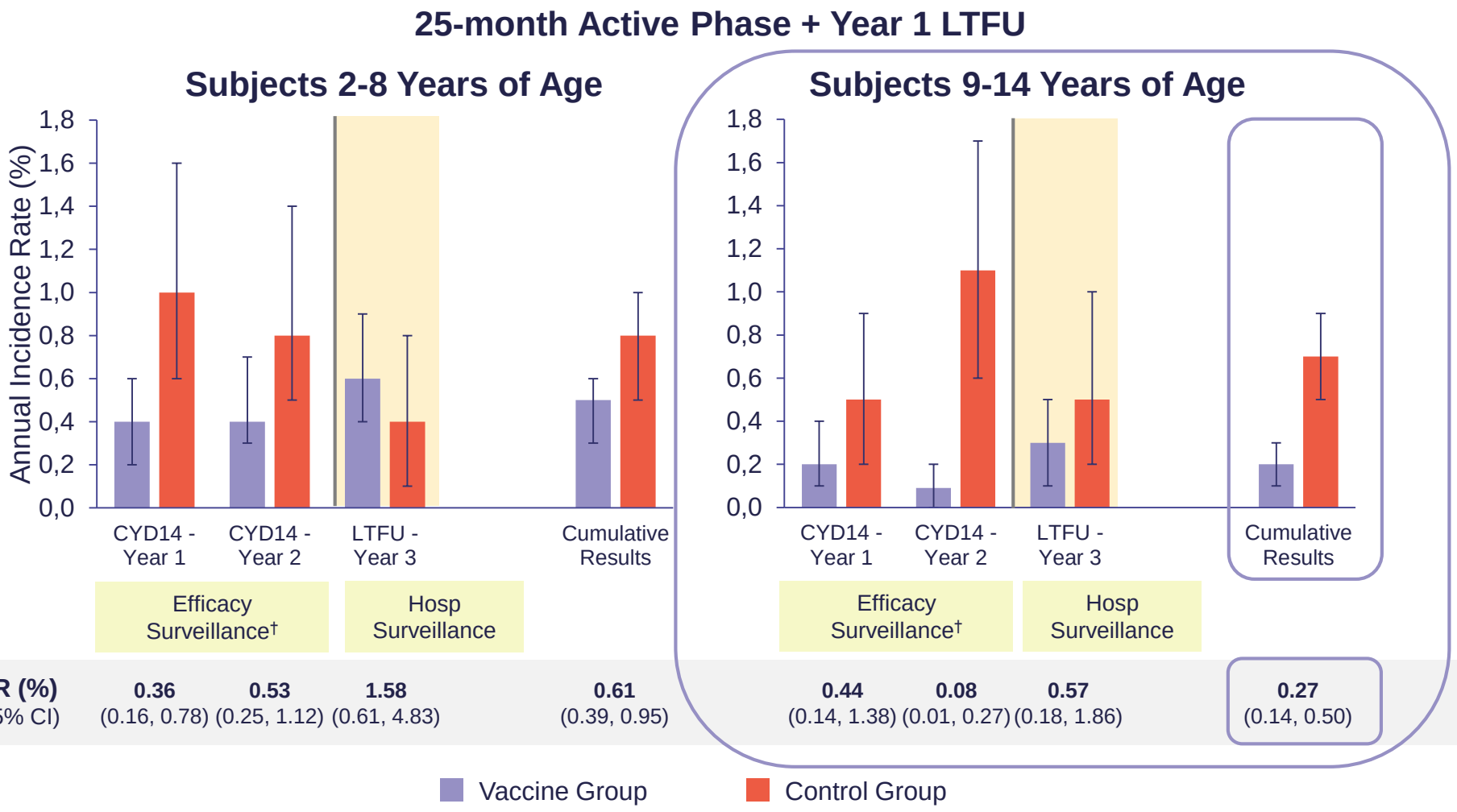
1. Hadinegoro, 2015, N Engl J Med.
2. Capeding, 2014, Lancet.
3. Villar, 2015, N Engl J Med.

