Dengue vaccine

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Ideal Dengue Vaccine Candidate

- **Tetravalent**
- **Low reactogenicity**
- **Life-long Immunogenicity**
- **Minimal or no repeat immunizations**
- **Economical**

Challenges in Dengue Vaccines development

- **Vaccine factor:** interference of tetravalent live vaccines
- **Agents factor:** involve in several countries in the world
- **Host factor:** wide spectrum of ages
- **Safety:** theoretical potential for immune enhanced disease (ADE/DHF)
- **How to evaluate Vaccine:**
  - Immunogenicity: no surrogate marker of protection
  - Efficacy: most of infection is mild disease

Dengue vaccine

Dengue Vaccine Currently in Clinical Trials

Vaccine candidate	Approach	Developer/partner	Clinical Trial Phase
Dengvaxia (Chimerivax)	Chimeric viruses YF 17D Back bone	Sanofi Pasteur Licensed: Brazil, El Salvador, Mexico, Paraguay, Philippines, Thailand, Indonesia…18 countries	3
Live Attenuated rDEN Δ30	Combination mutations: deletions and chimeras	NIAID LID/Butantan, Biological E, Panacea, VaBiotech	3
DENVax	Chimeric viruses DENV2 PDK 53 Backbone	CDC/Takeda	3
DEN-80E	Recombinant subunit E produced in insect cells	Hawaii Biotech/Merck	1, 2
Purified inactivated	Inactivated	GSK/FIOCRUZ	2
D1ME-VR-P	DNA vaccine comprising prM / E genes, CMV promoter	US Naval Medical Research Center	1

Dengue Vaccine

- Live-attenuated vaccine
  - Classical cell passage
  - Genetically modified
    - Chimerix: CYD, TDV (DENVax)
    - Gene deletion: rDEN Δ30
- Inactivated vaccine
  - Whole virus
  - Subunit
- DNA vaccine

Historical Dengue Vaccine in Clinical Trials

Phase I live attenuated tetravalent dengue trial in adult: an important step for dengue vaccine development (DEN04198)

Am. J. Trop. Med. Hyg., 66(3), 2002, pp. 264–272

SAFETY AND IMMUNOGENICITY OF TETRAVALENT LIVE-ATTENUATED DENGUE VACCINES IN THAI ADULT VOLUNTEERS: ROLE OF SEROTYPE CONCENTRATION, RATIO, AND MULTIPLE DOSES

ARUNEE SABCHAREON, JEAN LANG, PORNTHEP CHANTHAVANICH, SUTEE YOKSAN, RÉMI FORRAT, PHANORSI ATTANATH, CHUKIATE SIRIVICHAYAKUL, KRISANA PENGSAA, CHANATHEP POJJAROEN-ANANT, WATCHAREE CHOKEJINDACHAI, ACHARA JAGSUDEE, JEAN-FRANÇOIS SALUZZO, AND NATTH BHAMARAPRAVATI

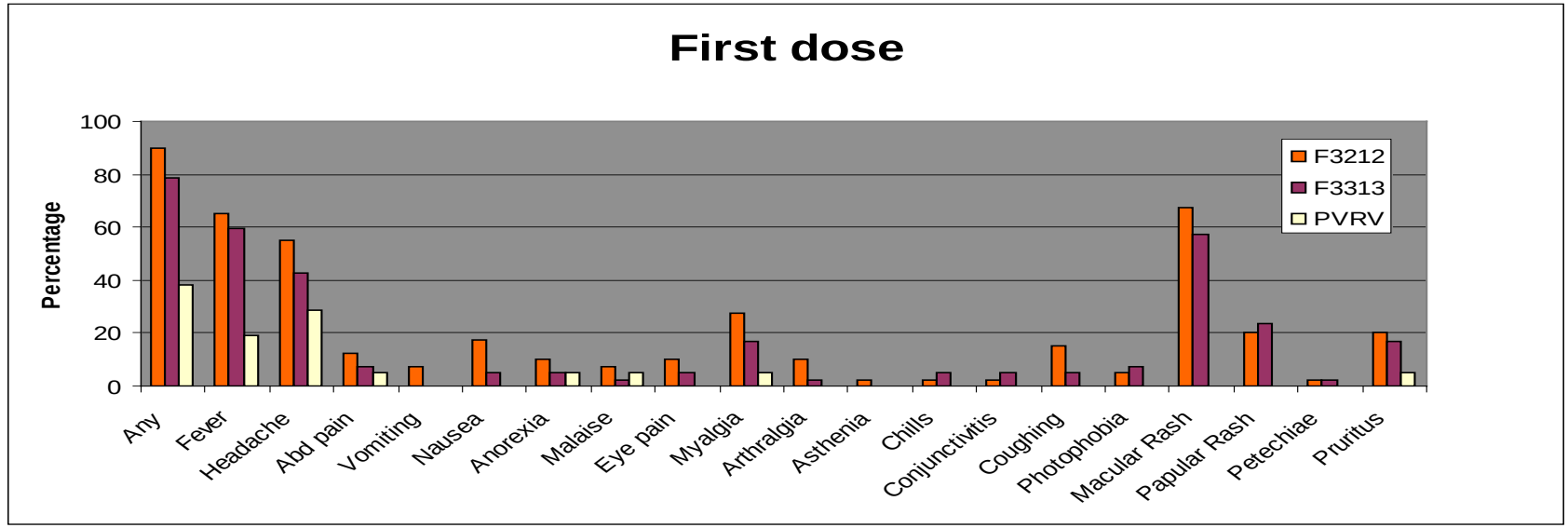
Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Aventis Pasteur, Lyon, France; Centre for Vaccine Development, Institute of Sciences and Technology for Research and Development, Mahidol University at Salaya, Nakhonpathom, Thailand; Army Institute of Pathology, Bangkok, Thailand

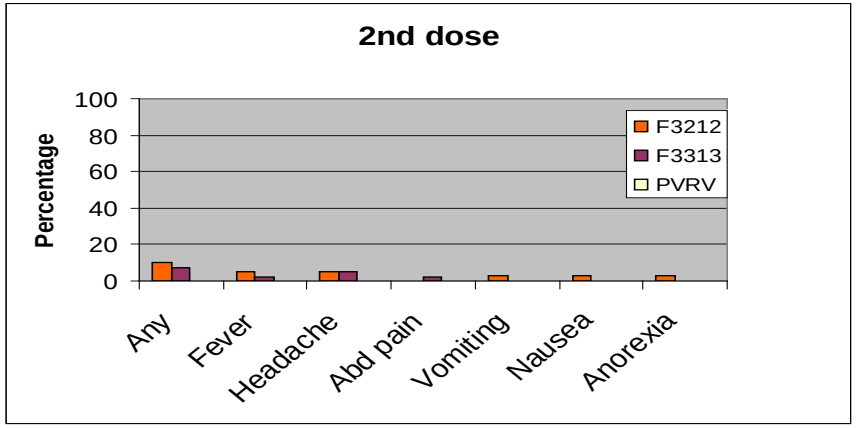
Abstract. Dengue fever, caused by four serotypes of a mosquito-borne virus, is a growing problem in tropical countries. Currently, there is no treatment or vaccine. We evaluated safety and immunogenicity of two doses, given six months apart, of seven formulations of dengue tetravalent live-attenuated vaccine (containing different concentrations of the component viruses) versus placebo in 59 flavivirus-seronegative Thai adults. The first dose was the more reactogenic. Most volunteers experienced clinically moderate fever, headache, myalgia, eye pain or rash 7–11 days after injection, generally lasting three days or less. Modest decreases in platelets and neutrophils were observed. After one dose, 58% of dengue recipients seroconverted (neutralizing antibody level ≥ 1:10) against ≥ 3 serotypes; 35% seroconverted against all four. After the second dose, seroconversion was 76% and 71%, respectively. All subjects seroconverted to serotype 3 after one dose. Serotype 4 elicited the lowest primary response but the highest increase in seroconversion after the second dose.

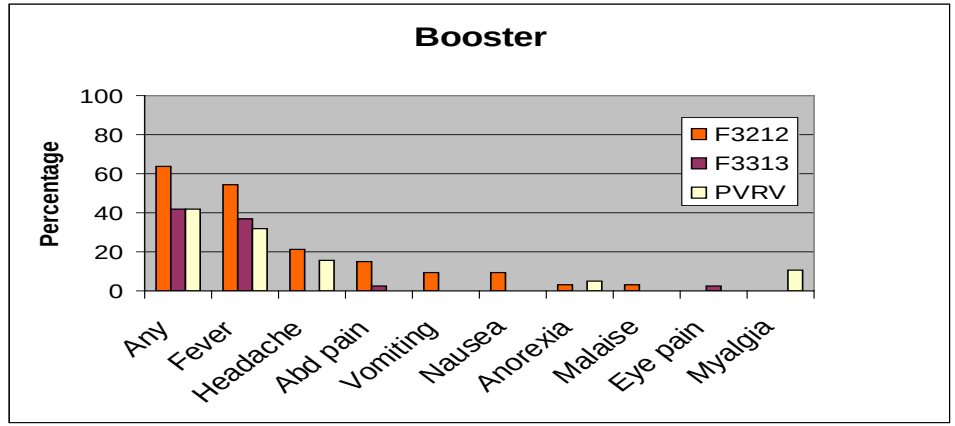
Safety and Immunogenicity after Tetravalent Live-attenuated Dengue Vaccine in Thai Children (DEN 06199)

Safety and Immunogenicity after Tetravalent Live-attenuated Dengue Vaccine in Thai Children (DEN 06199)

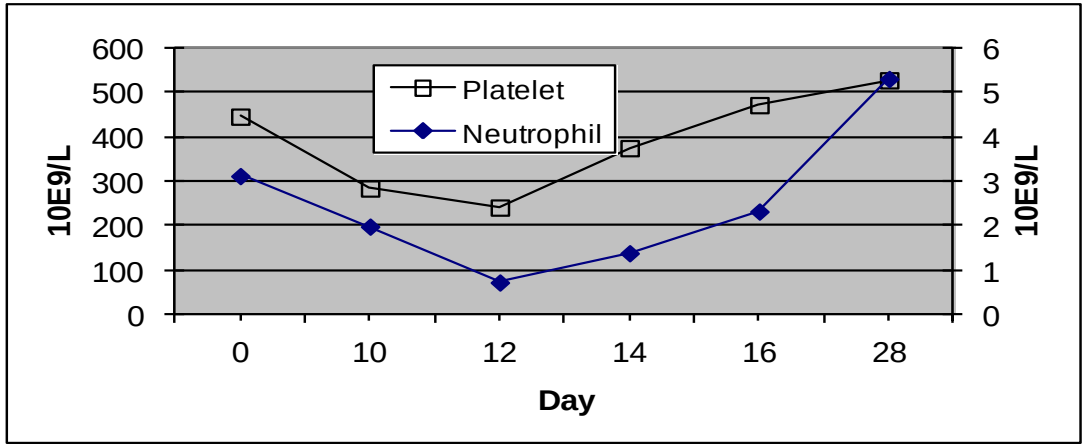
% Systemic AE after each dose
(100 naïve dengue subjects 5-12 yr old)

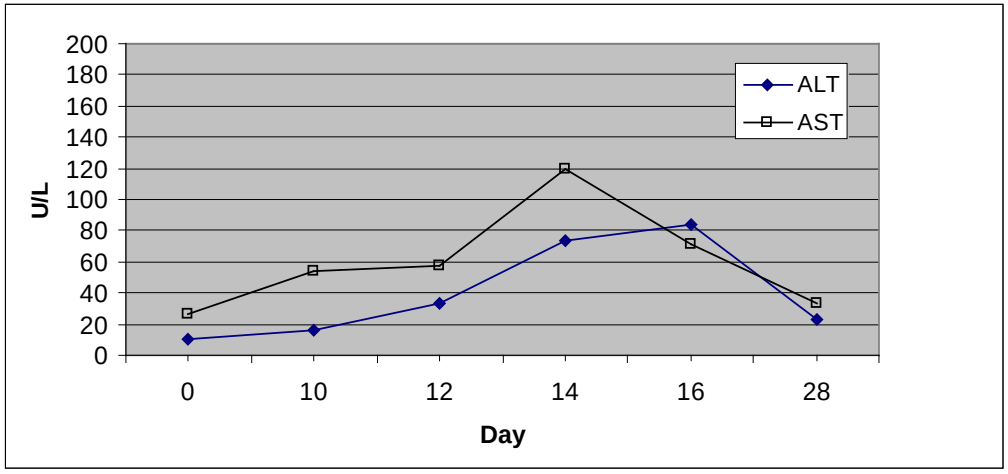






Safety and Immunogenicity after Tetravalent Live-attenuated Dengue Vaccine in Thai Children (DEN 06199)



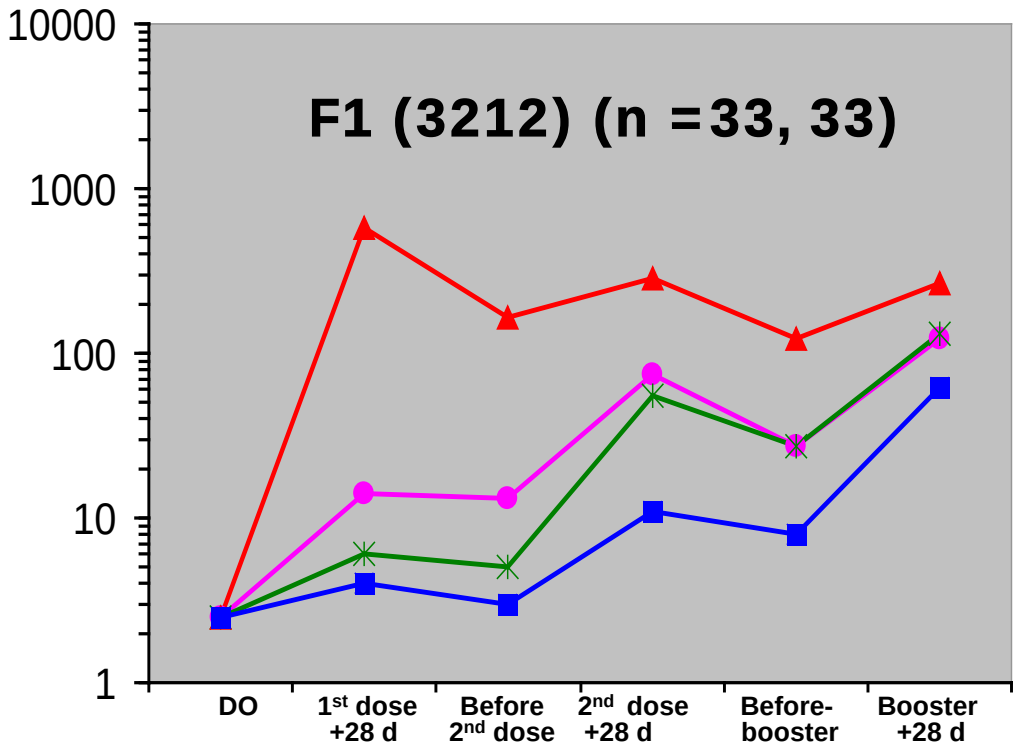


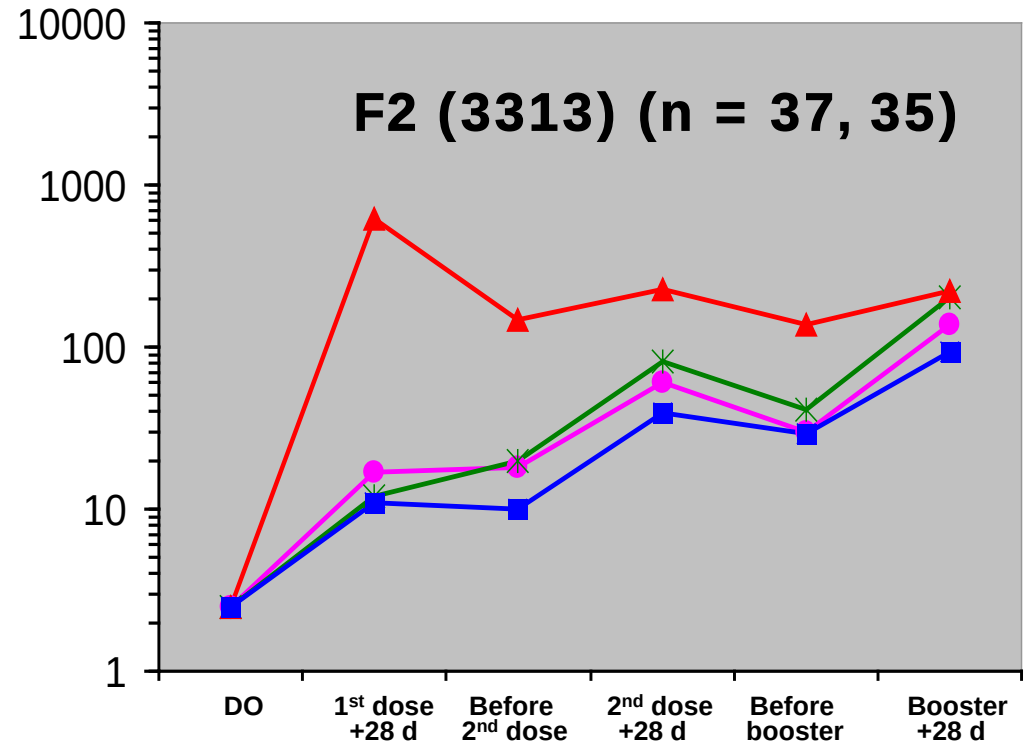
Dengue-like synd in a 7-year-old girl after the first dose

