SAGE deliberations on CYD-TDV ("Dengvaxia®")

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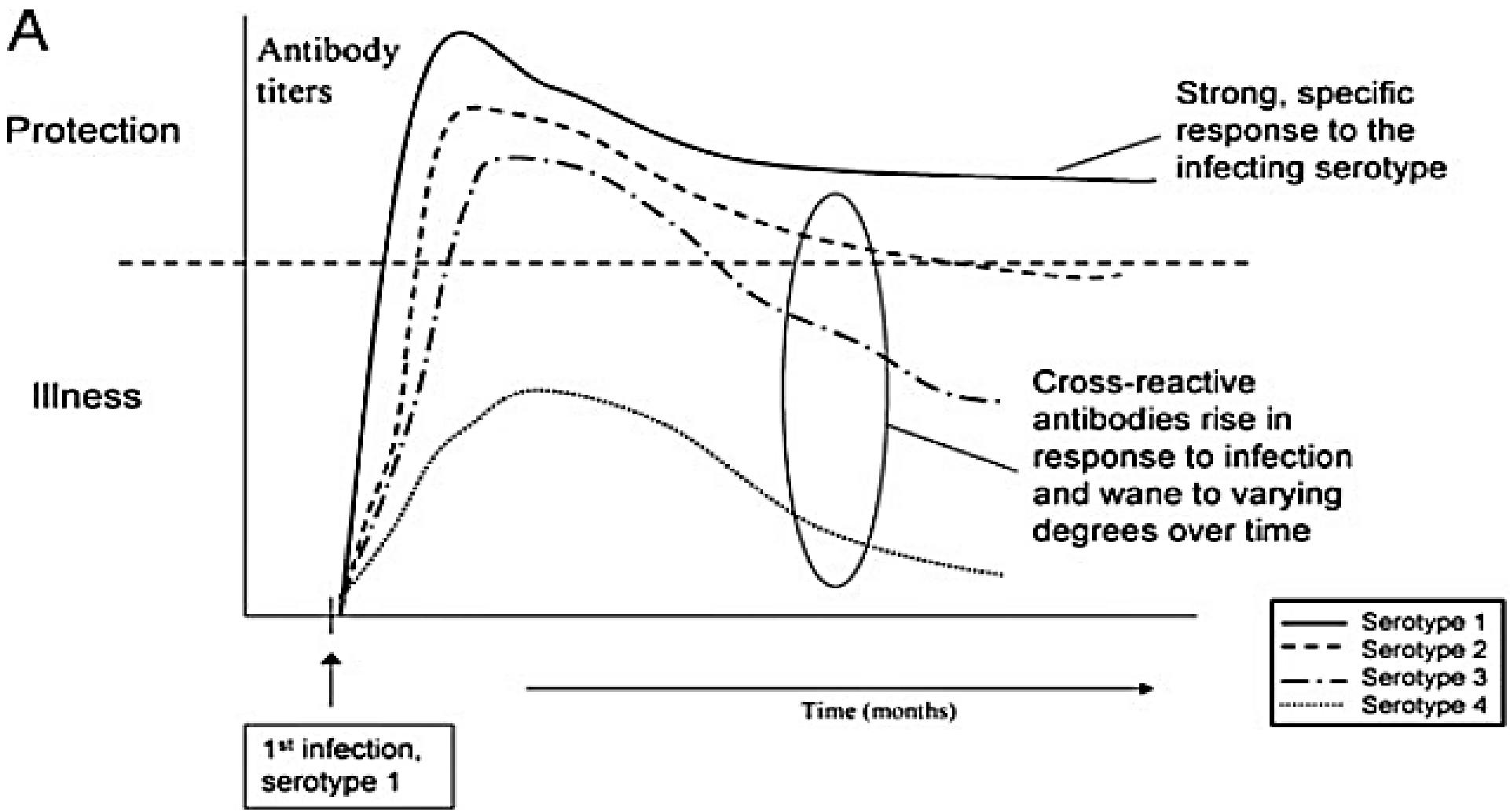
Homotypic and heterotypic antibodies



Anderson et al, A Shorter Time Interval Between First and Second Dengue Infections Is Associated With Protection From Clinical Illness in a School-based Cohort in Thailand. J Inf Dis. 2014

Phase II randomized controlled trial in Singapore

Yee Sin Leo,[1] Annelies Wilder-Smith,[2,3] Sophia Archuleta,[2,3] Lynette P. Shek,[4] Chia Yin Chong,[5] Hoe Nam Leong,[6] Chian Yong Low,[6] May-Lin Helen Oh,[7] Alain Bouckenooghe,[8] T. Anh Wartel[8,*] and Denis Crevat[10]