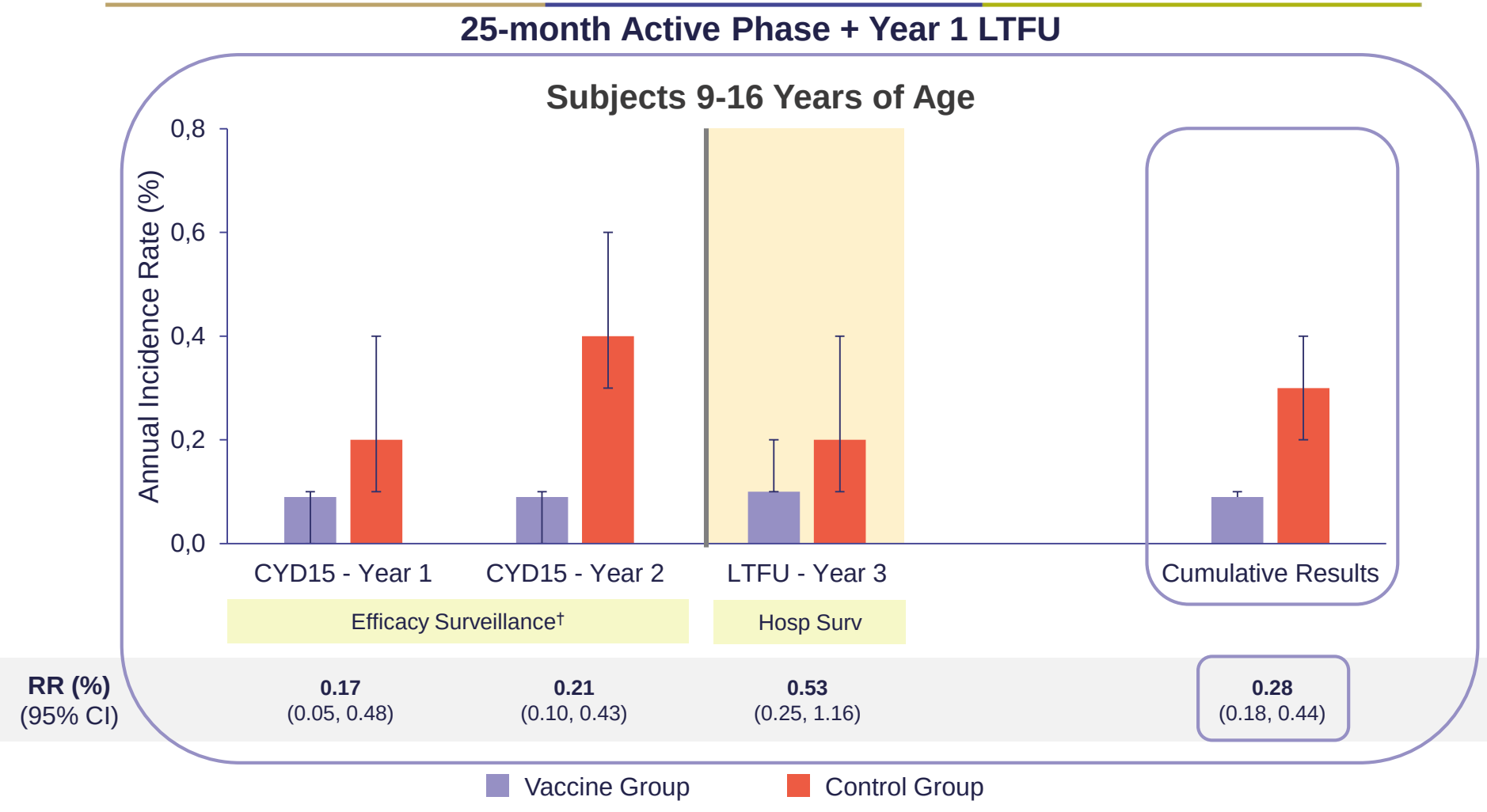
CYD14 ACTIVE AND HOSPITAL PHASE: HOSPITALIZED VCD AFTER VACCINATION BY AGE GROUP: 2-8/9-14y [1]



*CYD14 was conducted in Asia-Pacific in subjects 2 to 14 years of age.
†Active surveillance phase Year 1=day 0 to dose 3; Year 2=dose 3 to month 25; Cumulative Results=day 0 to year 3.
CI=confidence interval; LTFU=long-term follow-up; RR=relative risk; VCD=virologically confirmed dengue.