Systemic reactions	Max Intensity	Delay of onset	Duration (D)
Fever	Severe	D 5	5
Vomiting	Severe	D 5	5
Photophobia	Mod	D 4	7
Asthenia	Mod	D 4	7
Coughing	Mod	D 4	7
Headache	Mod	D 5	6
Abd Pain	Mod	D 5	5
Anorexia	Mod	D 5	6
Nausea	Mod	D 5	6
Myalgia	Mod	D 5	3
Rash	Mild	D 9	3

Safety and Immunogenicity after Tetravalent Live-attenuated Dengue Vaccine in Thai Children (DEN 06199)

GMT of Nab Titers

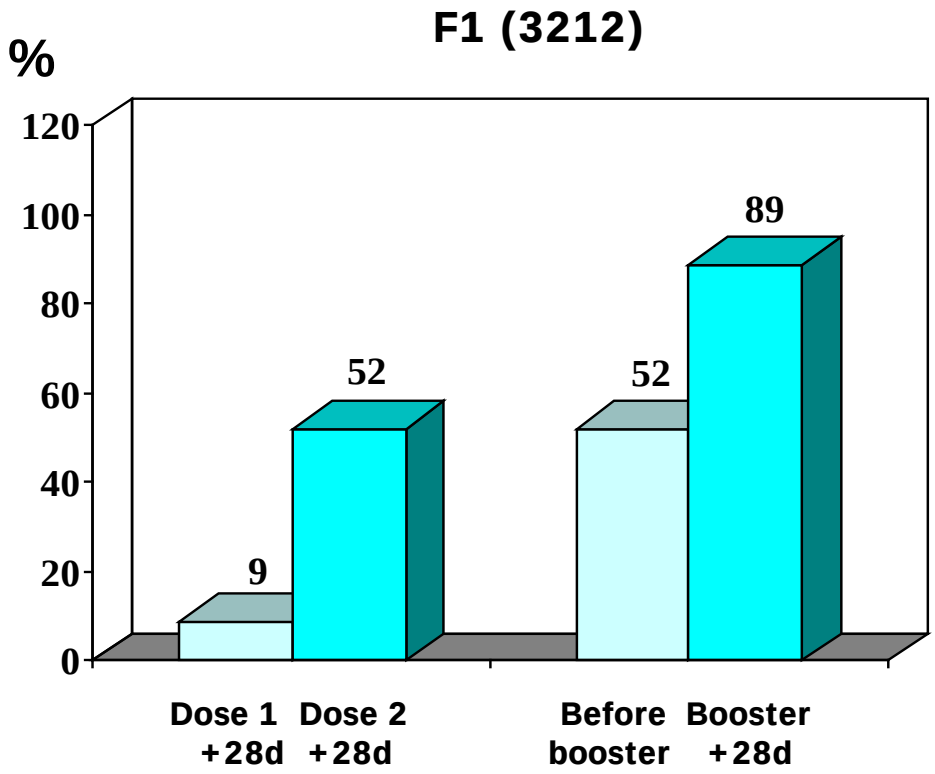


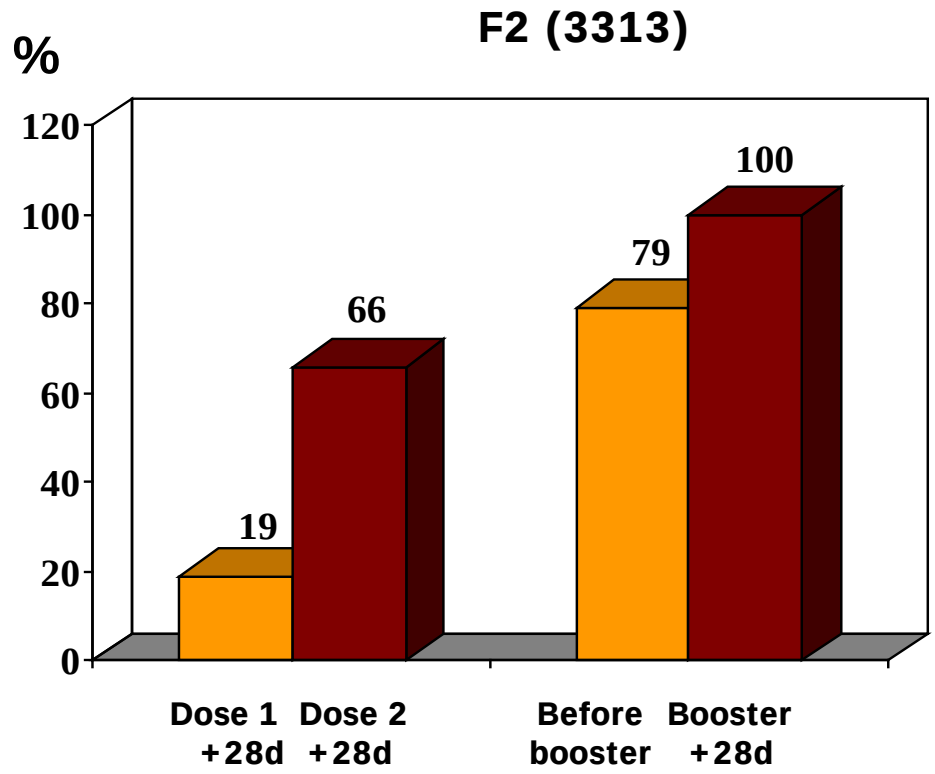


DEN1 DEN2 DEN3 DEN4

Safety and Immunogenicity after Tetravalent Live-attenuated Dengue Vaccine in Thai Children (DEN 06199)

% of 4 serotype seroconversion ($PRNT_{50}$ ≥1:10) after Dengue Vaccine Immunization





Safety and Immunogenicity after Tetravalent Live-attenuated Dengue Vaccine in Thai Children (DEN 06199)

Pediatr Infect Dis J, 2004;23:99–109
Vol. 23, No. 2

Printed in U.S.A.

Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children

ARUNEE SABCHAREON, MD, JEAN LANG, MD, PHD, PORNTHEP CHANTHAVANICH, MD, SUTEE YOKSAN, MD, PHD, REMI FORRAT, MD, PHANORSI ATTANATH, MSC, CHUKIATE SIRIVICHAYAKUL, MD, KRISANA PENGSAA, MD, CHANATHEP POJJAROEN-ANANT, MSC, LAURENT CHAMBONNEAU, MSC, JEAN-FRANCOIS SALUZZO, PHD AND NATTH BHAMARAPRAVATI, MD, DSC

Objective. **The safety and immunogenicity of tetravalent live-attenuated dengue vaccines after a three dose vaccination series were evaluated in Thai children.**

Method. **One hundred three healthy flavivirus-seronegative schoolchildren ages 5 to 12 years were randomized to receive either dengue vaccine containing 3, 2, 1 and 2 $\log_{10}$ of the 50% cell culture infective dose, respectively, of the live-attenuated dengue vaccine serotypes 1, 2, 3 and 4 per dose (F3212; $n = 40$) or 3, 3, 1 and 3 $\log_{10}$ of the 50% cell culture infective dose (F3313; $n = 42$) or purified Vero cell rabies vaccine (control group; Dose 1. After the third dose 89% of the subjects in Group F3212 seroconverted (neutralizing antibody response, ≥10) to all four serotypes, and all children in Group F3313 seroconverted.**

Conclusion. **This study demonstrates a moderate although improvable reactogenicity and high seroconversion rates against the four serotypes of dengue after a three dose schedule of tetravalent live-attenuated dengue vaccine in children.**

INTRODUCTION

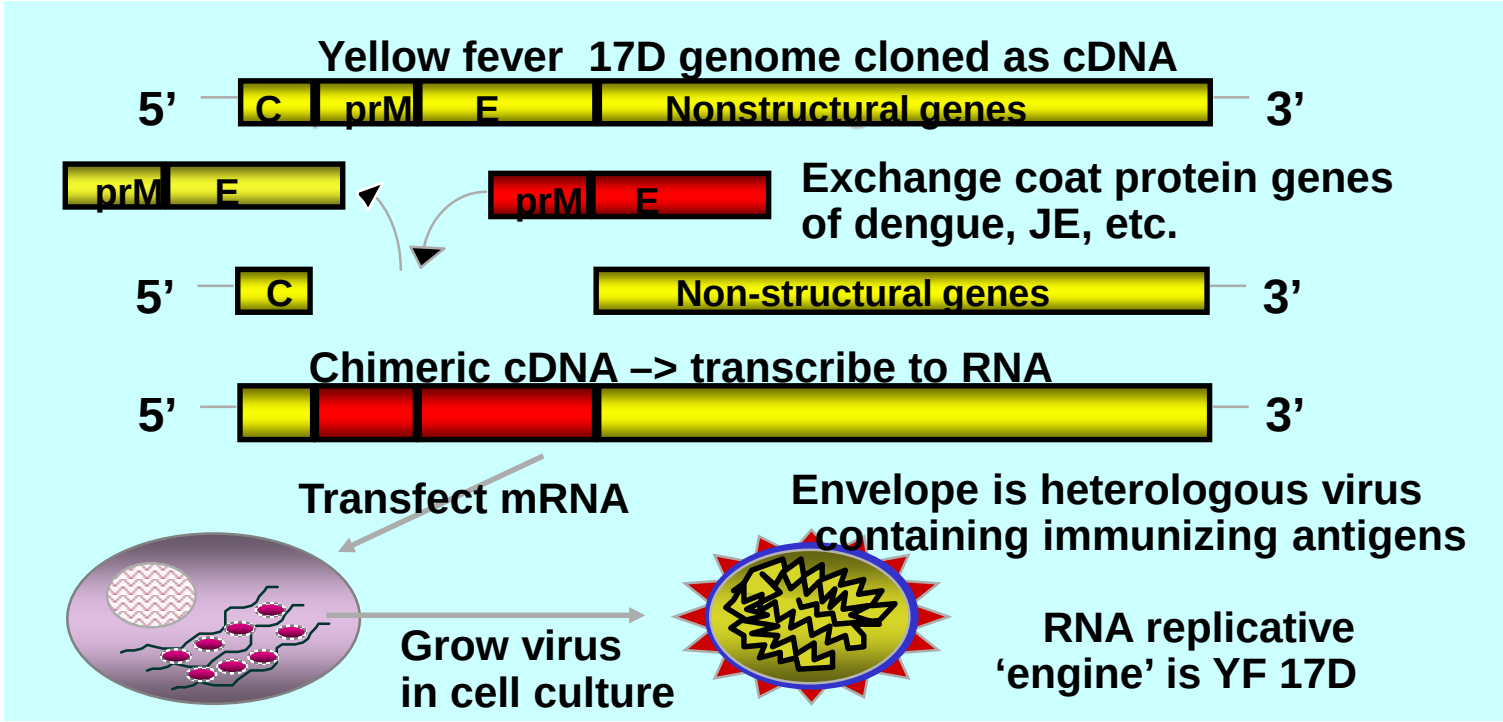
Dengue fever (DF), and especially the more severe dengue hemorrhagic fever (DHF), is a major global

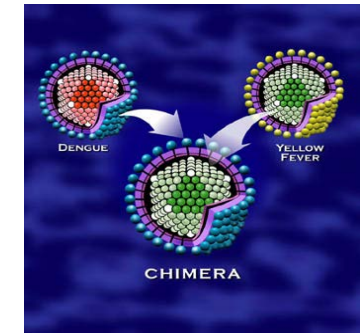
SUMMARY RESULTS

- 90 – 100% seroconversion to all dengue serotypes after 3-injection
- F2 (3313) vaccine has a better safety profiles and elicits a higher immune response.

