Dengue Vaccine (CYD-TDV "Dengvaxia®") Recap and Update on Clinical Trial Results

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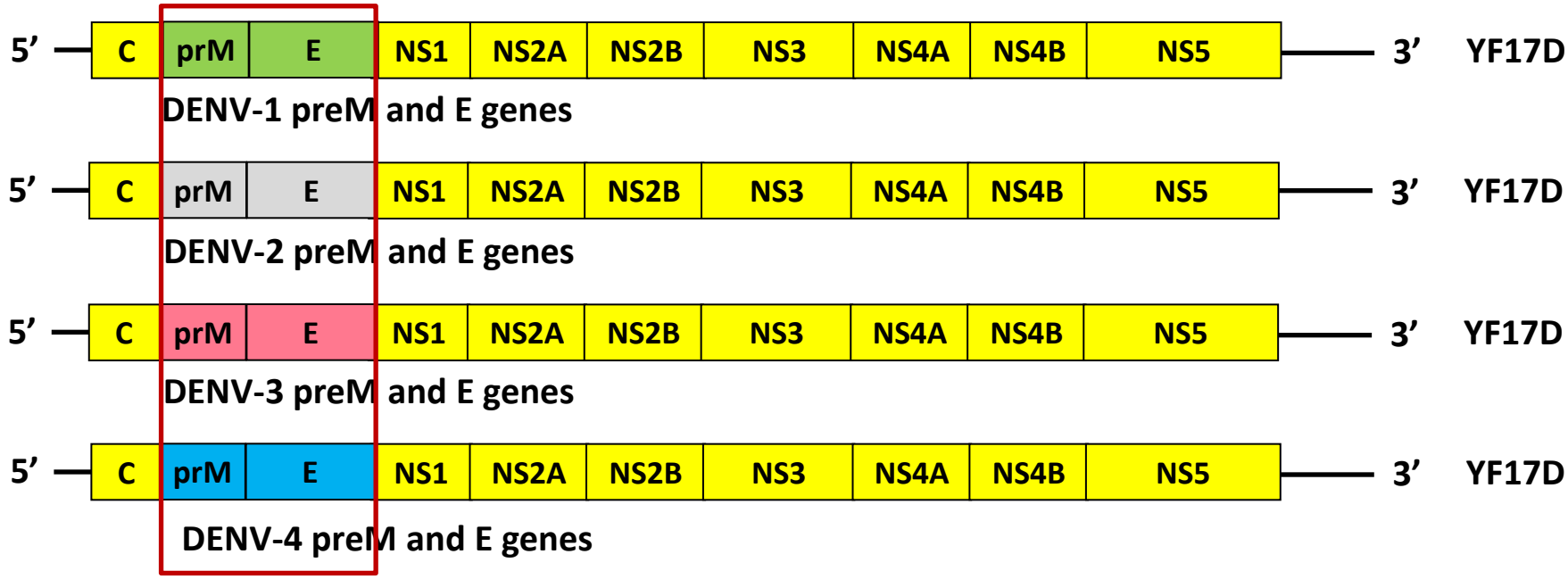
Declaration of interests: PS is member of IDMC for the Sanofi Pasteur dengue vaccine trials

CYD-TDV “Dengvaxia®”

- 17D Yellow fever vaccine backbone
- Pre-membrane (preM) and envelope (E) structural genes replaced with those from each of 4 dengue serotypes (DENV 1-4)
- 3 doses – given at 0, 6, and 12 months