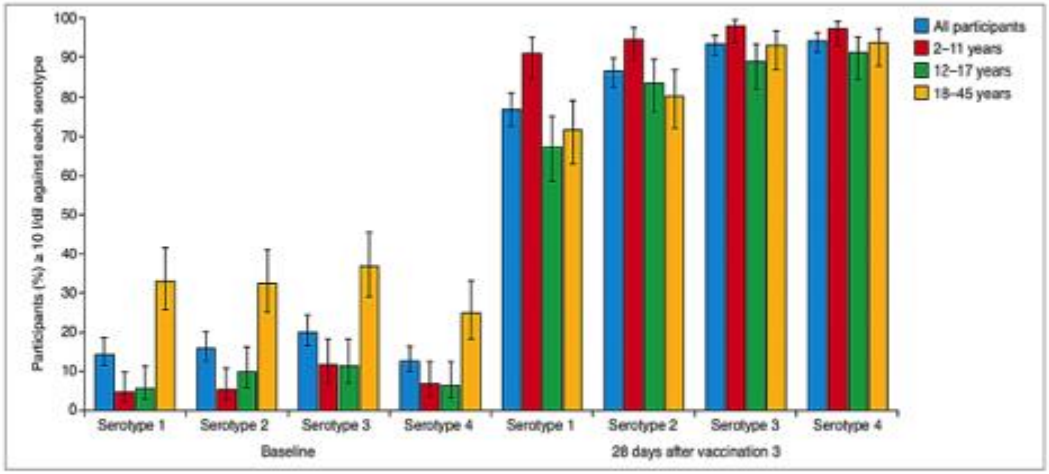


Figure 3. Seropositivity rates (percentage of participants $PRNT_{50}$ titer ≥ 10 1/dil) against each of the four dengue virus serotypes (1, 2, 3 and 4) at baseline and 28 d after the third vaccination in all participants and in each of the three age groups.

- **Vaccine efficacy varied by :**
  - **Serotype**
  - **Serostatus**
  - **Severity of disease**
  - **Age**

NEJM 2015

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,

So what data drove the SAGE 2016 decisions?

VE against Symptomatic, Severe and Hospitalized Dengue (ITT) (M0-M25)

Outcome	Cases in Vaccine group (n)	Cases in Placebo group (n)	Pooled (2-16 years)	Pooled (9-16 years)
Symptomatic VCD	563	694	**60.3%** (55.7-64.5)	**65.6%** (60.7-69.9)
Hospitalized VCD	57	104 (15%)	**72.7%** (62.3-80.3)	**80.8%** (70.1-87.7)
Severe VCD	13	31 (4.5%)	**79.1%** (60.0-89.0)	**93.2%** (77.3-98.0)

Longer-term Follow Up for Hospitalized Dengue: 2-5 year age group

	CYD14 (2-5 years)		
Time Period (Follow up)	**CYD group cases**	**Control group cases**	**RR (95%CI)**
Year 1 (Active)	8	6	**0.64** (0.20-2.32)
Year 2 (Active)	9	7	**0.64** (0.21-2.02)
Year 3 (Hospital)	15	1	**7.45** **(1.15-313.80)**
Year 4 (Hospital)	20	7	**1.42** (0.58-3.99)
Year 5 (Hospital/SEP)	6	2	**1.49** (0.27-15.15)
Cumulative Years 1-5	*58*	*23*	***1.26*** *(0.76-2.13)*

Seronegatives aged > 9

	CYD vaccine n*	Placebo n*	Vaccine Efficacy, % (95% CI)
≥ 9 years	16	17 (x2)	52.5 (5.9 to 76.1)

- From the immunogenicity subset up to year 4:
- 7/387 (1.8%) hospitalized vaccinees
- 4/204 (2%) hospitalized controls

SAGE GRADE 2= evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome

Insufficient data to determine increased risk in seronegative vaccinees aged 9-16

What recommendation would you have given if you had served on the WHO SAGE in April 2016?

- Unclear whether safety signal in 2-5 years olds was due to age or to a higher proportion of this age group being seronegative at vaccination, or both.
- Finding led Sanofi to seek vaccine licensure from age 9+ years, distant from the age group in which the signal was apparent. No signal in other age groups.
- Modelling of cost-effectiveness of the vaccine suggested most efficient to use when the target population had seroprevalence 70% or greater.
- Question remained as to whether vaccinated seronegatives 9y+ might be at increased risk of severe disease.
- This was highlighted as important unanswered question by both GACVS and SAGE; and Sanofi Pasteur was asked to provide more data in seronegatives

WHO recommendations for settings with seroprevalence > 70%

- Public Health benefit– Vaccine preventable disease incidence, seropositivity drives efficacy; booster by natural infection

- Safety benefit – high proportion of seropositives; seronegatives will have a higher or equal risk of secondary infections through natural exposure than potential vaccine induced secondary-like infections

Critique – Halstead position prior to use

- Known antibody –antibody dependent enhancement of infection (2003)*
- ‘Irrelevance of vaccine safety calculation when a vaccine has potential for immune enhancement’
- Critique of method used to calculate VE**

The Journal of Infectious Diseases
PERSPECTIVE

Critique of World Health Organization Recommendation of a Dengue Vaccine

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(See the correspondence by Halstead on page 2014.)