ChimeriVax™ Vaccine

- Collaboration with Acambis (Cambridge UK/US) since 1998
- Live attenuated chimeric virus derived from a YF 17D virus with genes encoding for the premembrane (prM) and envelope (E) proteins of each dengue serotype and produced on Vero cells





ChimeriVax™ Vaccine

Previous Studies

	Phase	Code	Populations	Country	Status
Non-endemic trial	I monovalent	**CYD01**	Adults (18-40 y) **n=56**	US FV naive	Completed 2002
Non-endemic trial	I tetravalent	**CYD02**	Adults (18-40 y) **n=99**	US FV naive	Completed 2005
Non-endemic trial	II a tetravalent	**CYD04**	Adults (18-45 y) **n=66**	US FV naive	Completed 2007
Endemic trial (Flavivirus naïve and positive)	I tetravalent	**CYD05**	Adults (18-45 y) n=18 Adoles (12-17 y) n=36 Children (2-11 y) n=72 **N=126**	Philippines Den++/-	Completed 2008
Non-endemic trial (mainly Flavivirus naïve)	I tetravalent	**CYD06**	Adults (18-45 y) n=18 Adoles (12-17 y) n=36 Children (2-11 y) n=72 **N=126**	Mexico Den+/--	Completed 2008
Non-endemic trial	I Tetravalent	**CYD10**	Adults (18-40 y) (DIV12 Trial, VDV1, VDV2 or YF primed) **N=48**	Australia FV naive	Completed 2007

ChimeriVax™ Vaccine

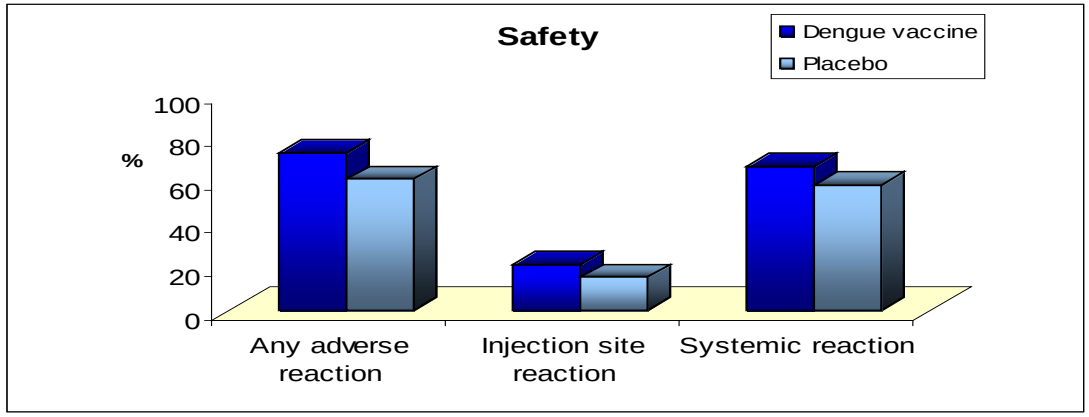
Safety: Post-Dose 1 of Dengue vs Control vaccine (% adverse events)

	CYD04 (US)		CYD05 (Ph)		CYD06 (Mex)	
	DV (n=33)	Placebo (n=33)	DV (n=84)	Typh (n=42)	DV (n=84)	YF (n=42)
Any Adverse event	84.8	66.7	79.8	95.2	72.6	66.7
Any Adverse reaction	81.8	60.6	65.5	92.9	60.7	52.4
Injection site reaction	18.2	15.2	29.8	83.3	32.1	21.4
Systemic reaction	78.8	57.6	60.7	52.4	50.0	42.9
Severe Injection site reaction	0	0	0	0	1.2	0
Severe Systemic reaction	15.2	6.1	0	2.4	7.1	0

- **Safety profile overall comparable to the control groups**
- **Most of Adverse Reactions are mild to moderate, and transient**
- **Few severe reactions occurred - transient solicited reactions or CPK elevation**

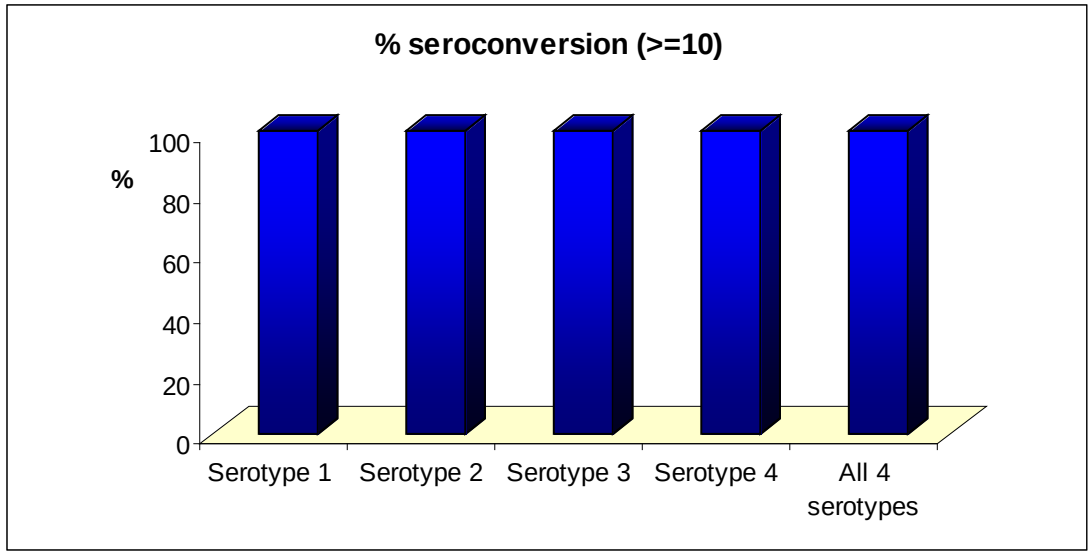
ChimeriVax™ Vaccine

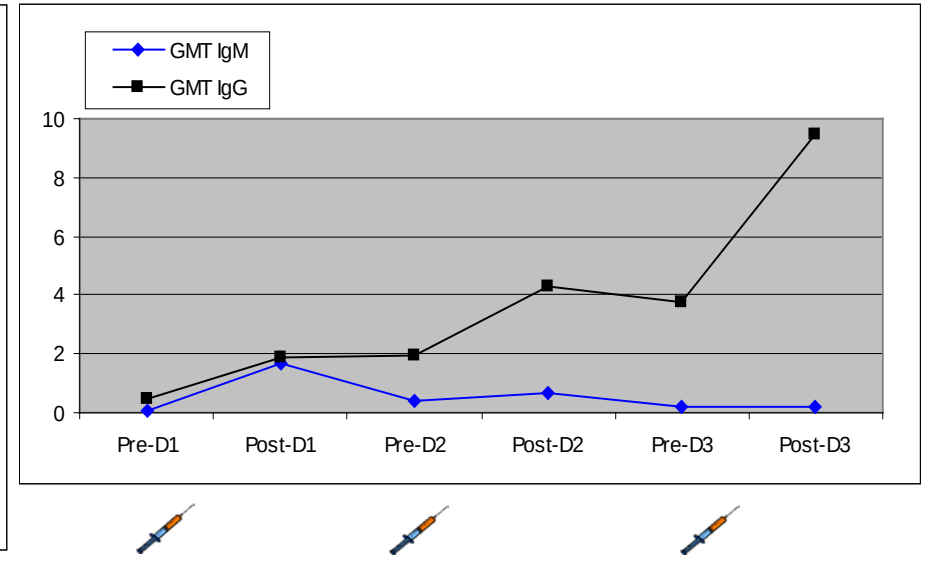
CYD04 US: Safety and immunogenicity after 3 doses



➔Satisfactory safety profile

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



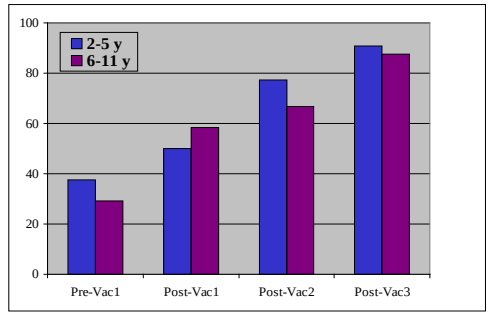


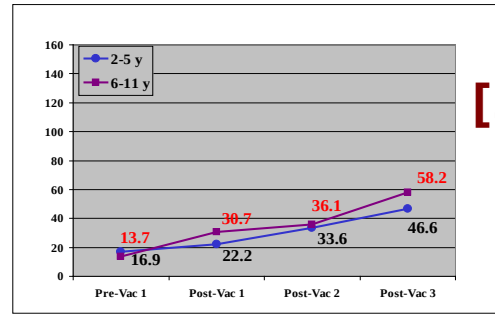
ChimeriVax™ Vaccine

CYD05 Ph : % sero+, GMT by serotype in Children

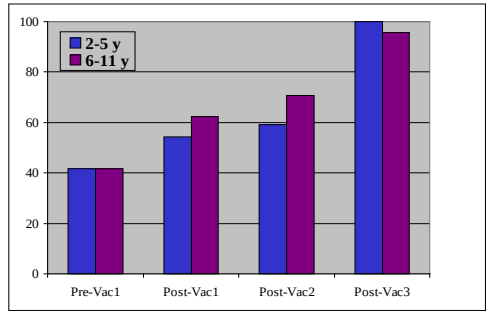
[2-5y, n=24] and [6-11y, n=24]

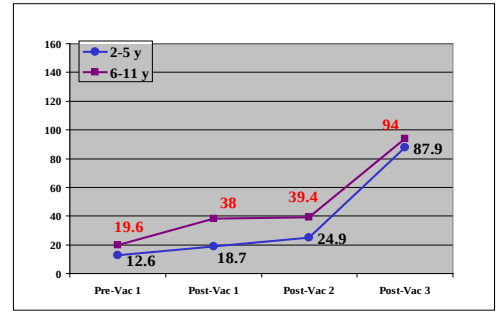
Serotype 1



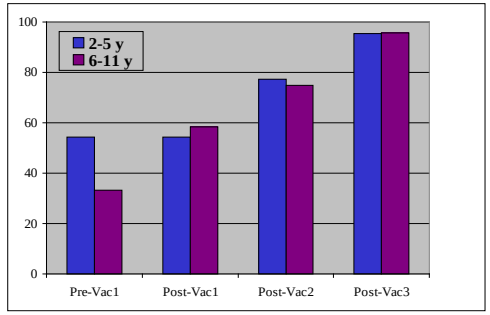


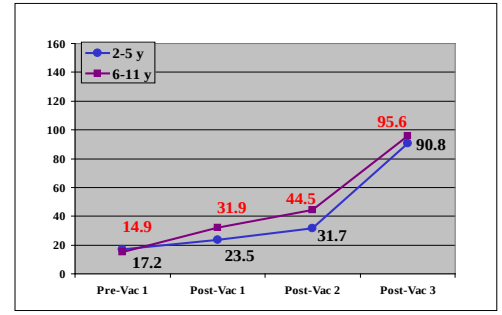
Serotype 2



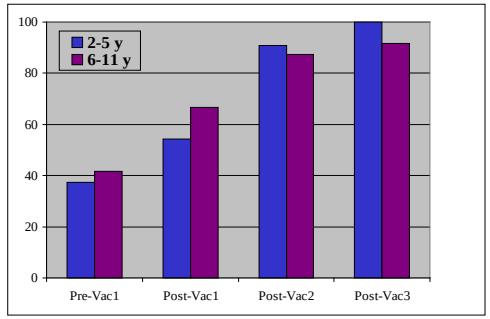


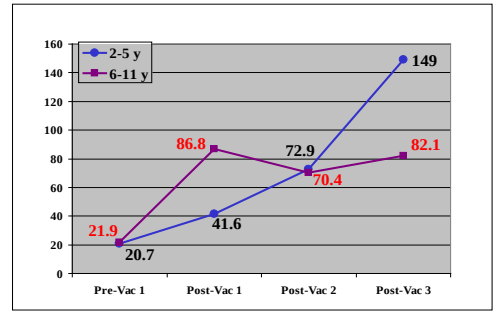
Serotype 3

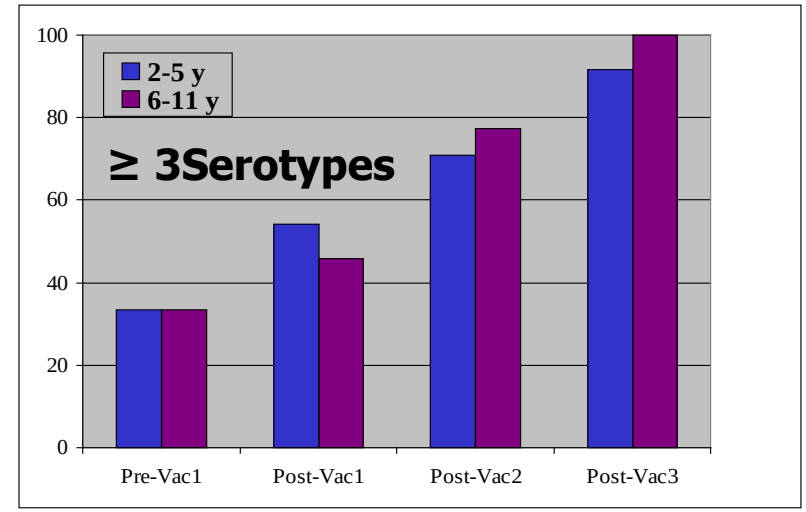


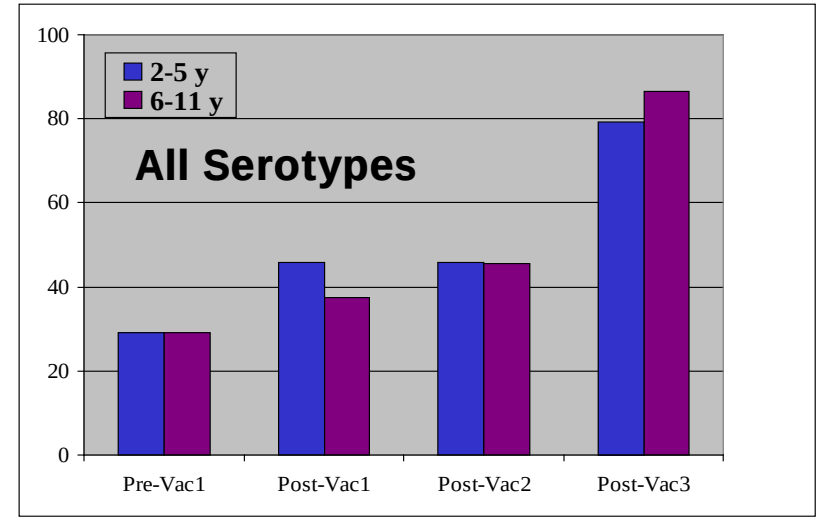


Serotype 4



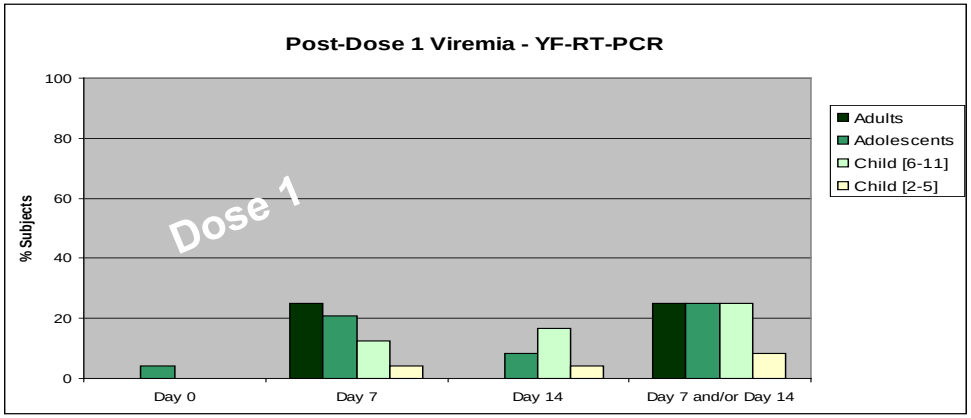






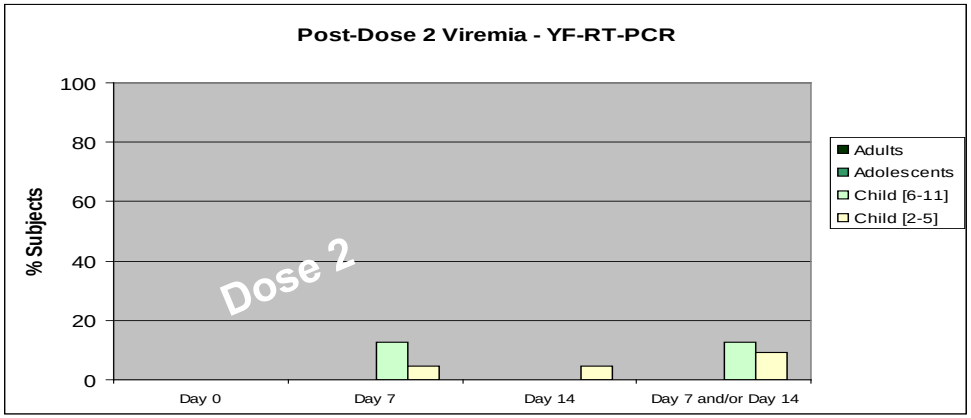
ChimeriVax™ Vaccine

CYD phase II: Safety



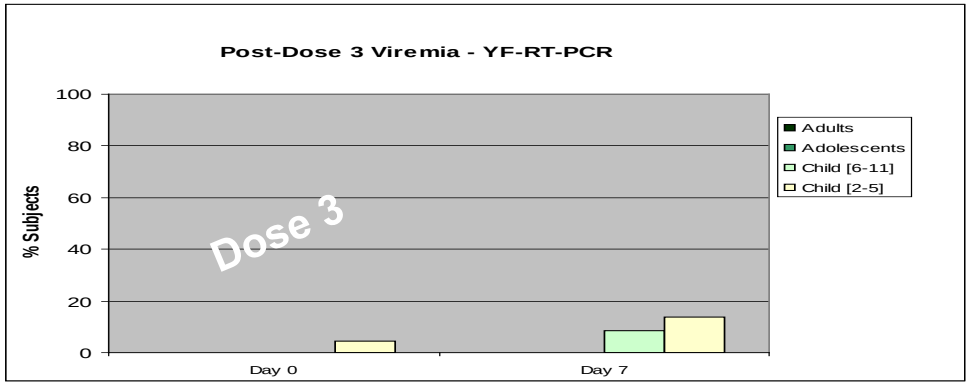
First Dose

- Viremia more frequently detected in adults/ados
- 2 CYD vaccinated subjects had viremia level ≥ LLOQ (maximum level 2.3 log10 pfu/mL)
- No samples were positive in Plaque assay
- Serotype 4 most detected followed by serotype 3