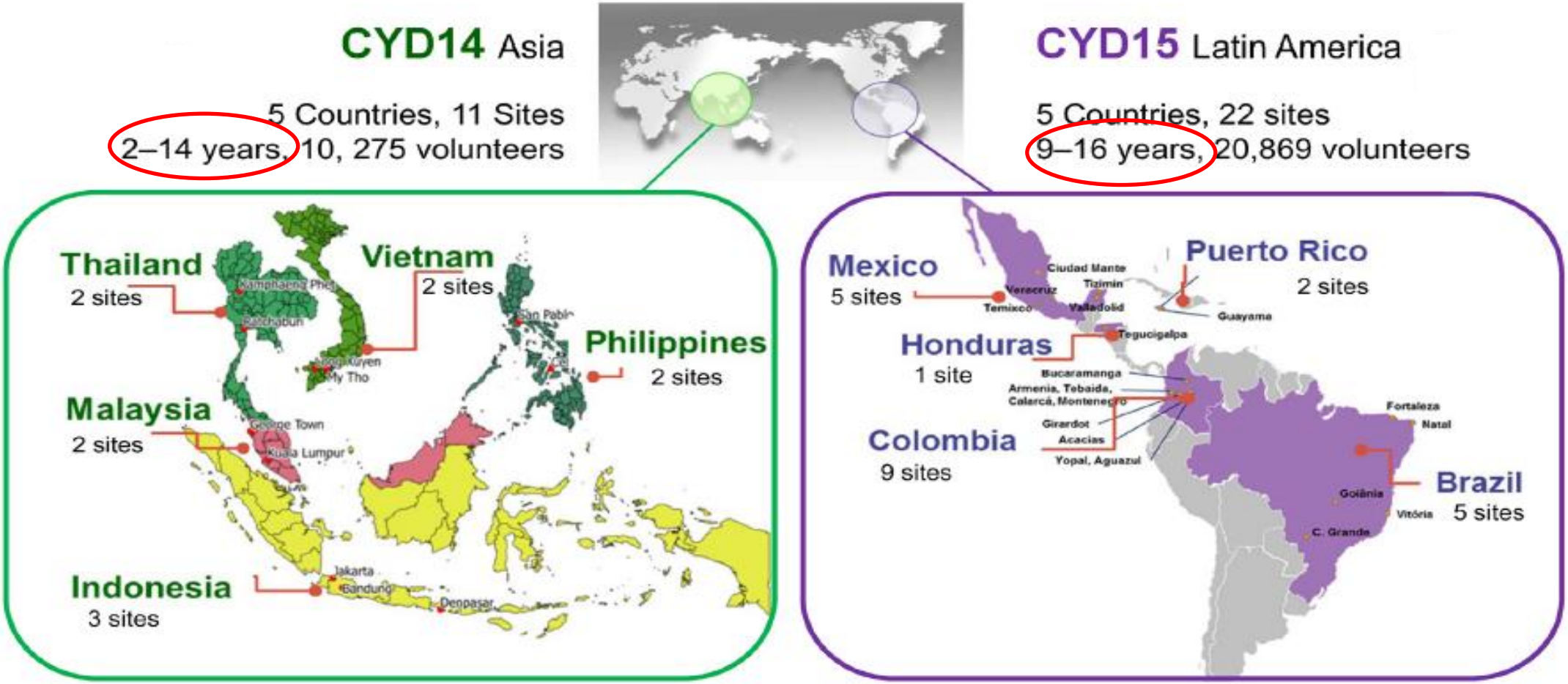
Status of CYD-TDV

(as of March 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.)

Phase 3 Trials of CYD-TDV

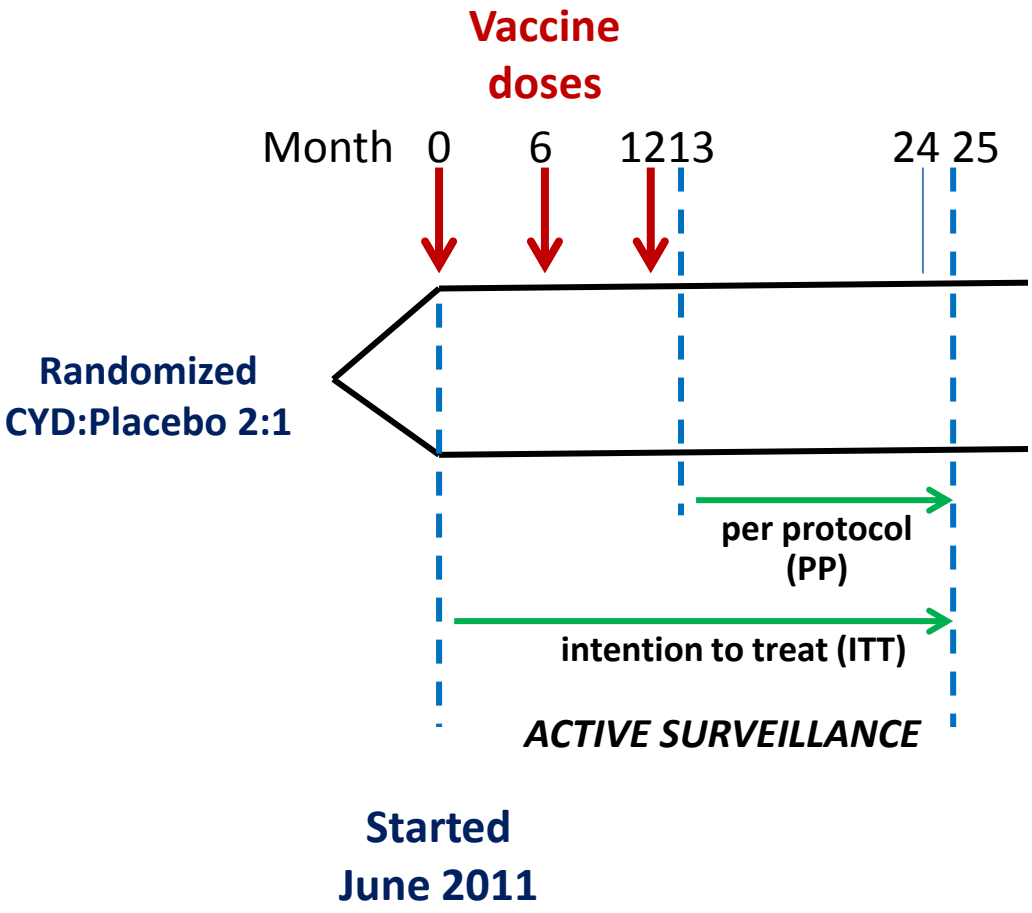
Included >30,000 children aged 2-16 years in 10 endemic countries in Asia and Latin America