Keywords. dengue virus; vaccine; dengue vaccine; pathogenesis; antibody dependent enhancement (ADE); safety; vaccine adverse event.

In mid-April 2016, the World Health Organization's (WHO's) Scientific Advisory Group of Experts on Immunization (SAGE) recommended that dengue-endemic countries consider using Sanofi Pasteur's chimeric yellow fever dengue vaccine (Dengvaxia) to immunize individuals aged 9–45 years in populations with high levels of dengue endemicity [1]. Dengvaxia was made by splicing yellow fever virus 17D genes with those of the 4 dengue virus (DENV) serotypes and is administered in 3 doses over 1 year [2]. The WHO's Dengue Vaccine Working Group developed recommendations to the SAGE based on published year 1–3 data from phase 3 clinical trials involving >35 000 children aged 2–16 years in 10 dengue-endemic countries [3–6]. These data were supplemented with unpublished data supplied by the manufacturer from up to 6 years after vaccination [7].

During the first 2 years after immunization, compared with placebo controls, Dengvaxia reduced the prevalence of dengue, mild and severe, by 57%, with a lower efficacy against illnesses caused by DENV-1 and DENV-2, compared with DENV-3 and DENV-4 [3–5]. However, during the third year after vaccination, the protective efficacy dropped to 16.7% (65 cases among 22 177 vaccine recipients vs 39 cases among 11 089 placebo recipients) [6]. An analysis of year 3 breakthrough dengue found the vaccine to be asymmetrically protective and enhancing [8]. In Asian sites, the dengue hospitalization rate was significantly higher among vaccinated children aged ≤5 years (20 of 2029 [0.99%]) than among controls (2 of 1005 [0.2%]), with a relative risk of 4.95 ($P = .03$) [8].

Concerning hospitalizations in seronegative children aged ≥9 years, the SAGE wrote, "There are few data to support or refute any risk in seronegatives >9 years of age. . .. In CYD14 and CYD15, over 70% of the population in this age group was seropositive, and this increased with age up to 16 years. The relative risks were below 1 over time in this age group (consisting of both seropositives and seronegatives)" [7]. Because only 8%–19% of children enrolled in clinical trials underwent blood sampling before receiving the vaccine, complete data based on the serological status at the time of vaccination of all 65 hospitalized children are not available.

In late 2015 and early 2016, Dengvaxia was licensed by the governments of Brazil, Costa Rica, El Salvador, Mexico, Paraguay, and the Philippines, where 1 million doses were purchased for nationwide vaccination of 9 year olds [9–11]. Although the SAGE concluded that Dengvaxia can be safely administered to seronegative individuals aged ≥9 years, several lines of evidence suggest that Dengvaxia, when given to seronegative individuals of any age, permitted hospitalizations due to breakthrough DENV infection during year 3. First, vaccination of seronegative individuals raises enhancing antibodies. Seronegative children composed a substantial portion of the total vaccinated individuals: the median DENV-seronegative prevalence varied from 54.2% among those aged 2–5 years to 21.5% among those aged 9–16 years [12]. These seronegative children responded to ≥1 dose of Dengvaxia by regularly developing DENV-1–4 neutralizing antibodies, although these children were poorly protected against dengue [3–5]. A similar protection outcome was observed in sera from 23 Singaporean adults who provided blood specimens 5 years after having received 3 phase 2 Dengvaxia doses. These individuals, who predominantly were seronegative when vaccinated, had low levels of circulating DENV neutralizing antibodies, which failed to protect mice against DENV-2 challenge [13]. The combination of poor protection against DENV infection of individuals with circulating DENV antibodies (monotypic immune equivalents) satisfies the known preconditions for antibody-dependent enhancement of infection [14].

Second, during year 3, based on serological status and DENV infection rates measured in children in Asian vaccination sites, 20 hospitalized 2–5-year-old children were estimated among 176

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DOI: 10.1093/infdis/jiw340

Scott B. Halstead; Critique of World Health Organization Recommendation of a Dengue Vaccine, The Journal of Infectious Diseases, Volume 214, Issue 12, 15 December 2016, Pages 1793–1795,
*Halstead SB. Neutralization and antibody dependent enhancement of dengue viruses. Adv Virus Res 2003; 60:421–67.
**Scott B. Halstead; Dengue Vaccine Efficacy: Not a Zero Sum Game, The Journal of Infectious Diseases, Volume 214, Issue 12, 15 December 2016, Pages 2014

Status of CYD-TDV

(as of May 2018)

- Licensed by 20 countries
  - Asia, Latin America, Australia
- Indication varies
  - Typically 9-45 years
  - Singapore (12-45 year-olds), Indonesia (9-16 year-olds) and Paraguay (9-60 year-olds)
- Vaccine introduction in public health programmes in two countries
  - **Philippines**: Routine, school-based programme - 4th grade children (9-10 year olds) in highly endemic regions (~1,000,000 children) – programme suspended.
  - **Brazil**: Paraná State – about 500,000 doses in 30 most highly endemic municipalities (28 municip. age 15-27y, 2 municip. age 9-44y.)