Second Dose

- 2 CYD vaccinated subjects had viremia level ≥ LLOQ (maximum level 1.8 log10 pfu/mL)
- No samples were positive in Plaque assay
- Serotype 4 only detected



Third Dose

- No vaccinated subjects had viremia level ≥ LLOQ
- No samples were positive in Plaque assay

CYD TDV Worldwide

Phase I, II trials – Safety and Immunogenicity

CYD22
Adults-ado
Children
JE+/-, Den+/-
Vietnam

CYD28
Child-Ado-Adults
Den+/-
Singapore

CYD12
Adults
FV naive
US

CYD11
Adults
FV naive
Mexico

CYD13 /CYD30
Adolescents
Den+/-
Latin Am

CYD24
Children
YF+, Den+/-
Peru

CYD05
Adults- Ado-
Children
Philippines
N= 126

CYD06
Adults- Ado-
Children
Mexico
N= 126

CYD23/57 (phase IIb)
(2009-2014)
Children
JE+/-, Den+/-
Ratchaburi, Thailand
N= 4002

Ph III trials large scale Safety and Efficacy Trials, 31,000 children and adults, 2011-2016

Phase III Lot-to-lot Consistency

Australia
CYD17
N= 715
FVFS: 06 Oct 2010

Phase III Safety and Immuno

Malaysia
CYD32
N=250
FVFS: 03 Dec 2010

Asia: IDN, MY, PH, TH, VN
CYD14, N= 10,278
FVFS: 04 Jun 2011

Latin America:
BZ, CB, HDR, MX, PRC
CYD15, N= 20,875
FVFS: 08 Jun 2011

ChimeriVax™ Vaccine

Trial designs

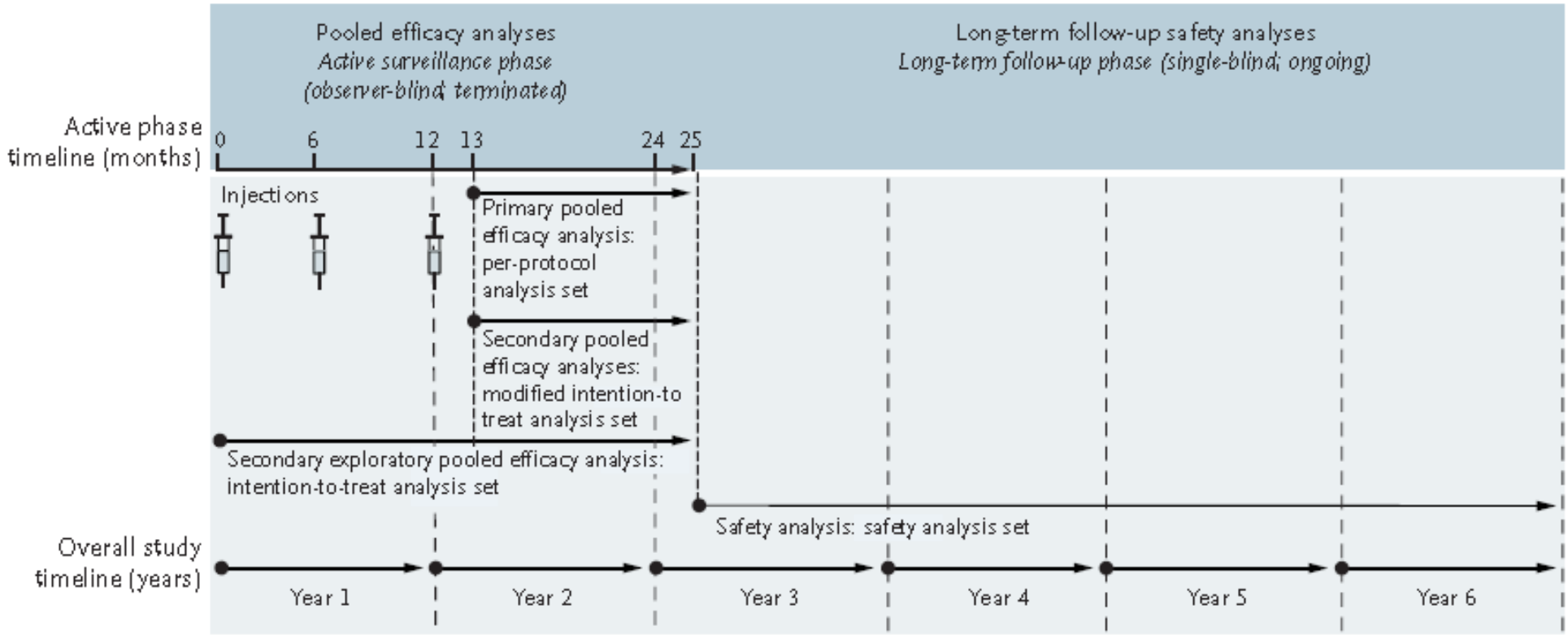


Figure 1. Overview of the Surveillance Phase and Long-Term Follow-up Phase of the CYD-TDV Candidate Vaccine Trials.

CYD-TDV is a candidate recombinant, live, attenuated, tetravalent dengue vaccine that has been assessed in two phase 3 randomized efficacy studies (called CYD14 and CYD15) involving a total of more than 31,000 participants between the ages of 2 and 16 years in Asian–Pacific and Latin American countries. In addition, 3203 of 4002 participants (80%) who were between the ages of 4 and 11 at initial enrollment in the phase 2b CYD23 trial in Thailand are being followed in the CYD57 trial. The trials had similar designs. According to the study designs, the long-term follow-up phase will continue for a total of 6 years after enrollment.

Phase 2b ChimeriVax

CYD23 Investigators, team & CRAs Quintiles

ChimeriVax™ Vaccine

Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial

Arunee Sabchareon, Derek Wallace, Chukiat Sirivichayakul, Kriengsak Limkittikul, Pornthep Chanthavanich, Saravudh Suvannadabba, Vithaya Jiwariyavej, Wut Dulyachai, Krisana Pengsaa, T Anh Wartel, Annick Moureau, Melanie Saville, Alain Bouckenooghe, Simonetta Viviani, Nadia G Tornieporth, Jean Lang

Summary

Background Roughly half the world's population live in dengue-endemic countries, but no vaccine is licensed. We investigated the efficacy of a recombinant, live, attenuated tetravalent dengue vaccine.

Methods In this observer-masked, randomised, controlled, monocentre, phase 2b, proof-of-concept trial, healthy Thai schoolchildren aged 4–11 years were randomly assigned (2:1) to receive three injections of dengue vaccine or control (rabies vaccine or placebo) at months 0, 6, and 12. Randomisation was by computer-generated permuted blocks of six and participants were assigned with an interactive response system. Participants were actively followed up until month 25. All acute febrile illnesses were investigated. Dengue viraemia was confirmed by serotype-specific RT-PCR and non-structural protein 1 ELISA. The primary objective was to assess protective efficacy against virologically confirmed, symptomatic dengue, irrespective of severity or serotype, occurring 1 month or longer after the third injection (per-protocol analysis). This trial is registered at ClinicalTrials.gov, NCT00842530.

Findings 4002 participants were assigned to vaccine (n=2669) or control (n=1333). 3673 were included in the primary analysis (2452 vaccine, 1221 control). 134 cases of virologically confirmed dengue occurred during the study. Efficacy was 30·2% (95% CI −13·4 to 56·6), and differed by serotype. Dengue vaccine was well tolerated, with no safety signals after 2 years of follow-up after the first dose.

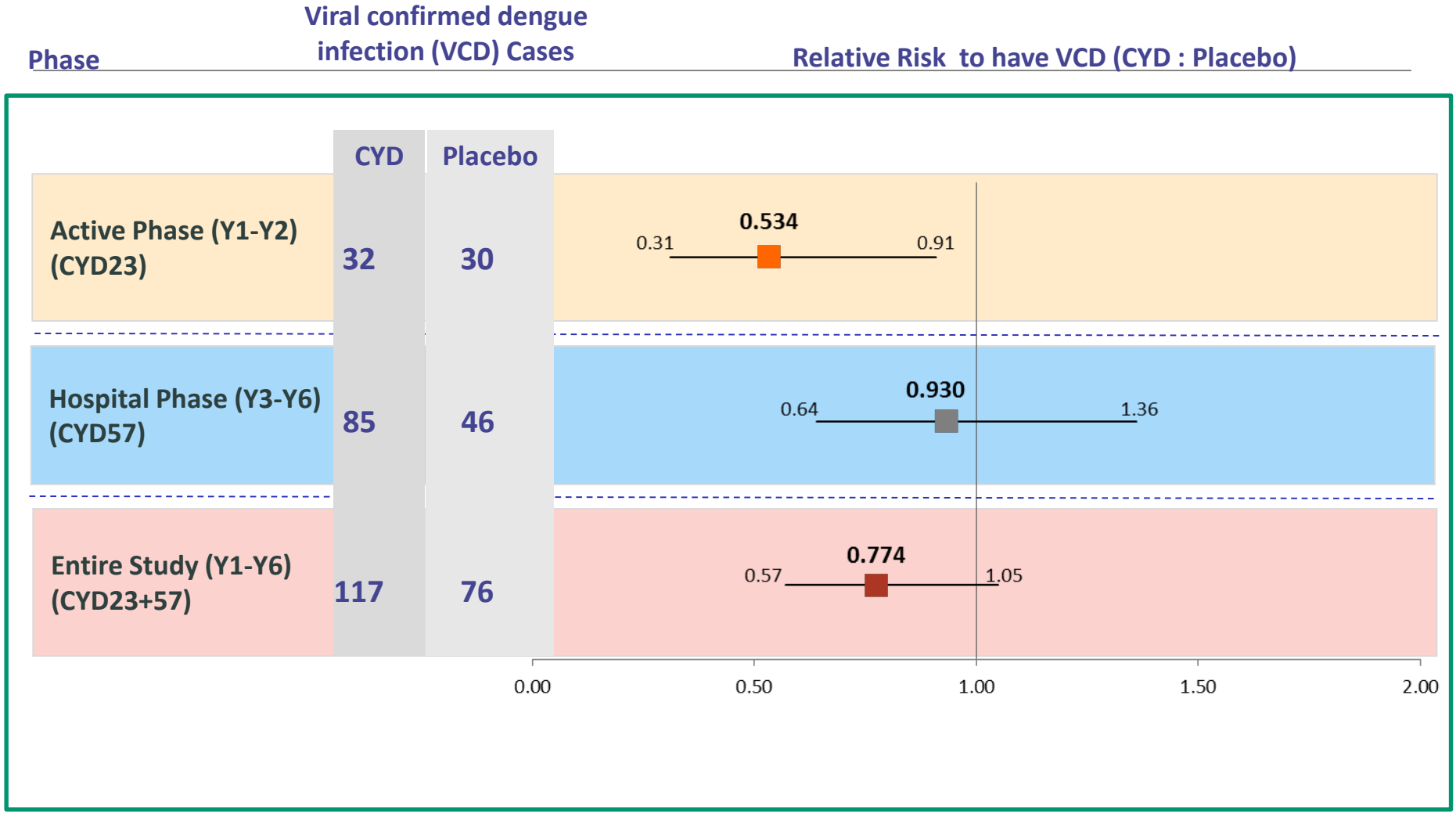
Interpretation These data show for the first time that a safe vaccine against dengue is possible. Ongoing large-scale phase 3 studies in various epidemiological settings will provide pivotal data for the CYD dengue vaccine candidate.

Funding Sanofi Pasteur.