Adapted from *Guy (2015)*

Also a previous Phase 2b trial (CYD23/57) with ~4000 participants in Thailand

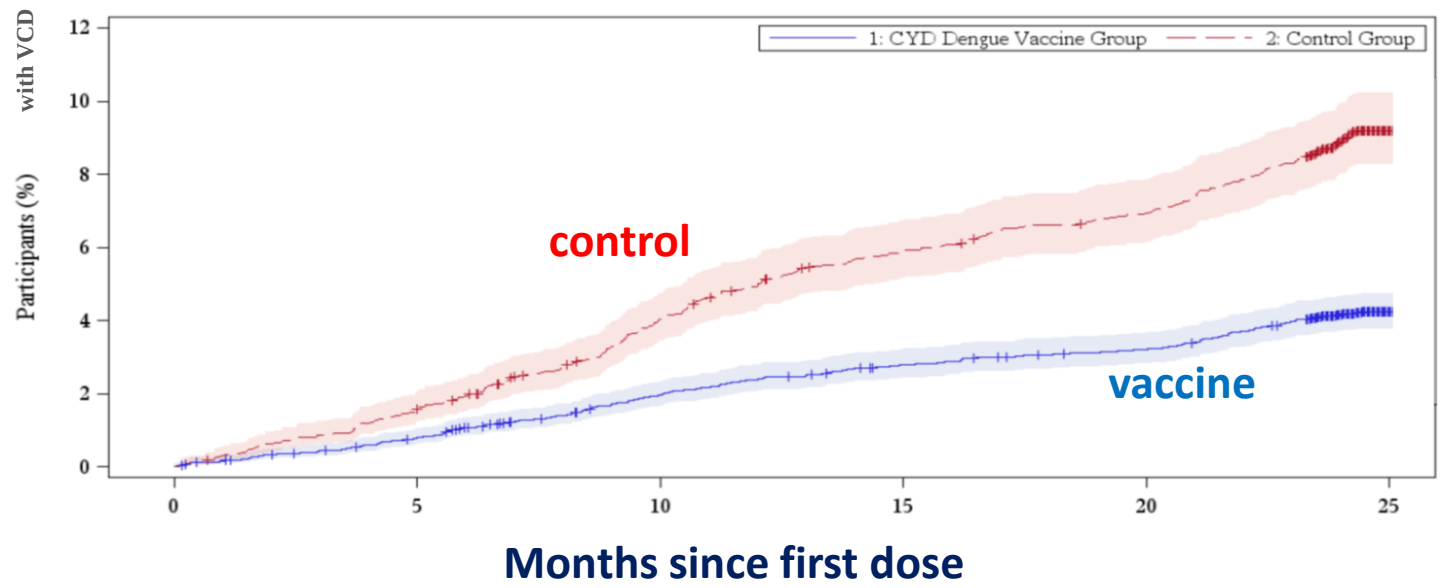
Study design overview (CYD14 & 15)