Press release from Sanofi, 29 Nov 2017

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.

Proposed Label Update

Based on the new analysis, Sanofi will propose that national regulatory agencies update the prescribing information, known as the label in many countries, requesting that healthcare professionals assess the likelihood of prior dengue infection in an individual before vaccinating. Vaccination should only be recommended when the potential benefits outweigh the potential risks (in countries with high burden of dengue disease). For individuals who have not been previously infected by dengue virus, vaccination should not be recommended.

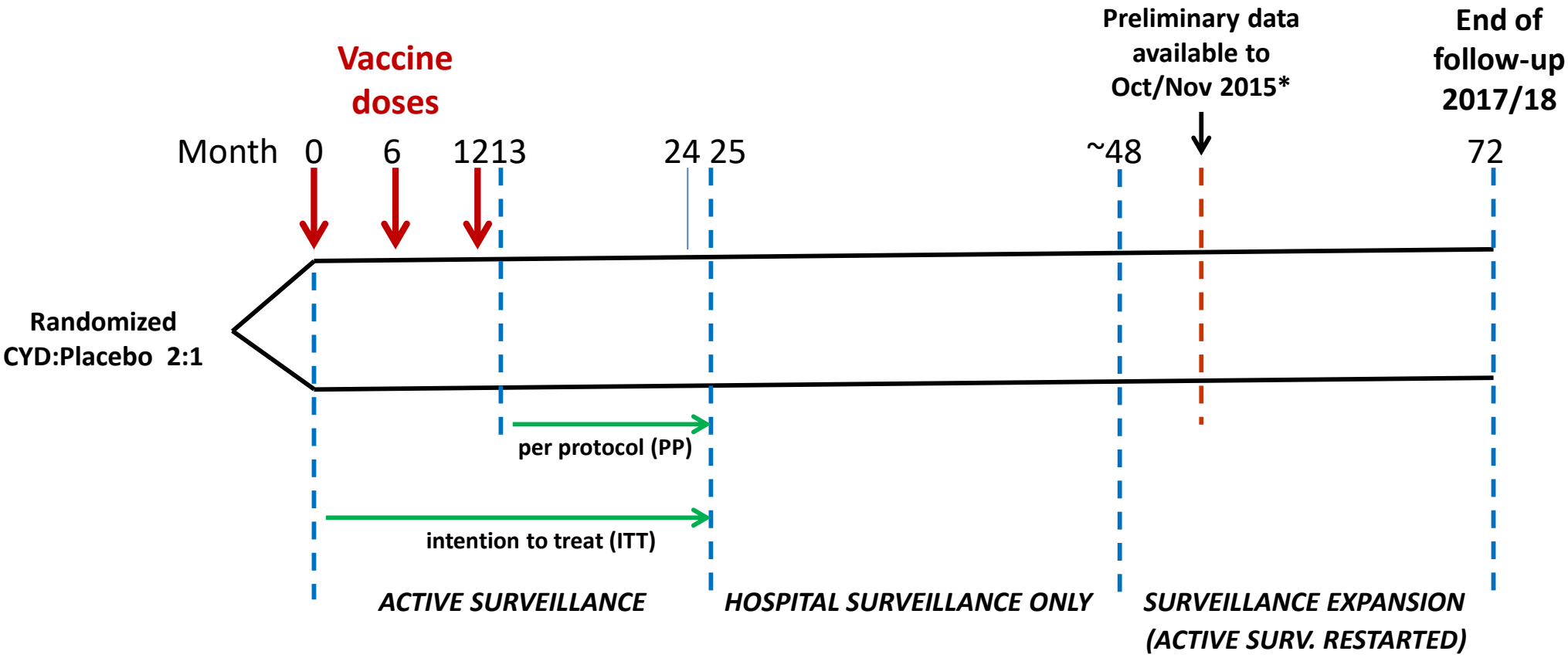
The Sanofi label proposal will be reviewed by national regulatory agencies in each of the countries where the vaccine is registered or under registration. Following their review, each agency might amend the company proposed label.

…analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection.

Proposed label update

…healthcare professionals assess the likelihood of prior dengue infection in an individual before vaccinating. Vaccination should only be recommended when the potential benefits outweigh the potential risks (in countries with high burden of dengue disease). For individuals who have not been previously infected by dengue virus, vaccination should not be recommended.