CYD23: summary

Overall Efficacy: 30.2%
No efficacy against DEN2

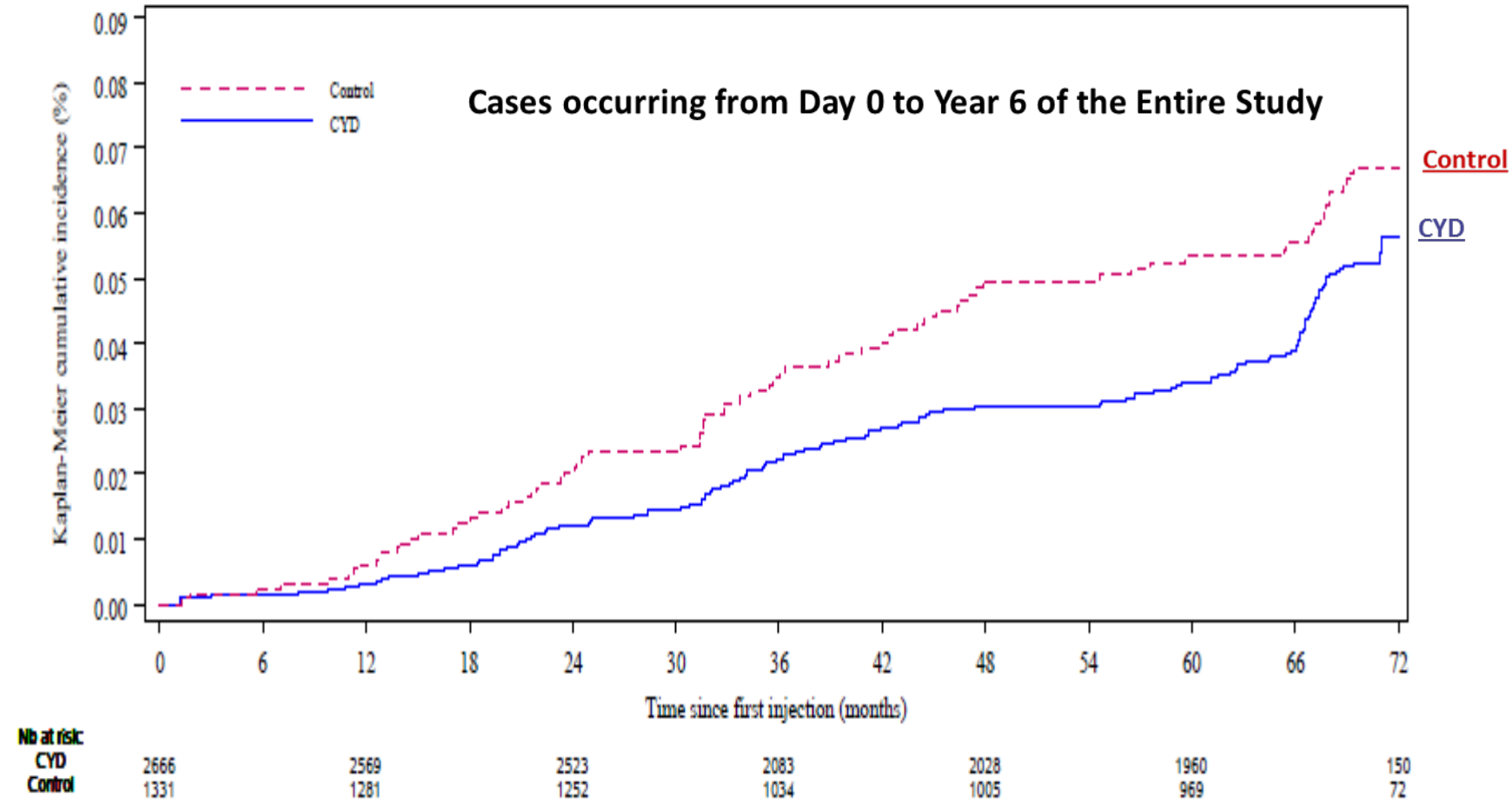
Dengue for Overall Population (4-11yo) Entire Studies



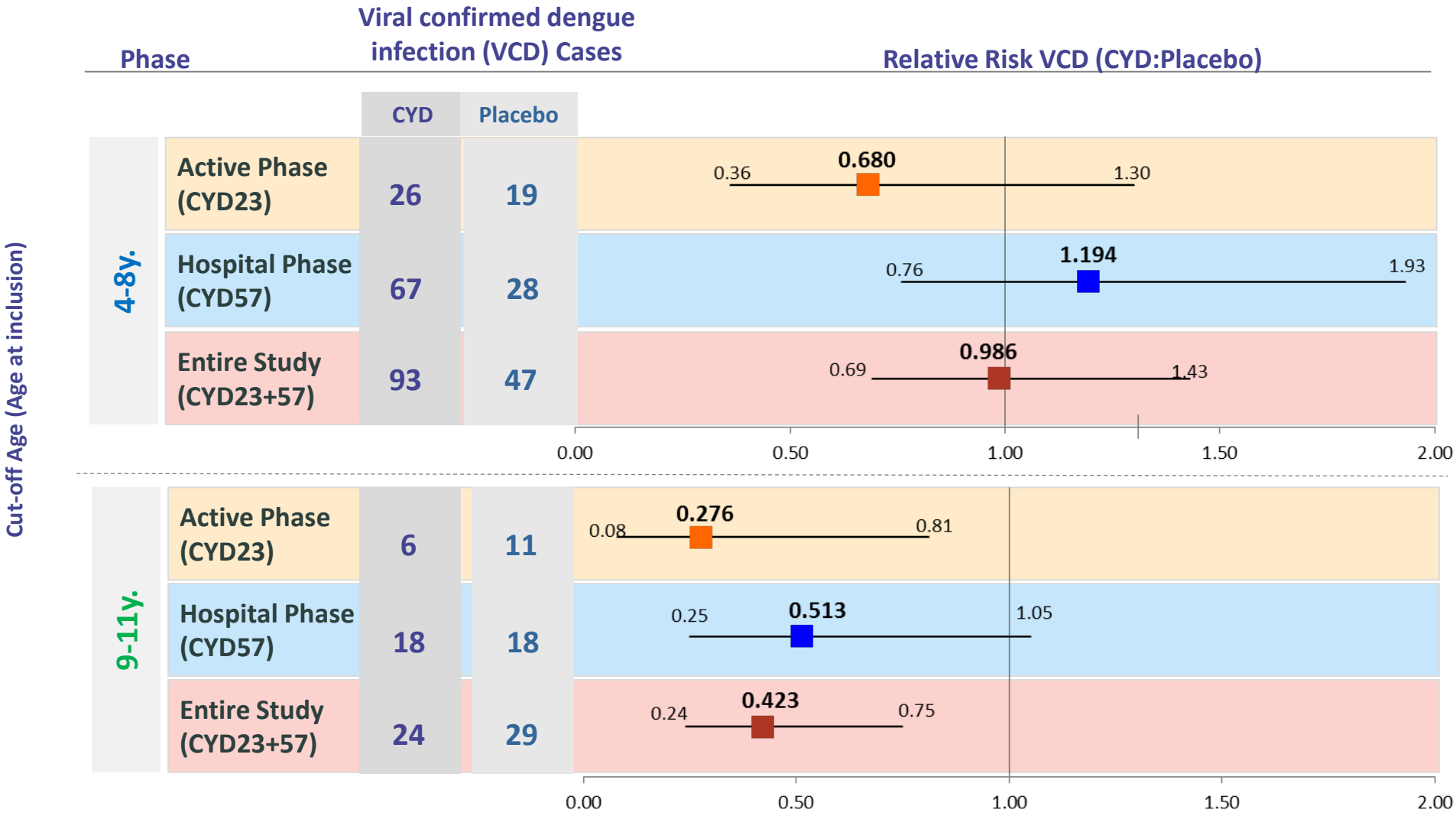
Randomization ratio is 2:1 for CYD vs. Placebo group

Active Phase: from D0 to the end of the Active Phase (Month 25)
Hospital Phase: from the end of the Active Phase until Year 6

Kaplan-Meier Curves for Dengue for the Overall Population Entire Studies



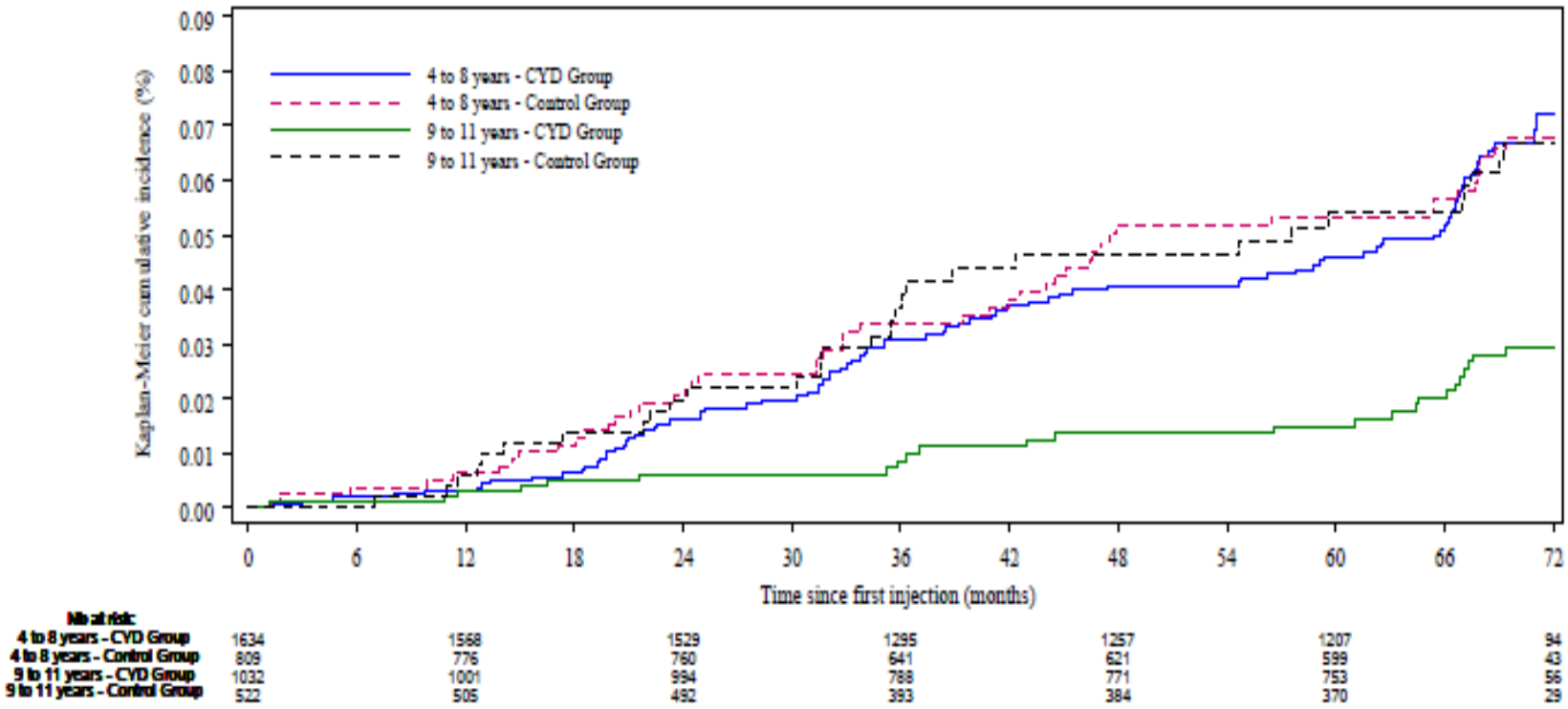
Dengue Subgroup Population (4-8 / 9-11 yo)



Randomization ratio is 2:1 for CYD vs. Placebo group

Active Phase: from D0 to the end of the Active Phase (Month 25)
Hospital Phase: from the end of the Active Phase until Year 6

Kaplan-Meier Curves for Subgroup Population (4-8 / 9-11 yo)



4-< 9y CYD

4-< 9y Control

9-11y Control

9-11y CYD

There is greater protection, that appears to be stable, against hospitalized or severe VCD in subjects ≥9 years of age observed over time.

ChimeriVax™ Vaccine

CYD14: summary

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

*Maria Rosario Capeding, Ngoc Huu 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**

Summary

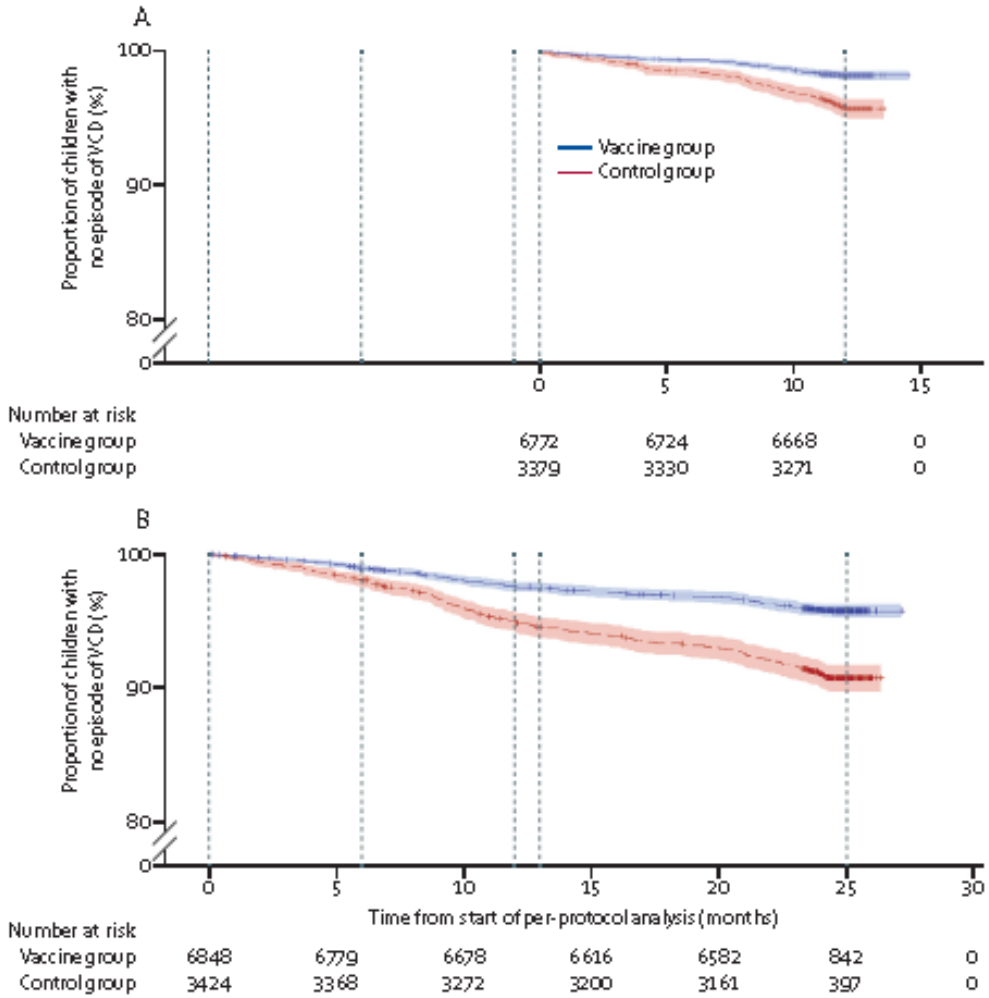
Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

Methods We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2–14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV), or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per procotol. This trial is registered with ClinicalTrials.gov, number NCT01373281.

Findings We randomly assigned 10 275 children to receive either vaccine (n=6851) or placebo (n=3424), of whom 6710 (98%) and 3350 (98%), respectively, were included in the primary analysis. 250 cases of virologically confirmed dengue took place more than 28 days after the third injection (117 [47%] in the vaccine group and 133 [53%] in the control group). The primary endpoint was achieved with 56·5% (95% CI 43·8–66·4) efficacy. We recorded 647 serious adverse events (402 [62%] in the vaccine group and 245 [38%] in the control group). 54 (1%) children in the vaccine group and 33 (1%) of those in the control group had serious adverse events that happened within 28 days of vaccination. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries.

Interpretation Our findings show that dengue vaccine is efficacious when given as three injections at months 0, 6, and 12 to children aged 2–14 years in endemic areas in Asia, and has a good safety profile. Vaccination could reduce the incidence of symptomatic infection and hospital admission and has the potential to provide an important public health benefit.

Funding Sanofi Pasteur.



Efficacy: 56.5%, (35.0% for DEN2)

ChimeriVax™ Vaccine

CYD15: summary

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 8, 2015 VOL. 372 NO. 2

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*

ABSTRACT

BACKGROUND

In light of the increasing rate of dengue infections throughout the world despite vector-control measures, several dengue vaccine candidates are in development.

METHODS

In a phase 3 efficacy trial of a tetravalent dengue vaccine in five Latin American countries where dengue is endemic, we randomly assigned healthy children between the ages of 9 and 16 years in a 2:1 ratio to receive three injections of recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) or placebo at months 0, 6, and 12 under blinded conditions. The children were then followed for 25 months. The primary outcome was vaccine efficacy against symptomatic, virologically confirmed dengue (VCD), regardless of disease severity or serotype, occurring more than 28 days after the third injection.