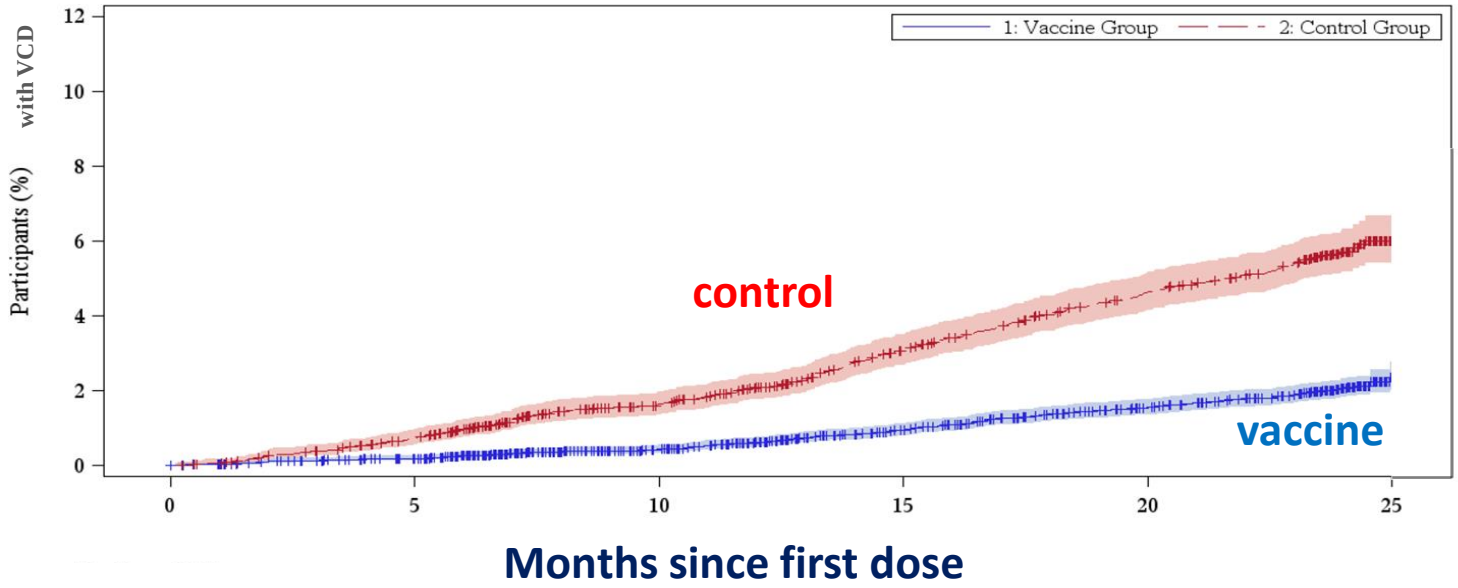
- Only ~13% (~4000) sample had serum sample stored prior to vaccination
- All had serum sample stored at M13, one month after 3rd dose

Virologically confirmed dengue cases in vaccine and placebo arms by time since first vaccination (M0-M25)

CYD14
(2-14 years)



CYD15
(9-16 years)



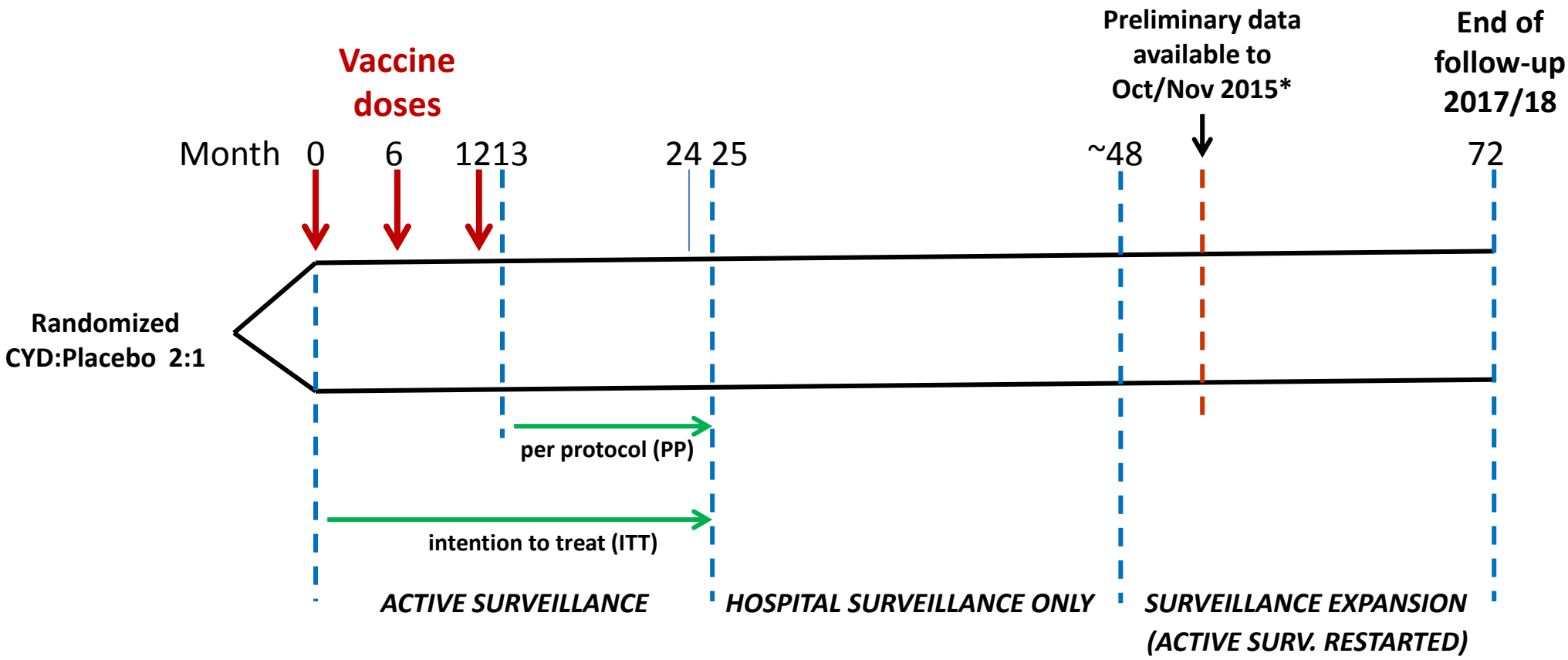
VE against Symptomatic, Severe and Hospitalized Dengue (ITT) (M0-M25)