Study design overview (CYD14 & 15)



Vaccine efficacy against symptomatic VCD in the 25 months after dose 1

(2-16 year-olds - MI method)

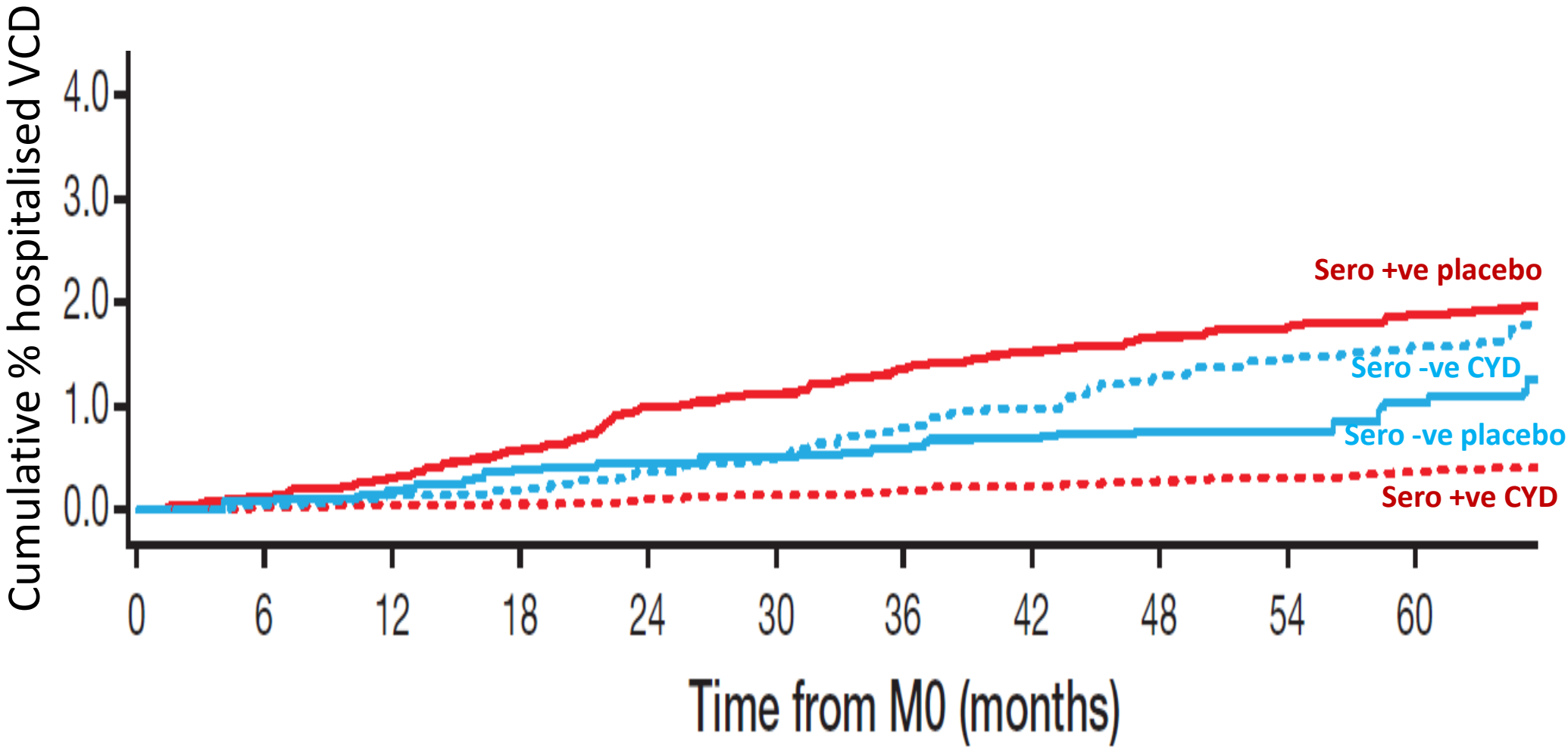
Sero-status at dose 1	Vaccine efficacy	95% confidence interval
Sero-positive	**72%**	58%, 82%
Sero-negative	**32%**	-9%, 58%

Relative risk of severe VCD comparing vaccinated to controls in the 66 months after dose 1

(2-16 year-olds - MI method)

Sero-status at dose 1	Relative risk (CYD:Control)	95% confidence interval
Sero-positive	**0.28**	0.15, 0.52
Sero-negative	**3.00**	1.10, 8.15

Time to hospitalized VCD – MI method - age 9-16 years



Impact for vaccinated subjects over 10 years (direct protection only)

Results for a vaccinated cohort of 1,000,000 vaccinees

Prevented number of hospitalisations over 10 years*

Endemic setting	Hospitalisations		
	Sero+	Sero-	All
90%	6419 [5713;7101]	348 [82;992]	6767 [5795;8093]
80%	6535 [5834;7116]	-7 [-436;612]	6528 [5398;7728]
70%	5611 [5219;6332]	-572 [-874;-287]	5039 [4344;6045]
60%	4303 [3833;5148]	-1484 [-1740;-698]	2820 [2093;4450]
50%	2978 [2724;3181]	-2039 [-2224;-1758]	939 [500;1423]
40%	2243 [2124;2484]	-1904 [-2337;-1314]	340 [-213;1170]
30%	143 [115;219]	-217 [-290;-188]	-74 [-176;31]
20%	74 [43;80]	-231 [-701;-122]	-157 [-658;-42]
10%	9 [6;11]	-57 [-89;-44]	-48 [-83;-33]