RESULTS

A total of 20,869 healthy children received either vaccine or placebo. At baseline, 79.4% of an immunogenicity subgroup of 1944 children had seropositive status for one or more dengue serotypes. In the per-protocol population, there were 176 VCD cases (with 11,793 person-years at risk) in the vaccine group and 221 VCD cases (with 5809 person-years at risk) in the control group, for a vaccine efficacy of 60.8% (95% confidence interval [CI], 52.0 to 68.0). In the intention-to-treat population (those who received at least one injection), vaccine efficacy was 64.7% (95% CI, 58.7 to 69.8). Serotype-specific vaccine efficacy was 50.3% for serotype 1, 42.3% for serotype 2, 74.0% for serotype 3, and 77.7% for serotype 4. Among the severe VCD cases, 1 of 12 was in the vaccine group, for an intention-to-treat vaccine efficacy of 95.5%. Vaccine efficacy against hospitalization for dengue was 80.3%. The safety profile for the CYD-TDV vaccine was similar to that for placebo, with no marked difference in rates of adverse events.

CONCLUSIONS

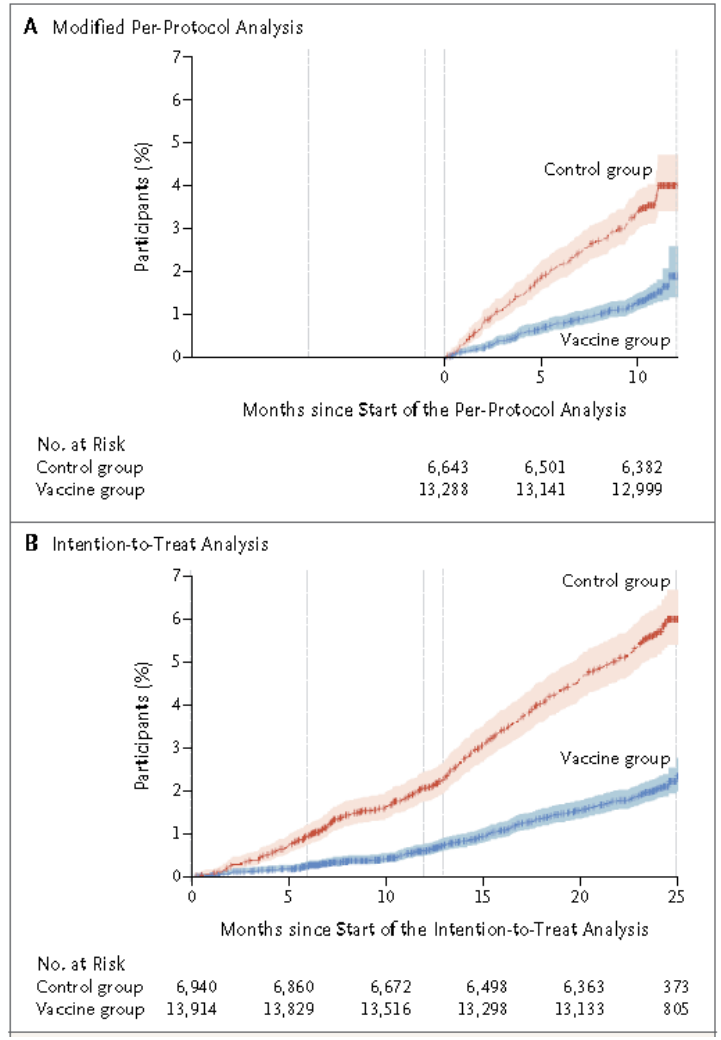
The CYD-TDV dengue vaccine was efficacious against VCD and severe VCD and led to fewer hospitalizations for VCD in five Latin American countries where dengue is endemic. (Funded by Sanofi Pasteur; ClinicalTrials.gov number, NCT01374516.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Dayan at Sanofi Pasteur, Discovery Dr., Swiftwater, PA, 18370, or at gustavo.dayan@sanofipasteur.com.

*A complete list of investigators in the CYD15 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

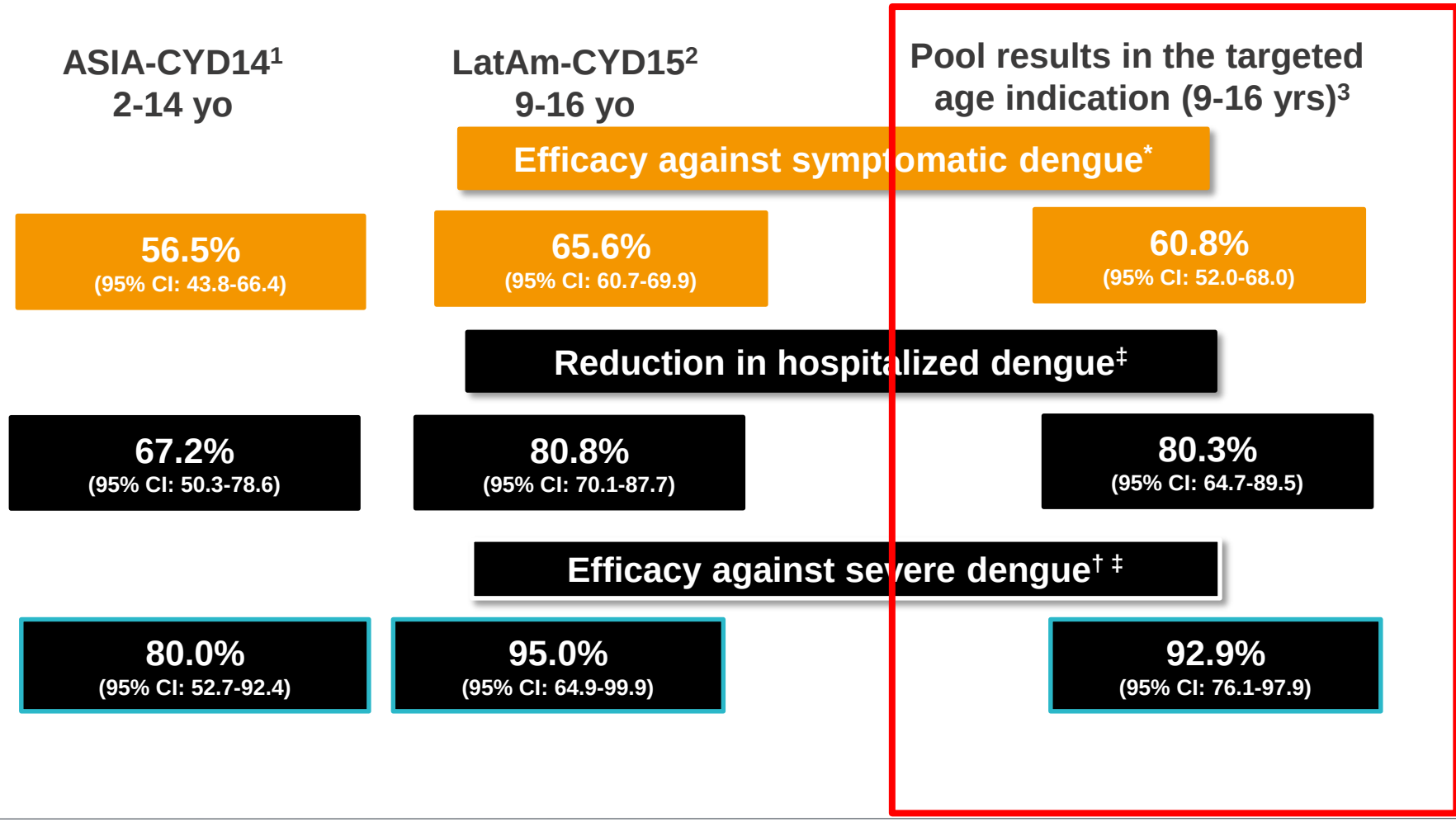
This article was published on November 3, 2014, at NEJM.org.

N Engl J Med 2015;372:113-23.
DOI: 10.1056/NEJMoa1411037



Efficacy: 64.7%, (42.3% for DEN2)

TWO PHASE III EFFICACY TRIALS DEMONSTRATED A CONSISTENT EFFICACY AND SAFETY PROFILE DURING THE 25 MONTHS (ACTIVE PHASE)



*Per protocol, 12 months post-dose 3 ; †Dengue hemorrhagic fever, World Health Organization (WHO) 1997 criteria, intent to treat; ‡Intent to treat, 25 months postdose 1.

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

ChimeriVax™ Vaccine

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 24, 2015 VOL. 373 NO. 13

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

S.R. Hadinegoro, J.L. Arredondo-García, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, H.I. Hj Muhammad Ismail, H. Reynales, K. Limkittikul, D.M. Rivera-Medina, H.N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T.A. Wartel, B. Zambrano, and M. Saville, for the CYD-TDV Dengue Vaccine Working Group*

ABSTRACT

BACKGROUND

A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian–Pacific and Latin American countries. We report the results of long-term follow-up interim analyses and integrated efficacy analyses.

METHODS

We are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety end point during follow-up in years 3 to 6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. We estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15.

RESULTS

Follow-up data were available for 10,165 of 10,275 participants (99%) in CYD14 and 19,898 of 20,869 participants (95%) in CYD15. Data were available for 3208 of the 4002 participants (80%) in the CYD23 trial included in CYD57. During year 3 in the CYD14, CYD15, and CYD57 trials combined, hospitalization for virologically confirmed dengue occurred in 65 of 22,177 participants in the vaccine group and 39 of 11,089 participants in the control group. Pooled relative risks of hospitalization for dengue were 0.84 (95% confidence interval [CI], 0.56 to 1.24) among all participants, 1.58 (95% CI, 0.83 to 3.02) among those under the age of 9 years, and 0.50 (95% CI, 0.29 to 0.86) among those 9 years of age or older. During year 3, hospitalization for severe dengue, as defined by the independent data monitoring committee criteria, occurred in 18 of 22,177 participants in the vaccine group and 6 of 11,089 participants in the control group. Pooled rates of efficacy for symptomatic dengue during the first 25 months were 60.3% (95% CI, 55.7 to 64.5) for all participants, 65.6% (95% CI, 60.7 to 69.9) for those 9 years of age or older, and 44.6% (95% CI, 31.6 to 55.0) for those younger than 9 years of age.

CONCLUSIONS

Although the unexplained higher incidence of hospitalization for dengue in year 3 among children younger than 9 years of age needs to be carefully monitored during long-term follow-up, the risk among children 2 to 16 years of age was lower in the vaccine group than in the control group. (Funded by Sanofi Pasteur; ClinicalTrials.gov numbers, NCT00842530, NCT01983553, NCT01373281, and NCT01374516.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Saville at Sanofi Pasteur, 2 Ave. Pont Pasteur, 69367 Lyon CEDEX 07, France, or at melanie.saville@sanofipasteur.com.

*A complete list of investigators in the CYD-TDV Dengue Vaccine Working Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 27, 2015, at NEJM.org.

N Engl J Med 2015;373:1195-206.
DOI: 10.1056/NEJMoa1506223

CYD23/57+14+15: summary

Efficacy in first 25 months:

All: 60.3% (CI 55.7-64.5)
>9 yr old: 65.6% (CI 60.7-69.9)
<9 yr old: 44.6% (CI 31.6-55.0)

Safety precaution:

*Vaccine AE: mild
* Unexplained higher incidence of dengue admission in age <9 yr in vaccine gr in some studies.

Dengvaxia® approved in 18 countries


Mexico


Paraguay


Thailand


Australia


Philippines
(Public Programme)


Guatemala


Bolivia


Honduras


Brazil
(Public Programme)


Indonesia


Cambodia


Venezuela


El Salvador


Peru


Argentina


Costa Rica


Singapore


Malaysia

Ongoing regulatory submission in other endemic countries.

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November 29, 2017

Sanofi updates information on dengue vaccine

- New analysis of long-term Dengvaxia® data found differences in vaccine performance based on prior dengue infection
- Company will ask regulators to update product label to reflect new information

PARIS, FRANCE – November 29, 2017 – Sanofi will ask health authorities to update information provided to physicians and patients on its dengue vaccine Dengvaxia® in countries where it is approved. The request is based on a new analysis of long-term clinical trial data, which found differences in vaccine performance based on prior dengue infection.

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.

"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.

About half of the world's population lives in countries where four serotypes of dengue virus are in circulation. Every year an estimated 390 million dengue infections are reported. People can be infected with dengue up to four times in their lifetime and they can get severely ill after any of these infections. Surveillance data from some endemic countries indicate that between 70 and 90 percent of people will have been exposed to dengue at least once by the time they reach adolescence. There are many factors that can lead to severe dengue infection. However, the highest risk of getting more severe disease has been observed in people infected for the second time by a different dengue virus.

Dengvaxia is currently indicated in most of the countries for individuals 9 years of age and older living in a dengue-endemic area. In this indicated population, Dengvaxia has been shown to prevent 93 percent of severe disease and 80 percent of hospitalizations due to dengue over the 25 month phase of the large-scale clinical studies conducted in 10 countries in Latin America and Asia where dengue is widespread.

Press release from SP: 29 NOV2017

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.

WHO update

What is the absolute risk of severe dengue in the vaccinated and unvaccinated trial populations by serostatus?

The risk depends on the yearly incidence of dengue. Based on the incidence in the epidemiological settings of the trials, for persons aged 9 years and above, the new analysis indicates that

- the 5-year risk of severe dengue in vaccinated seronegative persons (4 per 1,000 seronegative persons vaccinated) is similar to the risk of severe dengue in unvaccinated seropositive persons (4.8 per 1,000 seropositive persons unvaccinated).

- The risk of severe dengue is lower in unvaccinated seronegative persons (1.7 per 1,000 seronegative persons unvaccinated). The risk of severe dengue in vaccinated seropositive persons is the lowest (less than 1 per 1,000 seropositive persons vaccinated).

- There is no evidence that clinical manifestations of disease were more severe in vaccinated seronegative persons compared to unvaccinated seropositive persons. For the entire vaccinated population, overall, the risk of severe dengue is reduced compared to a non-vaccinated population.

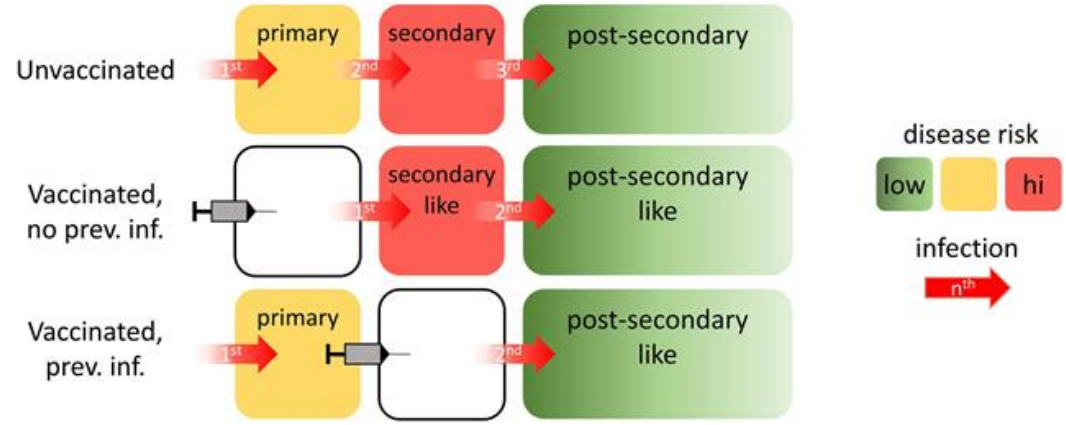

Image from: Flasche S, Jit M, Rodriguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. PLoS Med. 2016;13:1–19. doi:10.1371/ journal.pmed.1002181.