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)

Vaccine efficacy varied according to:

- **Age:** increased with age
- **Serotype:** higher against serotypes 3 and 4
- **Disease severity:** higher against hospitalised and severe dengue
- **Serostatus at vaccination:** higher in seropositives

Study design overview (CYD14 & 15)



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)*

Longer-term Follow Up for Severe Disease: 2-5 year age group

Age Group	Time Period (follow-up)	CYD14			CYD15
		CYD (n)	Control (n)	RR (95%CI)	
2-5 Years	Year 1-2 (Active)	7	5	**0.697** (0.19-2.79)	**2-5 year-olds not included in trial population**
	Year 3-5 (Hospital/SEP)	13	1	**6.473** (0.97-275.1)	
	Cumulative Years 1-5	*20*	*6*	**1.660** *(0.64-5.05)*	

Note - 2:1 randomisation

VE against symptomatic VCD by serostatus before vaccination (ITT – M0-M25)

Study Population	Cases in Vaccine group (n)	Cases in Placebo group (n)	Pooled (2-16 years)	Pooled (9-16 years)
Seropositive at baseline	26	57	**78.2%** (65.4-86.3)	**81.9%** (67.2-90.0)
Seronegative at baseline	32	27	**38.1%** (-3.4-62.9)	**52.5%** (5.9-76.1)

VE against hospitalised VCD by age and serostatus before vaccination (ITT – full follow-up period)

Age Group	Seropositive at baseline		Seronegative at baseline	
	CYD group (%)	Control group (%)	CYD group (%)	Control group (%)
2-8 years	9/481 (1.9)	11/236 (4.7)	17/330 (5.2)	5/173 (2.9)
9-16 years	7/1546 (0.5)	15/752 (2.0)	7/382 (1.8)	4/204 (2.0)

Pool of CYD14, CYD15, and CYD57. *Includes only subjects from the Full Analysis Set for Immunogenicity

Conclusions and basis for SAGE recommendations

- 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.