1. Hadinegoro, 2015, N Engl J Med.

CYD15 ACTIVE AND HOSPITAL PHASE: HOSPITALIZED VCD AFTER VACCINATION BY AGE GROUP: 9-16y [1]



*CYD15 was conducted in Latin America in subjects 9 to 16 years of age.
†Active surveillance phase Year 1=day 0 to dose 3; Year 2=dose 3 to month 25; Cumulative Results=day 0 to year 3.
CI=confidence interval; LTFU=long-term follow-up; RR=relative risk; VCD=virologically confirmed dengue.

1. Hadinegoro, 2015, N Engl J Med.

NO IMPORTANT DIFFERENCE IN CLINICAL SIGNS, SYMPTOMS & BIOLOGY DURING ONGOING LTFU VERSUS ACTIVE PHASE & PLACEBO GROUP IN SUBJECTS 9–16 YEARS OF AGE[1]

LENGTH OF HOSPITALIZATION

Similar for both the 25-month active phase and the ongoing LTFU phase in CYD14 and CYD15

DURATION OF FEVER AND CLINICAL SYMPTOMS

Similar for both the 25-month efficacy phase and the ongoing LTFU phase in CYD14 and CYD15

FREQUENCIES OF SIGNS AND SYMPTOMS

No clinically important differences observed for the frequencies of various signs and symptoms during the 25-month efficacy phase and the ongoing LTFU phase in CYD14 and CYD15

VIREMIA AND CYTOKINE PATTERN

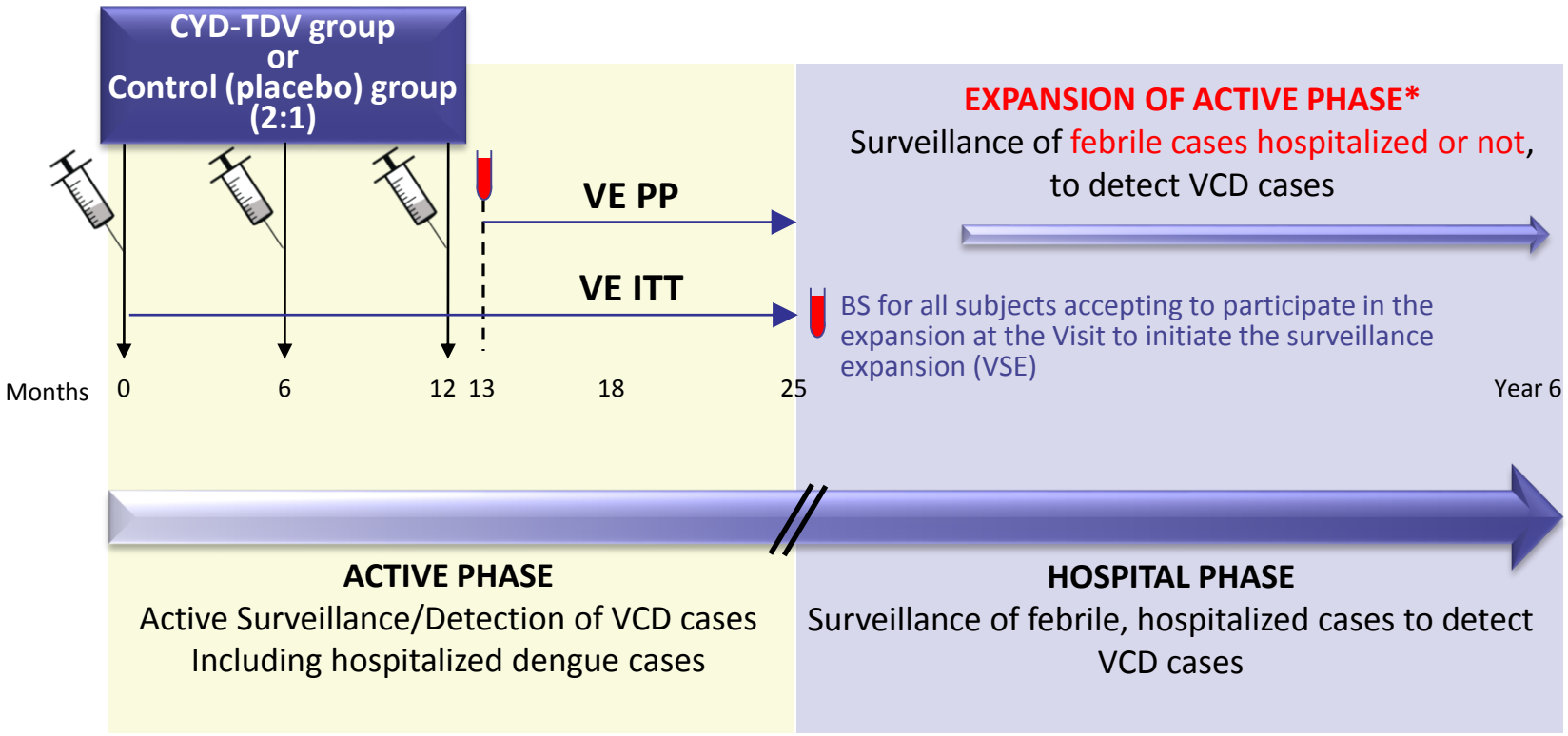
- Similar levels of viremia observed in vaccine vs control groups (CYD14 and CYD15).
- No cytokine pattern associated with increased disease enhancement in vaccine *vs* placebo.