Very high

High

Moderate

Low

Very low

Ethical Dilemma

70% seroprevalence:

Every 1 excess case of hospitalized dengue in vaccinated seronegatives would be offset by 7 hospitalized cases prevented in vaccinated seropositives

1 excess severe dengue in vaccinated seronegatives by 4 severe cases prevented in vaccinated seropositives.

85% dengue seroprevalence:

Every 1 excess case of hospitalized dengue in vaccinated seronegatives would be offset by 18 cases prevented in vaccinated seropositive persons

1 excess severe dengue in vaccinated seronegatives by 10 prevented severe cases in vaccinated seropositives

Considerations at SAGE 2018

A number of dimensions:

- Population benefit versus individual risk
- Ethical considerations
- Risk perceptions and communication
- Screening tests versus serosurveys
- Programmatic issues
- Vaccine coverage estimates

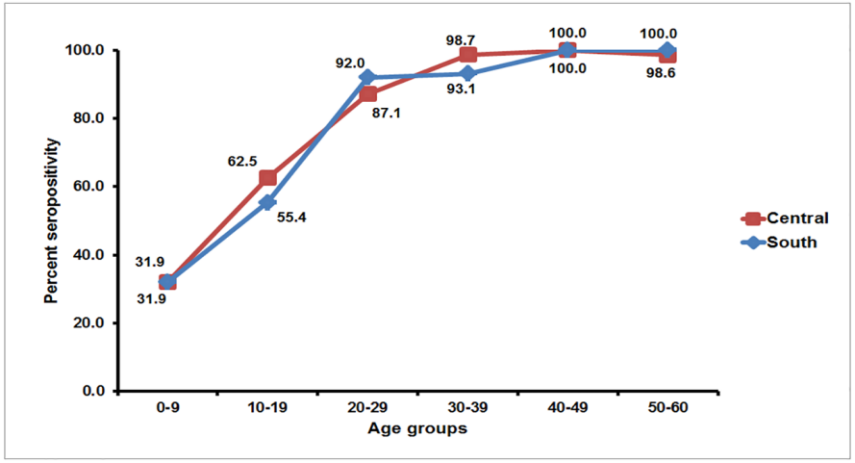
Came down to an evaluation of:

Population Seroprevalence Criteria without Screening	***Pre-Vaccination Screening***

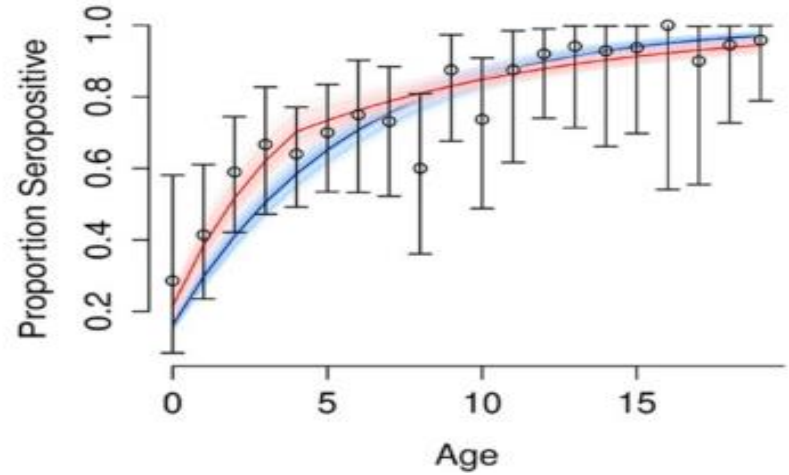
1. Benefits and Harm

Population Seroprevalence Criteria without Screening	*Pre-Vaccination Screening*
BENEFIT Overall substantial population benefit in areas with high seroprevalence predicted.	**BENEFIT** Maximizing the benefit (high efficacy and good safety) in seropositive while avoiding harm in correctly identified seronegatives.
HARM An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.	**HARM** Some seronegative individuals will be put at increased risk of severe dengue if vaccinated due to a false positive screening test result.