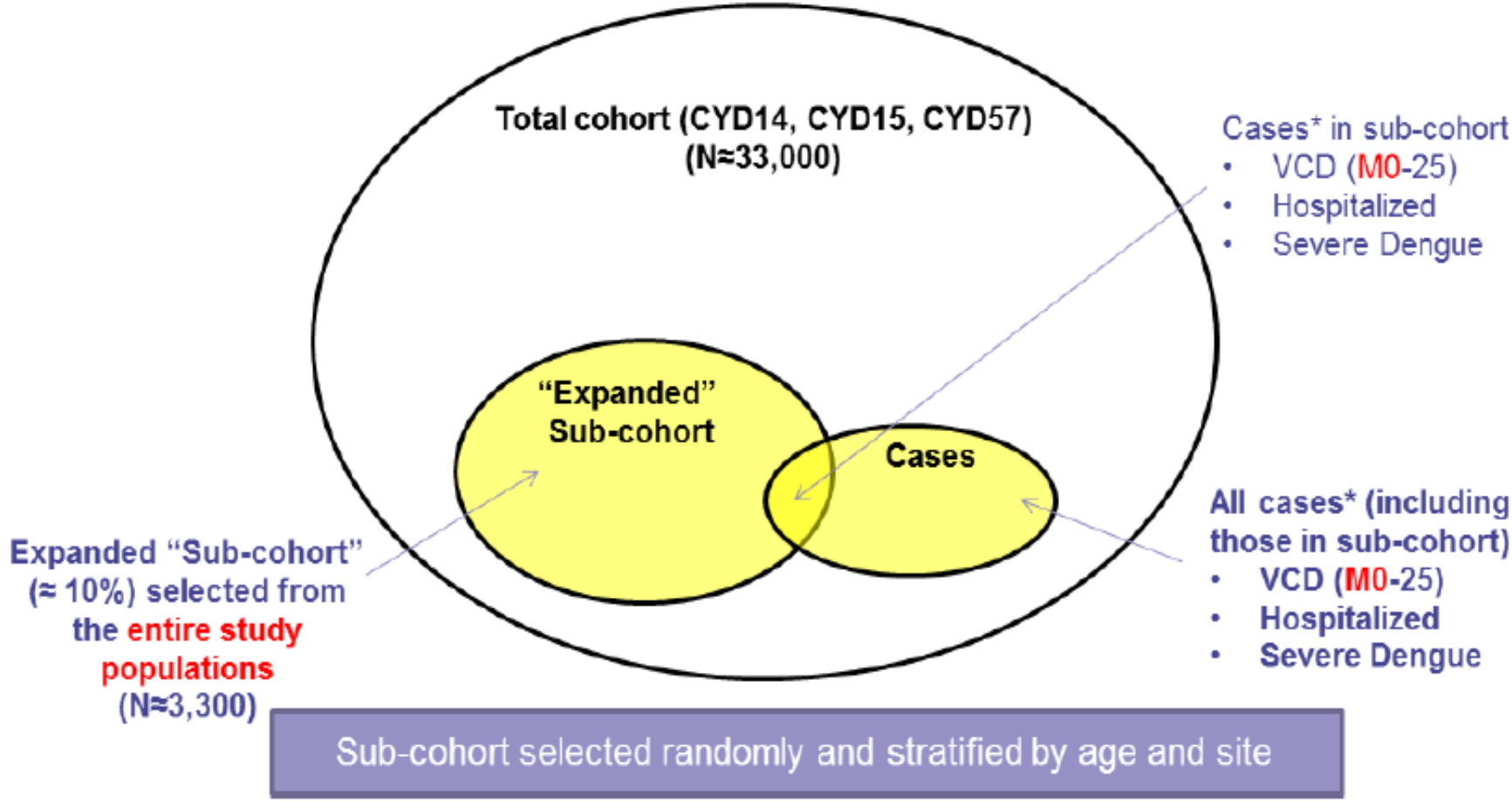
Results from additional analyses conducted since the last SAGE recommendations

- To address the question of the potential risk in seronegatives, Sanofi Pasteur utilised a new assay* on sera collected at month 13 (post-dose 3), which was designed to be able identify those who were seronegative at the time of vaccination (i.e. was not affected by the vaccine).
- Rationale for the assay was that the NS1 protein in Dengue virus is different from the NS1 protein in Yellow Fever virus
- The CYD vaccine has gene encoding NS1 from Yellow Fever.
- The CYD vaccine is unlikely to produce antibodies against the Dengue NS1 protein.
- Thus, the assay can be used to differentiate previous exposure to natural dengue virus from previous CYD vaccination.

* developed in the laboratory of Dr. Ernesto Marques, University of Pittsburgh.

Case-cohort design

Using sub-cohort randomly selected from entire study populations



Three methods of analysis used

Based on:

- From Month 13 onwards:
  - **NS1 assay** at month 13.
- From Month 0 onwards:
  - **Multiple Imputation (MI)** by which PRNT50 results are inferred prior to vaccination using NS1 data and other predictors.
  - **Probability Weighted Targeted Minimum Loss-Based Estimation (TMLE).**

All 3 methods gave similar results, only MI and some NS1 results will be shown

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	**73%**	59%, 82%
Sero-negative	**32%**	-9%, 58%

CYD14+CYD15 pooled data

Relative risk of hospitalised 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	**0.32**	0.23, 0.45
Sero-negative	**1.75**	1.14, 2.70