Risk of severe dengue (/1000)	Non Vaccine	Vaccine
Seronegative	1.7	4
seropositive	4.8	1

?

The relative risk or hazard ratio (95% confident interval) of hospitalized virologically confirmed dengue (VCD) and severe VCD based on age and pre-vaccination serostatus (Sridhar et al., N Engl J Med, 379(4), 327-340.) .

outcome	age group (year)	estimated pre-vaccination serostatus	incidence of VCD post-vaccination [n/total number (%)]		relative risk or hazard ratio (95% CI)
			vaccine	control	
hospitalized VCD	2-8	positive	93.6/313.2 (29.9)	89.8/156.4 (57.4)	0.50 (0.33-0.77)
		negative	137.4/192.8 (71.3)	37.2/100.6 (37.0)	1.95 (1.19-3.19)
	9-16	positive	58.8/1502.9 (3.9)	137.7/729.8 (18.9)	0.21 (0.14-0.31)
		negative	64.2/375.1 (17.1)	25.3/207.2 (12.2)	1.41 (0.74-2.68)
severe VCD	2-8	positive	23.9/313.2 (7.6)	20/156.4 (12.8)	0.58 (0.26-1.30)
		negative	30.1/192.8 (15.6)	5/100.6 (5.0)	3.31 (0.87-12.54)
	9-16	positive	11.2/1502.9 (0.7)	33.4/729.8 (4.6)	0.16 (0.07-0.37)
		negative	14.8/375.1 (3.9)	3.6/207.2 (1.7)	2.44 (0.47-12.56)

Policy recommendations on the use of the first licensed dengue vaccine

SAGE concluded that for countries considering CYD-TDV vaccination as part of their dengue control programme, a pre-vaccination screening strategy, in which only dengue-seropositive persons are vaccinated, is the preferred option.

Screening tests could be used to identify persons who have had a previous dengue infection. Ideally, a test with the highest specificity should be used to minimize the inadvertent use of vaccine in seronegative persons. Two types of tests could be considered: serological assays such as dengue IgG ELISA, and rapid diagnostic tests (RDT). The ELISA assays do not provide point-of-care information on an individual's serostatus, and the currently available RDTs have not yet been validated for the purpose of screening for previous dengue infection. Nevertheless, either could be considered in high prevalence settings until better tests become available.

Given that no test will be 100% specific, some seronegative individuals may be vaccinated due to a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is less than 100%. Hence, the limitations of CYD-TDV will need to be clearly communicated to those offered vaccination.

2018, 93, 329–344 No 23

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

8 JUNE 2018, 93th YEAR / 8 JUIN 2018, 93e ANNÉE
No 23, 2018, 93, 329–344
http://www.who.int/wer

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Meeting of the Strategic Advisory Group of Experts on immunization, April 2018 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 17–18 April 2018. This report summarizes the discussions, conclusions and recommendations.[2]

Report from the WHO Department of Immunization, Vaccines and Biologicals and Regional updates

The report from the Director of the WHO Immunization Vaccines and Biologicals programme focused on the theme "Immunization in a changing world." In line with WHO's mission to keep the world safe, promote health, and serve the vulnerable, as detailed in the WHO 13th Global Plan of Work (GPW 13), it was noted that immunization makes important contributions to all 3 objectives.[3] The Global Vaccine Action Plan (GVAP) goal on new vaccine introduction has been accomplished, but other GVAP goals have not yet been achieved. In particular, gaps and inequity in coverage remain. Population growth, population migration within and between countries, and ever increasing urbanization challenge even the current coverage levels. Population growth in Africa causes coverage to plateau even though ever more children are being vaccinated – African countries need to vaccinate half a million additional children every year just to keep up with growth. The recent diphtheria outbreaks in Bangladesh, Bolivarian Republic of

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, avril 2018 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni les 17 et 18 avril 2018. Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.[2]

Rapport du Département Vaccination, vaccins et produits biologiques de l'OMS et bilans régionaux

Le directeur du programme Vaccination, vaccins et produits biologiques de l'OMS a présenté un rapport axé sur le thème «Vaccination dans un monde en évolution». Il a observé que la vaccination contribue de manière importante aux 3 objectifs de la mission de l'OMS, tels qu'énoncés dans le 13e programme général de travail (PGT13) de l'OMS: préserver la sécurité mondiale, promouvoir la santé et servir les populations vulnérables.[3] Parmi les objectifs du Plan d'action mondial pour les vaccins (GVAP), celui qui traite de l'introduction des nouveaux vaccins a été atteint, mais d'autres restent inachevés. Il subsiste en particulier des lacunes et des inégalités en matière de couverture vaccinale. La croissance démographique, les migrations de population à l'intérieur des pays et d'un pays à l'autre, ainsi que l'urbanisation toujours croissante, présentent d'importantes difficultés, ne serait-ce que pour maintenir les niveaux de couverture actuels. En Afrique, la croissance démographique se traduit par un plafonnement de la couverture, bien que le nombre d'enfants vaccinés ne cesse d'augmenter: pour suivre le rythme de la croissance, il

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06.2018
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[1] See www.who.int/immunization/sage/en/index.html, accessed April 2018.
[2] Presentations and background materials used for the SAGE meeting together with the list of SAGE members and summarized declarations of interests are available at www.who.int/immunization/sage/meetings/2018/april/en (accessed April 2018).
[3] WHO. Draft thirteenth general programme of work 2019–2023 (available at http://www.who.int/about/what-we-do/gpw-thirteen-consultation/en/, accessed April 2018).

[1] Voir www.who.int/immunization/sage/en/index.html, consulté en avril 2018.
[2] Les communications et les documents de travail utilisés pour la réunion du SAGE, ainsi que la liste des membres du SAGE et une synthèse de leurs déclarations d'intérêts sont disponibles à l'adresse: www.who.int/immunization/sage/meetings/2018/april/en (consulté en avril 2018).
[3] OMS. Projet de treizième programme général de travail 2019-2023 (disponible à l'adresse: http://www.who.int/about/what-we-do/gpw-thirteen-consultation/fr/, consulté en avril 2018).

329

Weekly epidemiological record, 8 JUNE 2018, No 23, 2018, 93, 329-344.

Antibody testing

- **PRNT is currently most accurate test for flavivirus but laborious, expensive and variation among LABs and tests.**
- **HAI and ELISA are cheaper and can be tested for large samples.**
- **ELISA had 99.4% sensitivity and 100% specificity* but standardization for different available tests are needed.**
- **HAI had 94.4% sensitivity and 62.5% specificity*.**

***Lukman *et al*. Biomed Res Int 2006.**

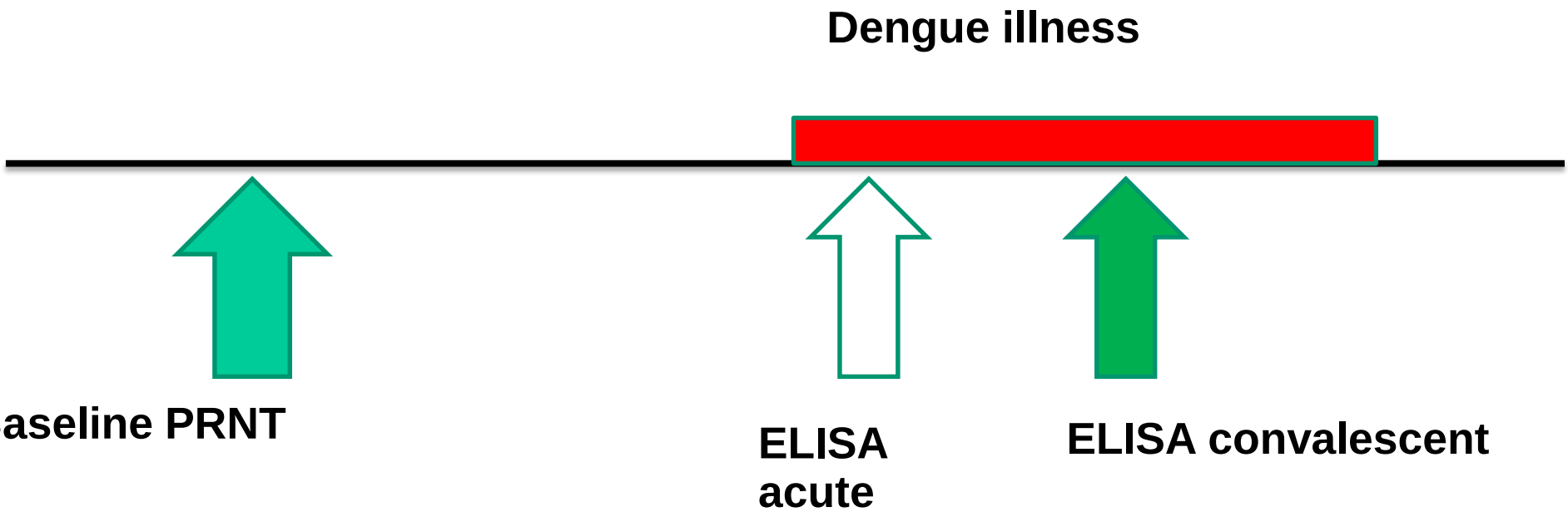
Antibody testing

- Antibody may cross react with other flavivirus (Zika, Japanese Encephalitis, Yellow fever, etc.) causing false positivity.
- Waning of antibody causes false negativity.
- There has been no study primarily aiming to assess antibody tests to diagnose previous infection to dengue.
- There has been no gold standard, although PRNT may be the best.

PRNT and ELISA

for diagnosis of previous dengue infection

Dengue cohort in Ratchaburi



PRNT test for diagnosis of previous dengue infection*

Pre-illness PRNT	ELISA (gold standard)	
	Primary infection	Secondary infection
Negative	5	11**
Positive	0	34

sensitivity = 75.5%, specificity = 100%
PPV = 100%, NPV = 31.3%

* unpublished data from dengue cases in dengue cohort in Ratchaburi, 2005-6

** 10 cases had positive PRNT for JE

IgG ELISA test for diagnosis of previous dengue infection*

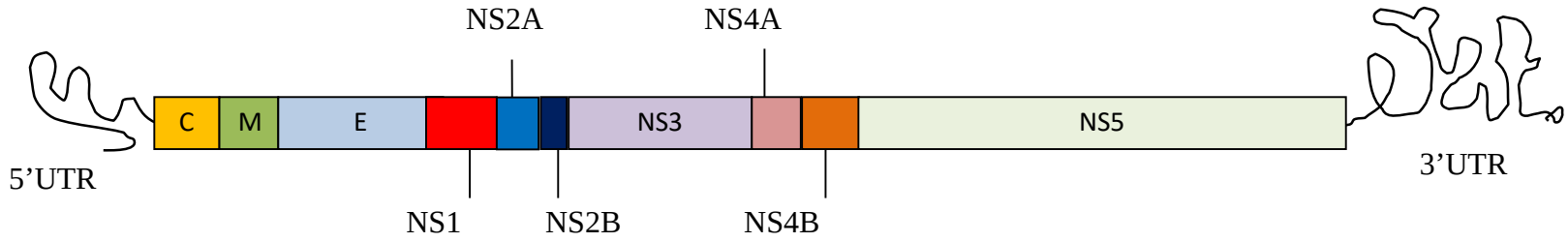
IgG ELISA in acute sample	ELISA (gold standard)	
	Primary infection	Secondary infection
Negative	5	27
Positive	0	19

sensitivity = 41.3%, specificity = 100%
PPV = 100%, NPV = 15.2%

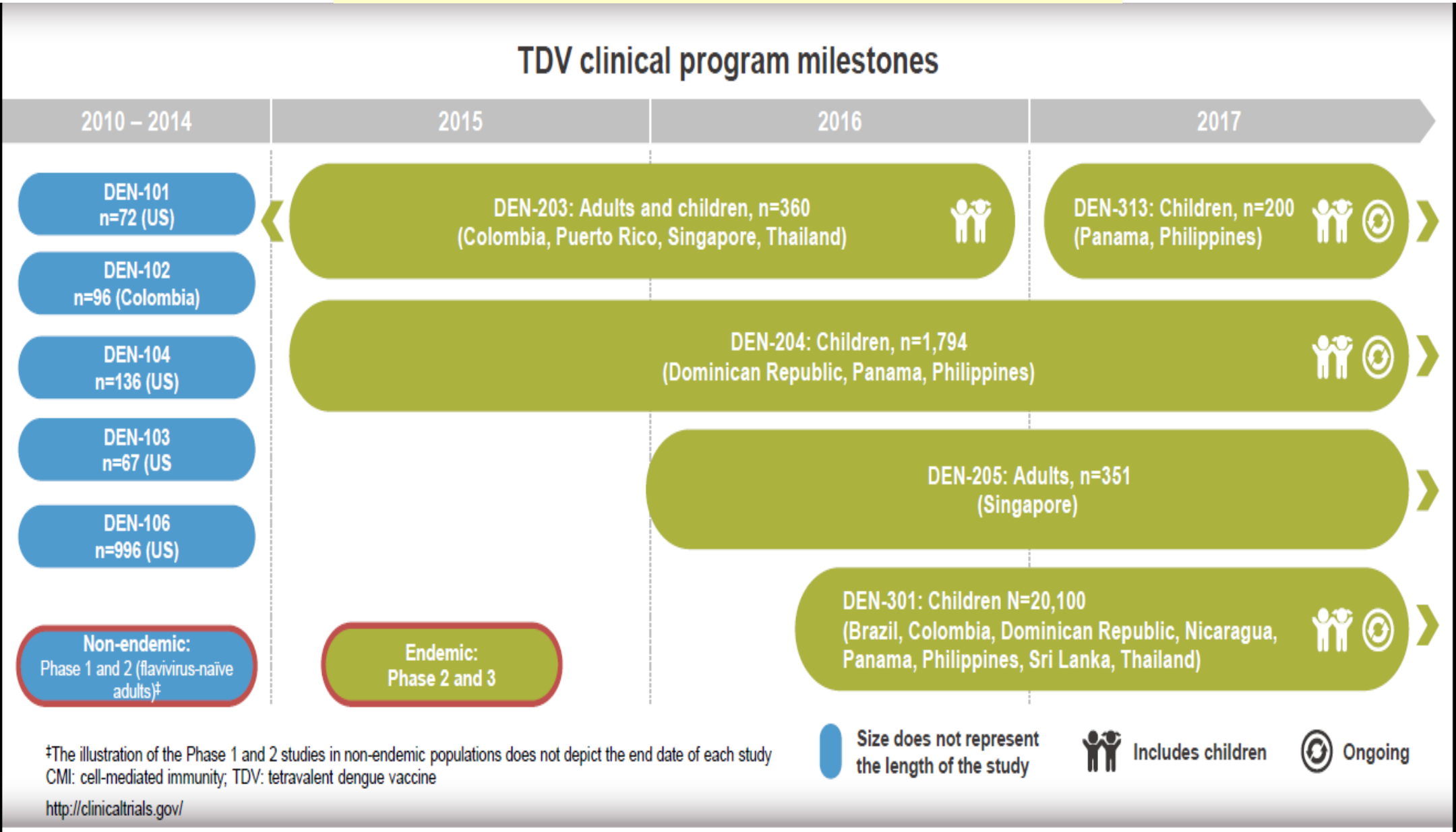
* unpublished data from dengue cases in dengue cohort in Ratchaburi, 2005-6