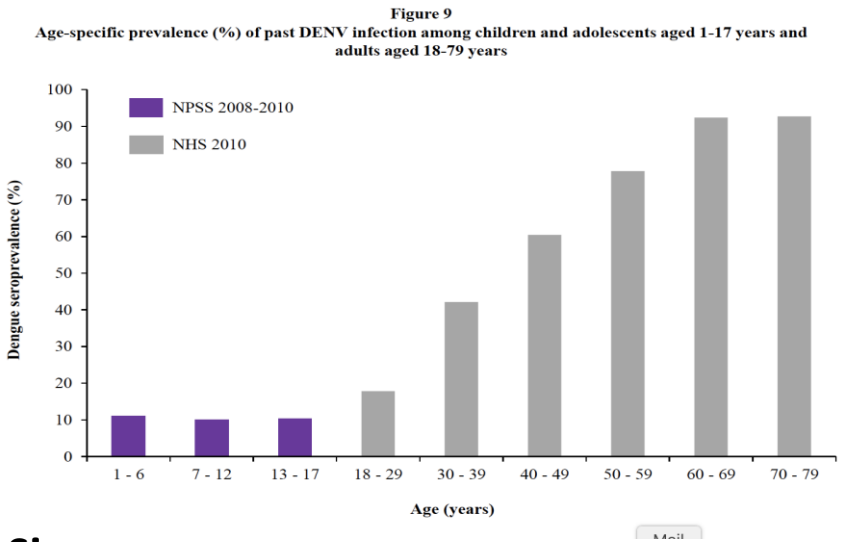
Heterogeneity of seroprevalence between and within countries



Thailand. Vongpunsawad et al. PLoS ONE 2017



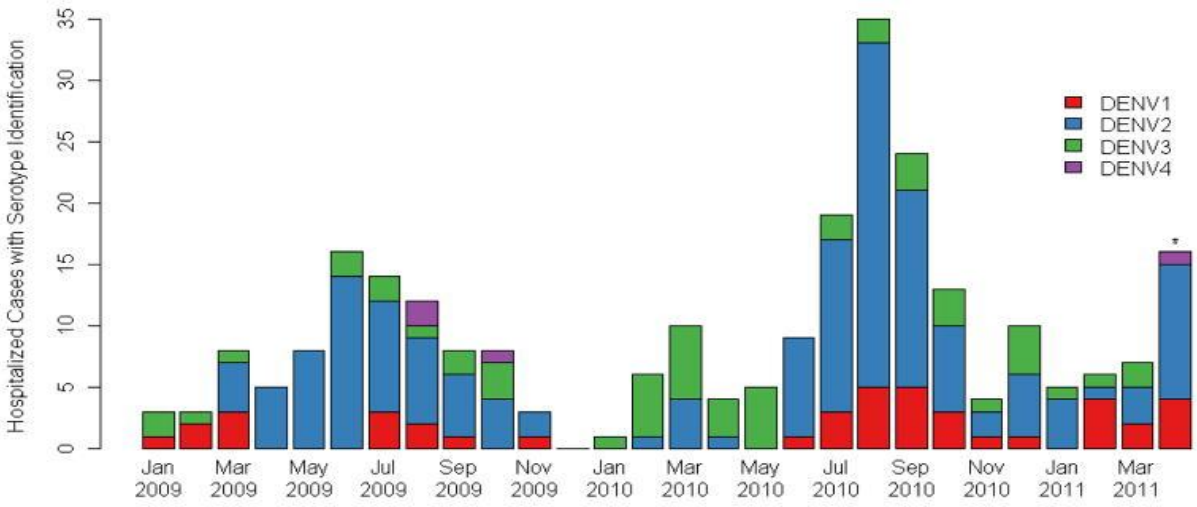
Philippines. L'Azou M, et al.*N Engl J Med* 2016



Singapore Ang et al, Epi News Bulletin 2014

https://mrcdata.dide.ic.ac.uk/_dengue/dengue.php

Temporal and spatial heterogeneity of dengue transmission



- Altstadt et al. **Space-time analysis of dengue in rural Thailand reveals important temporal intervals.** Trop Med Int Health. 2012 Sep; 17(9): 1076–1085.

Spatial heterogeneity at small scale

Salje et al. Dengue diversity across spatial and temporal scales. Science 2017

Yoon et al. Fine scale spatiotemporal clustering of dengue virus transmission in rural Thai villages. PLoS Negl Trop Dis 2012

Spatial heterogeneity dependent on socioeconomic factors, population density, ecological factors:

Kamphaeng Phet, Thailand, school based cohort study:

Seroprevalence differences within 5-10km:
1255 children, aged 9: 67 to 92%.
For all school children: 46 to 94%
(Tim Endy, Katie Anderson, personal communication)

3. Population eligible for vaccination

Population Seroprevalence Criteria without Screening	***Pre-Vaccination Screening***
• Subnational areas with seroprevalence >80% in 9 year olds are predicted by modelling to be rare, those with seroprevalence >90% by the age of 9y very rare.	• Modelling predicts vaccine eligibility will be higher on a population basis compared to the seroprevalence criteria strategy, as all seropositive persons in the population are eligible. • Strategy can be used in both high and moderate transmission settings, although pre-test probability will be higher in high transmission settings.