CYD14+CYD15+CYD23/57 pooled data

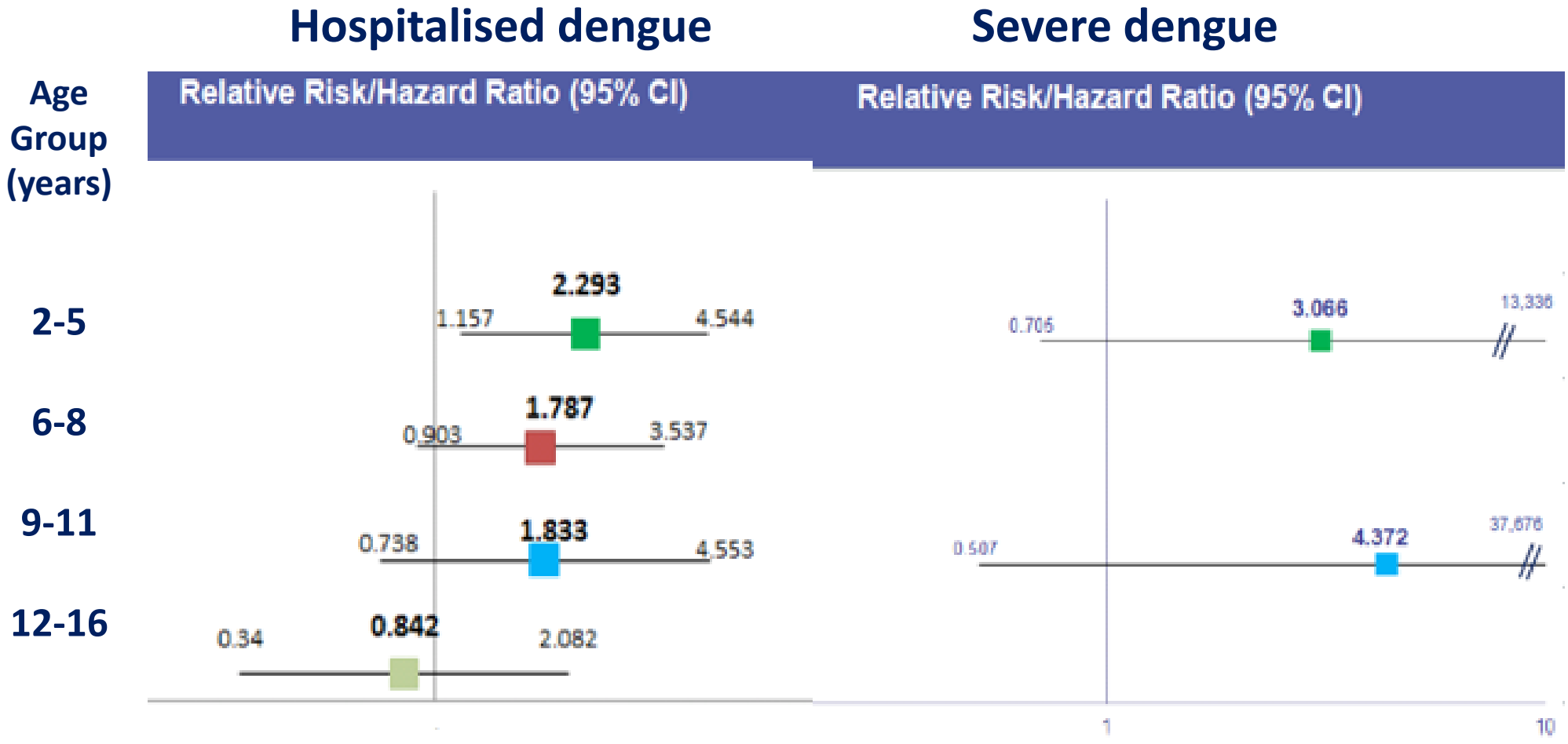
Relative risk of severe VCD comparing vaccinated to controls in the 66 months after dose 1

(2-16 year-olds - MI method)

Sero-status at dose 1	Relative risk (CYD:Control)	95% confidence interval
Sero-positive	**0.31**	0.17, 0.58
Sero-negative	**2.87**	1.09, 7.61

CYD14+CYD15+CYD23/57 pooled data

Relative risk of hospitalised VCD and severe VCD in seronegatives in the 66 months after dose 1, comparing vaccinated to controls (MI method)