TDV

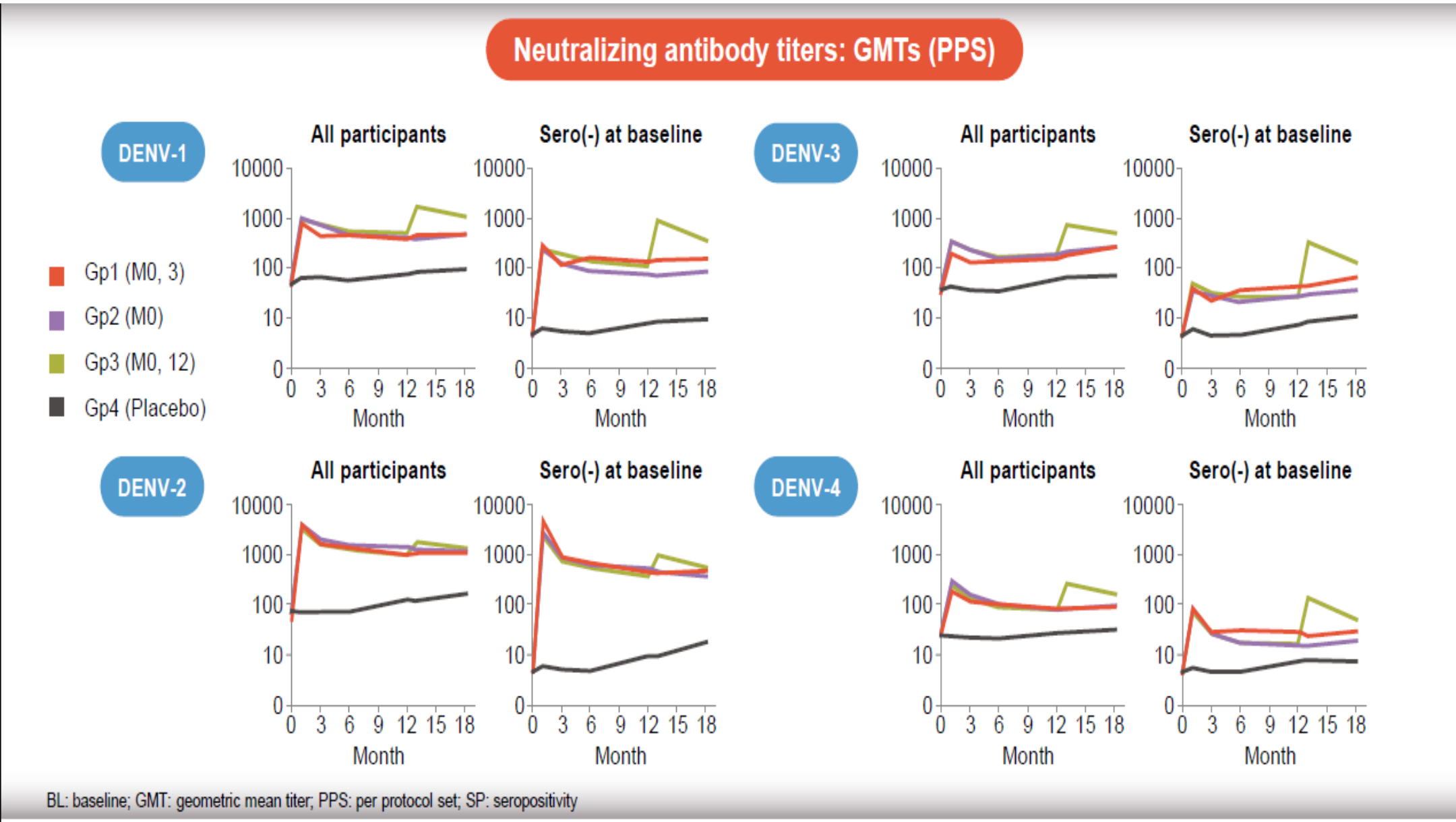
- Developed by Takeda (Inviragen)
- Using DEN-2 (16681) PDK 53 as a backbone and replaces genes encoding pre-membrane and envelope protein with genes from DEN-1, DEN-3 and DEN-4.
- Major difference from CYD vaccine: the core and other non-structural proteins are of DEN-2, not yellow fever



TDV

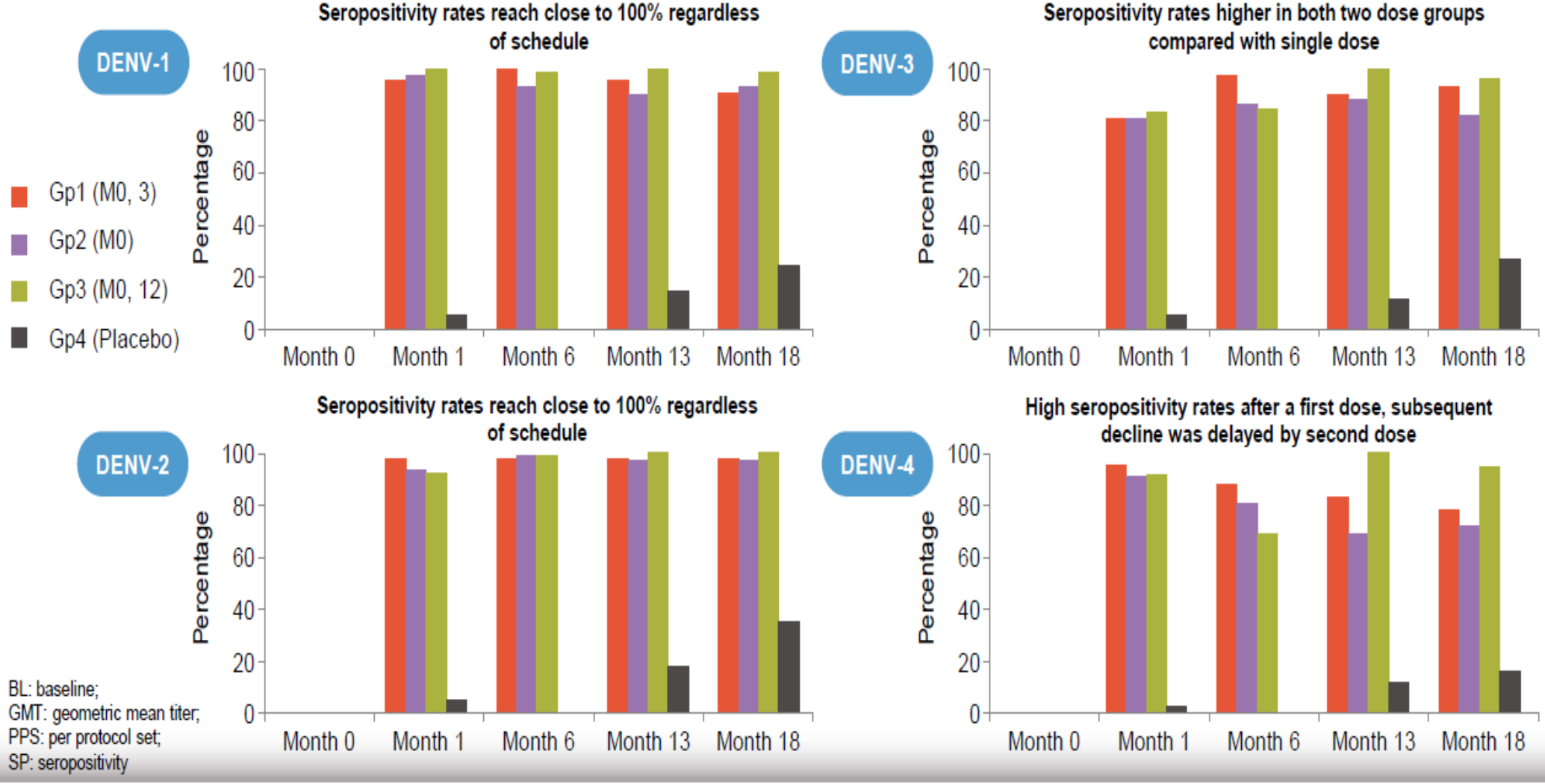

TDV clinical program milestones
2010 – 2014
2015
2016
2017
DEN-101
n=72 (US)
DEN-102
n=96 (Colombia)
DEN-104
n=136 (US)
DEN-103
n=67 (US
DEN-106
n=996 (US)
DEN-203: Adults and children, n=360
(Colombia, Puerto Rico, Singapore, Thailand)
DEN-313: Children, n=200
(Panama, Philippines)
DEN-204: Children, n=1,794
(Dominican Republic, Panama, Philippines)
DEN-205: Adults, n=351
(Singapore)
DEN-301: Children N=20,100
(Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Sri Lanka, Thailand)
Non-endemic:
Phase 1 and 2 (flavivirus-naïve adults)‡
Endemic:
Phase 2 and 3
‡The illustration of the Phase 1 and 2 studies in non-endemic populations does not depict the end date of each study
CMI: cell-mediated immunity; TDV: tetravalent dengue vaccine
http://clinicaltrials.gov/
Size does not represent the length of the study
Includes children
Ongoing

TDV


Neutralizing antibody titers: GMTs (PPS)
DENV-1
DENV-2
DENV-3
DENV-4
All participants
Sero(-) at baseline
Gp1 (M0, 3)
Gp2 (M0)
Gp3 (M0, 12)
Gp4 (Placebo)
10000
1000
100
10
0
0 3 6 9 12 15 18
Month
BL: baseline; GMT: geometric mean titer; PPS: per protocol set; SP: seropositivity

TDV

Seropositivity rates among participants seronegative at baseline (PPS)



BL: baseline;
GMT: geometric mean titer;
PPS: per protocol set;
SP: seropositivity

TDV

Incidence of symptomatic dengue in TDV vaccinee VS placebo recipient during 18 months surveillance in Phase 2 study in children aged 2-17 years (Xavier Sáez-Llorens et al., 2017)

Incidence:

	Group 1 (M0,3)	Group 2 (M0)	Group 3 (M0,12)	Group 4 Placebo	Total
	N=200	N=398	N=998	N=198	N=1794
N febrile episodes evaluated	102	199	451	109	861
N virologically confirmed dengue cases (%)	**4** (2%)	**3** (0.8%)	**14** (1.4%)	**9** (4.6%)	**30**
	21 (1.3%)				

Relative risk:

TDV Rate (%)	Placebo Rate (%)	Relative risk of dengue in vaccinees (95% CI)
1.3%	4.6%	0.29 (0.13 – 0.72)

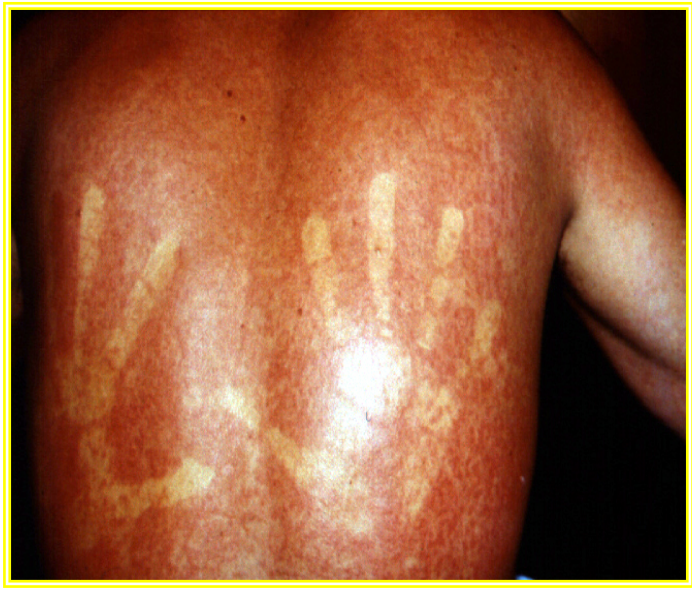
Severity:

No increase in severity of dengue cases in vaccinees versus control participants (no severe dengue)

Gene Deletion Vaccine

- Developed by Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases
- Use reverse genetic and recombinant DNA technology
- Deletion of 30 nucleotides at the position 172-143 from 3' untranslated region could well attenuate DEN-1 and DEN-4
- Chimeric recombination for DEN-2 (so-called rDEN2/4Δ30)
- Additional deletion of 31 nucleotides at the position 258-228 (so-called rDEN-3Δ30/31) for DEN-3

Gene Deletion Vaccine



- TV003 (comprising rDEN-1Δ30, rDEN-2/4Δ30, rDEN-3Δ30/31, and rDEN-4Δ30; 3log10PFU for each serotype)
- TV005 (comprising 3log10PFU for each rDEN-1Δ30, rDEN-3Δ30/31, and rDEN-4Δ30; and 4log10PFU for rDEN-2/4Δ30
- Phase 2 clinical trial on DEN-4Δ30: vaccine was safe but caused asymptomatic rash (65%), mild neutropenia (20-25%) and vaccine viremia (52%) (Durbin et al., 2005), leading to changing amino acid at the codons 200 and 201 of NS5 from Lys-His to Ala-Ala (DEN-4Δ30-200,201). Replacement of DEN-4Δ30-200,201 in TV003 is TV004.
- A phase 2 clinical trial in adults: TV003 caused few asymptomatic maculopapular rash and vaccine viremia in 79% and 71% of vaccine recipients, respectively. Vaccine viremia were form DEN-3 (63%), DEN-1 (21%), DEN-4 (17%), and DEN-2 (4%) (Kirkpatrick et al., 2016). A phase 3 study is ongoing.

Whole-virus Inactivated Vaccine

- Developed by GSK/FIOCRUZ
- Simple in production but the difficulty is viral culture
- Need potent adjuvant
- Study in monkey revealed that, after vaccination and challenge, monkey had no viremia but genetic material was still detectable (Robert Putnak et al., 2005).
- Phase 1 clinical trial of 2 doses (2.5 or 5 µg/dose) of purified inactivated DEN-1 vaccine with aluminum hydroxide administered on day 0 and 28 : vaccine was safe and was able to induce neutralizing antibody in dengue naïve people aged 18-50 years (Martinez et al., 2015).

Subunit Vaccine

- At least 3 vaccine:
  - recombinant subunit protein containing 80% of envelope protein from N-terminal portion (r80E)
  - consensus dengue envelope protein domain III (cED III)
  - recombinant lipidated envelope glycoprotein domain III
- r80E with ISCOMATRIX™ adjuvant can induced a potent viral neutralizing antibody as well as memory response (Clements et al., 2010).
- r80E from DEN-2 with AS05 or AS08, given 3 months apart in rhesus monkeys found that the monkeys had no dengue viremia but dengue genomes were still detectable after challenge (Robert Putnak et al., 2005) .
- In human phase 1 study, it was immunogenic and well tolerated (Manoff et al., 2015).

DNA Vaccine

- Developed by inserting genes encoding target protein (i.e. envelope protein for dengue vaccine) into vector virus (e.g. adenovirus, measles virus)
- Advantage: high producibility, stability in room temperature, induce both humoral and cell-mediated immunity, no interference among serotypes
- Disadvantage: poor immune response
- A three-dose tetravalent DNA vaccine using a pCMVkan expression vector injected via intramuscular electroporation : vaccine was able to induce neutralizing antibody in mice (Prompetchara et al., 2014).