LTFU=long-term follow-up; VCD=virologically confirmed dengue.

1.Hadinegoro, 2015, N Engl J Med.

SPGLB.DENG.15.05.0092

NEXT STEP: EXPANSION OF CYD14 AND CYD15 ACTIVE PHASE TO CAPTURE ALL VCD CASES OF ANY SEVERITY



- Evaluate the potential risk of increased severity of dengue disease.
- Evaluate the potential for waning protection during long-term follow-up in a vaccinated population.

*Subjects who do not want to re-enter to the Surveillance expansion, will continue in the Hospital phase: Only one BS (acute) will be collected to detect VCD
*Subjects who withdrew the trial will be also invited to participate in the Surveillance expansion.
BS=blood sample; ITT=intent to treat; PP=per protol; VCD=virologically confirmed dengue; VE=vaccine efficacy

CONCLUSION: FAVORABLE EFFICACY AND SAFETY PROFILE FOR SUBJECTS 9-16 YEARS OF AGE IN DENGUE ENDEMIC AREA[1]

Key efficacy results – 25-months Active Phase :

- Overall VE of 65.6% against symptomatic VCD.
- VE against severe dengue and dengue leading to hospitalizations was consistently demonstrated.
- VE against symptomatic VCD of each serotypes and in both dengue seropositive and seronegative subjects

Confirmation of consistent VE of the candidate dengue vaccine for VCD due to any serotype, severity, and prior dengue exposure based pooled efficacy results of CYD14 and CYD15

Key safety Results – 25 months Active phase and up to 2 years of LTFU:

Continued lower risk of hospitalization

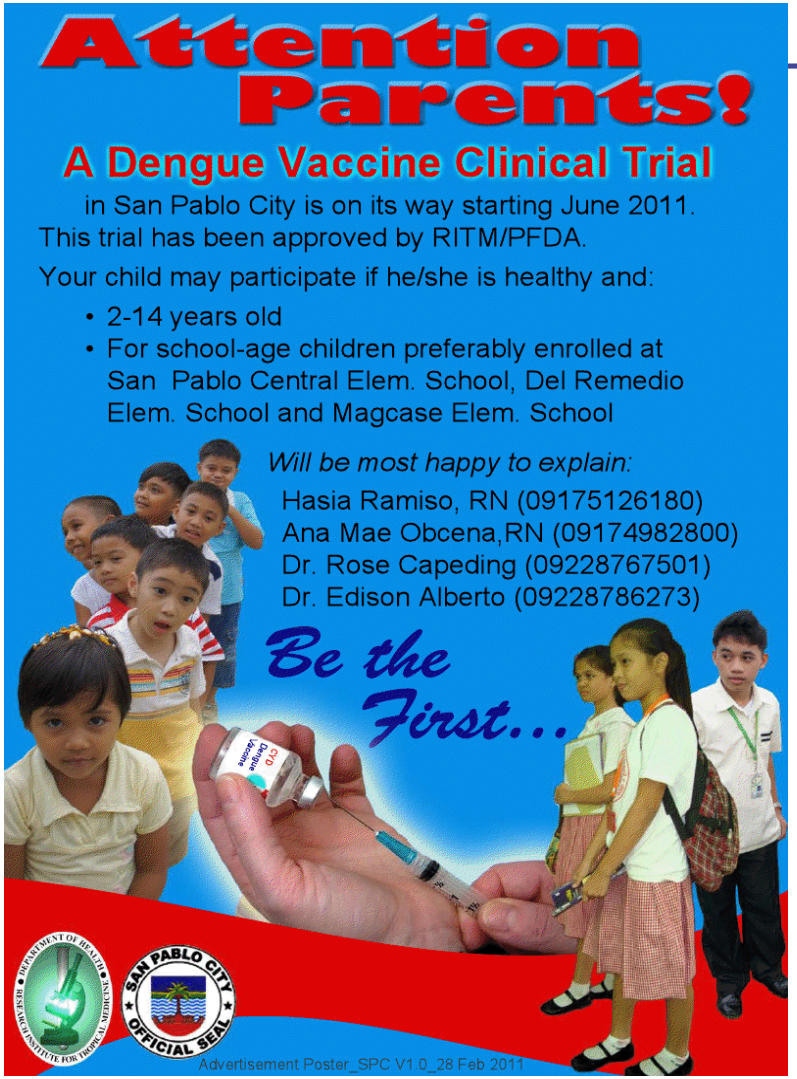
SAE profile similar between the vaccine and the placebo group

SAEs consistent with medical disorders in the age group

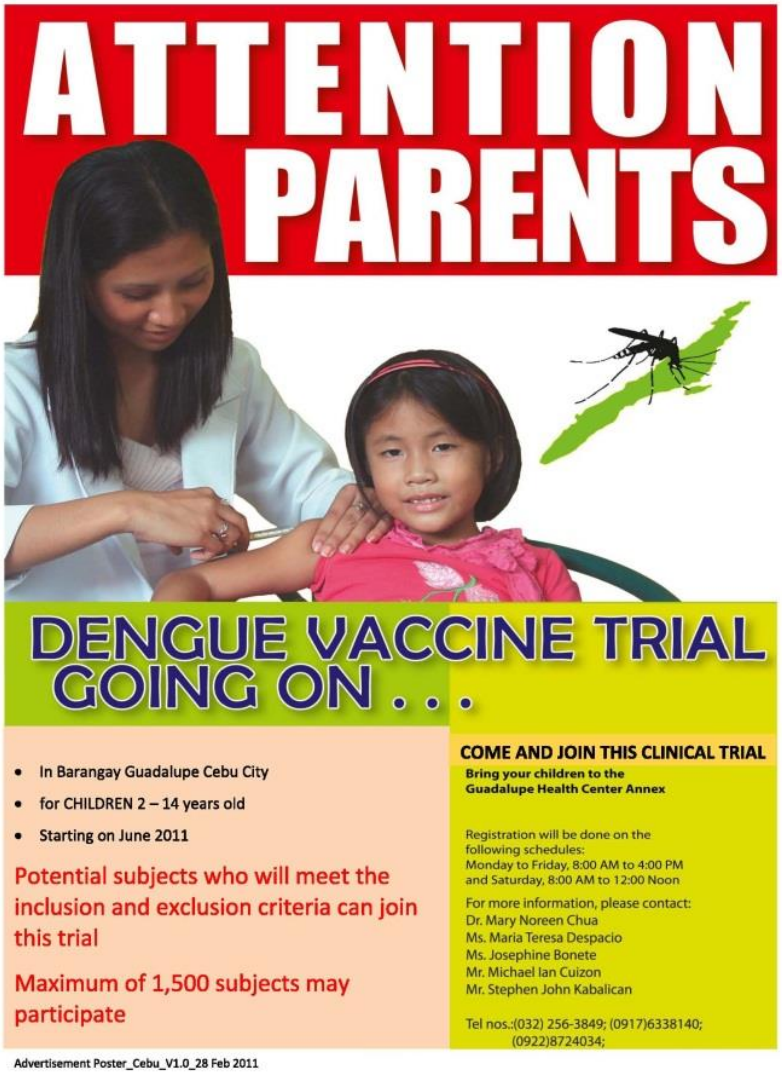
No evidence of sensitization

Reduction of severe **VCD in vaccine group**

Long term Follow-up from efficacy trials (CYD14 CYD15) will provide additional evidence in individuals aged <9 years.[1]