CYD14+CYD15+CYD23/57 pooled data

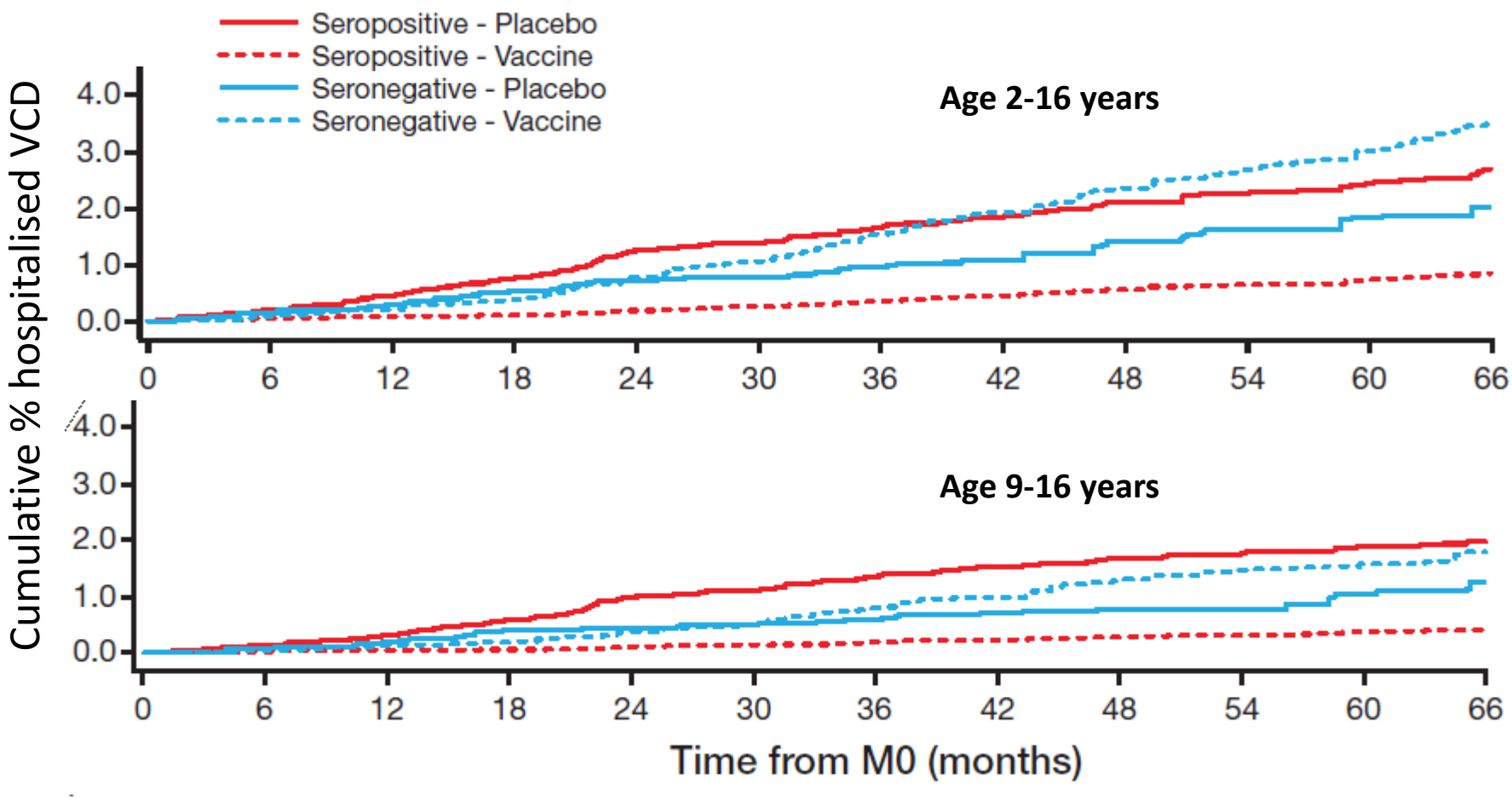
Cases of severe VCD in seronegatives in the 53 months from Month 13 , comparing vaccinated to controls (NS1 method)

Age group (years)	Cases of severe VCD	
	Vaccine	Control
2-5	16	3
6-8	9	1
9-11	10	1
12-16	2	0
Total	**37**	**5**

Note - 2:1 randomisation

CYD14+CYD15+CYD23/57 pooled data

Cumulative risk of hospitalized VCD – MI method



CYD14+CYD15+CYD23/57 pooled data

Benefit-risk assessment

Incidence rates (IRs) and attributable risks (ARs) in <9y and 9+y age groups (MI method)

		Seropositive			Seronegative		
		IR, control group (%)	IR, vaccine group (%)	AR (%)	IR, control group (%)	IR, vaccine group (%)	AR (%)
9+ yrs	Hospitalized	1.883	0.375	-1.508	1.093	1.571	0.4782
	Severe (IDMC)	0.480	0.075	-0.405	0.174	0.404	0.230
< 9 yrs	Hospitalized	5.051	2.430	-2.621	3.345	5.722	2.377
	Severe (IDMC)	1.160	0.614	-0.547	0.364	1.229	0.865

No. of cases prevented in seropositives aged 9+ years for each additional case in seronegatives, in 5 years following vaccination

Seroprevalence	Hospitalised cases	Severe cases
50%	3.15	1.76
70%	7.36	4.11
80%	12.61	7.04