4. Risk perception

Population Seroprevalence Criteria without Screening	***Pre-Vaccination Screening***
• Loss in vaccine confidence (dengue vaccines and possibly other vaccines). • Inability of vaccinees to know own serostatus may lead to increased vaccine hesitancy.	• Risk of false positive test: seronegative individuals will be misclassified as seropositive and unintentionally vaccinated as no test will be 100% specific.

5. Implementation challenges

Population Seroprevalence Criteria without Screening

- Dengue transmission exhibits a high spatiotemporal heterogeneity. To identify subnational areas with seroprevalence above 80% by age 9 years, multiple small-scale age-stratified seroprevalence studies need to be conducted..
- Providing appropriate information to those eligible for vaccination of the potential risks and benefits will be more challenging than for other vaccines.

Pre-Vaccination Screening

- Pre-vaccination blood sampling may lead to decreased acceptance of the vaccination programme
- No rapid diagnostic test (RDT) has been validated or licensed for the indication of screening for past dengue infection.
- Unlikely that any test will have a 100% specificity, thereby still putting some truly seronegatives at risk.
- Tests with high sensitivity are needed to ensure that a large proportion of seropositives will benefit from CYD-TDV.

6. Population impact

Population Seroprevalence Criteria without Screening	***Pre-Vaccination Screening***
Given that areas with seroprevalence above 80% by age 9y are predicted to be rare, population impact is likely to be low.	Population impact on reduction of hospitalized dengue modelled at approximately 20% over 30 years.

Recommendation

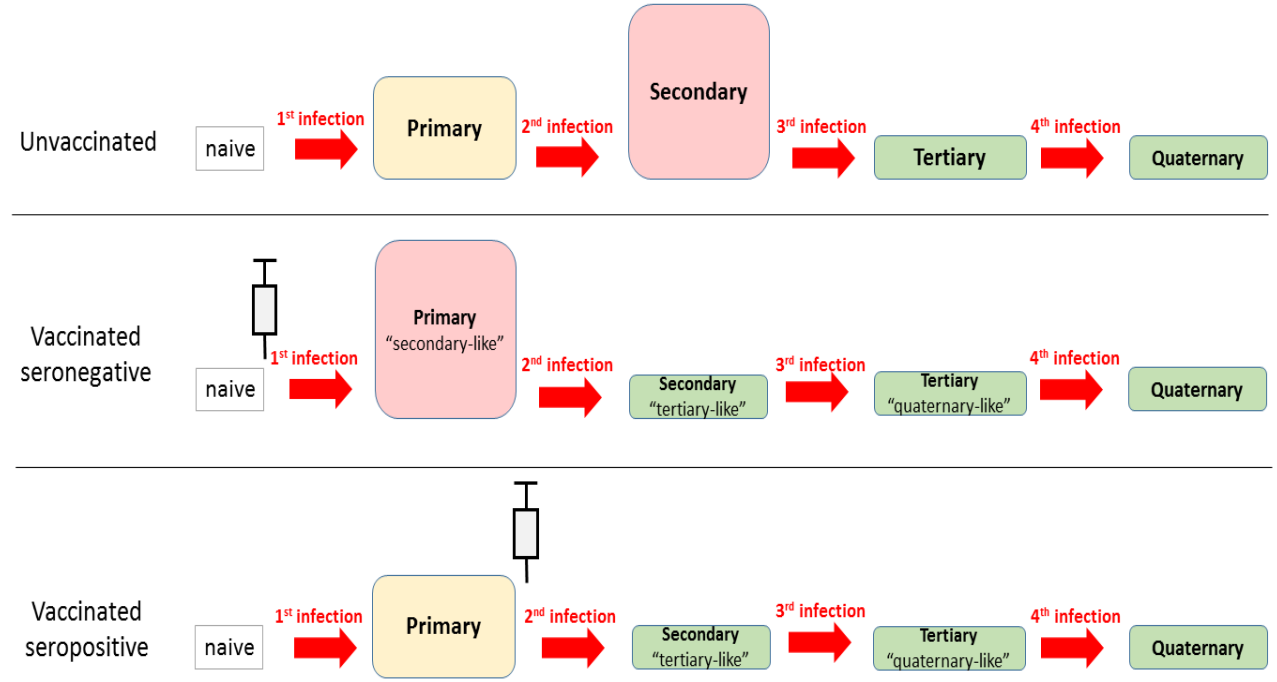
Pre-Vaccination Screening

- For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” would be the preferred option, in which only dengue-seropositive persons are vaccinated

-

Explanatory hypothesis: "Silent infection" mode of action

- Vaccination primes the immune system similarly to infection:
  1. Temporary high degree of cross-immunity in at least seronegative recipients
  2. Seronegative recipients have secondary-like breakthrough infection once cross-immunity wanes
  3. Seropositive recipients have tertiary-like breakthrough infection once cross-immunity wane



Ferguson et al., Science 2016; Flasche et al., PLoS Med. 2016