San Pablo City

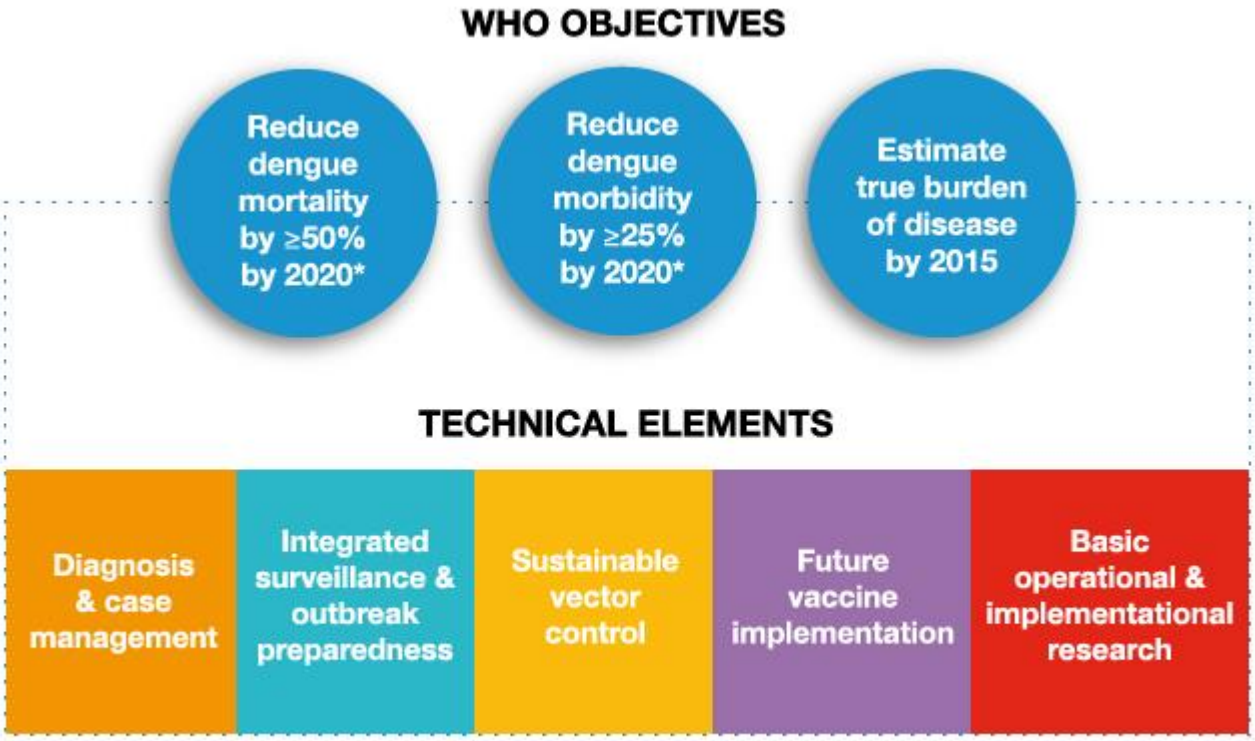


Cebu City

A Glimpse of the Future

An invitation to the parents of the forth coming dengue vaccine clinical trial (year 2011)

WHO HAS SET OBJECTIVES TO REDUCE THE BURDEN OF DENGUE BY 2020



*2010 is baseline year.

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

Results from the CYD14 and CYD15 efficacy studies support the potential of the leading candidate dengue vaccine to contribute to reaching the 2020 WHO target of reducing the global burden of dengue.

Dengue as a serious public health concern continues…

Dengue vaccine development moves on…
and progressing towards registration

Acknowledgements:
Clinical Trial Teams of CYD 14 and CYD 15