Dengue Vaccine (CYD-TDV "Dengvaxia®") Clinical Trial Results

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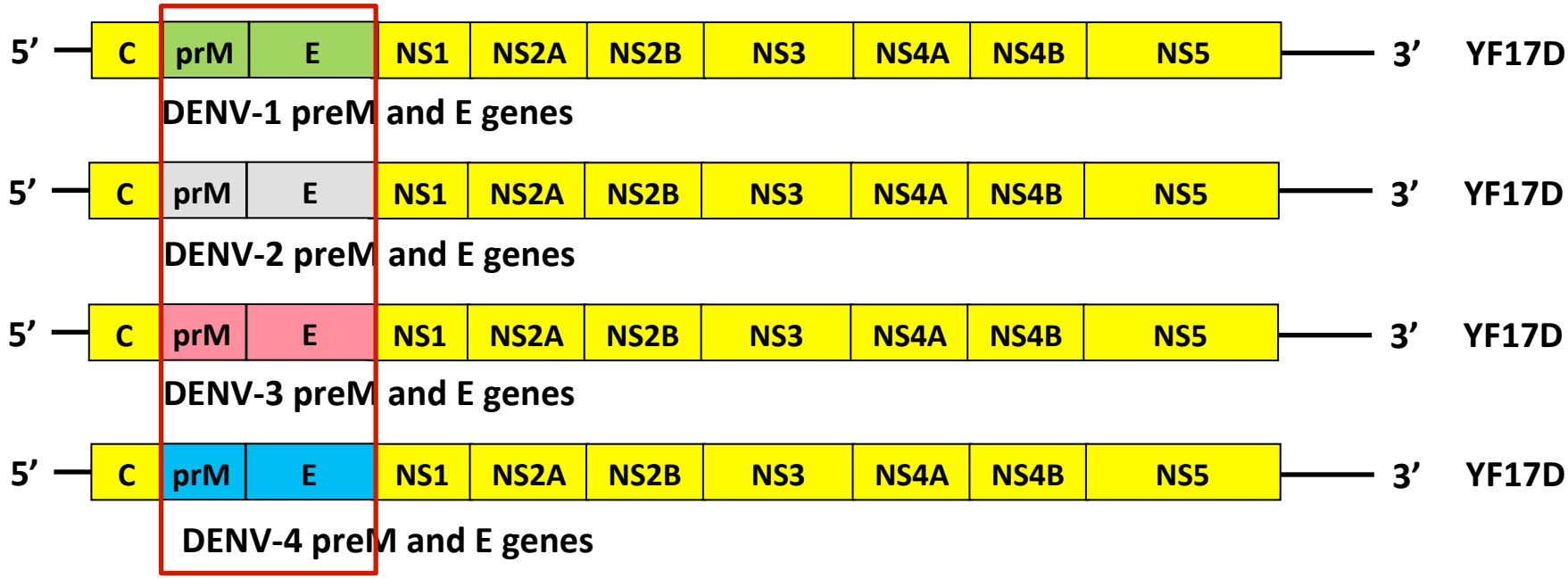
(for Stephen Thomas)

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 (DENV1-4)
- 3 doses – given at 0, 6, and 12 months



Status of CYD-TDV

(as of 4 April 2016)

- Licensed by 5 countries
  - 4 in Latin America (Mexico, Brazil, El Salvador, Paraguay)
  - 1 in Asia (Philippines)
- Indication varies
  - 9-45 years in 4 countries
  - 9-60 years in 1 country (Paraguay)
- Vaccine introduction in one country (Philippines)
  - Routine, school-based program targeting 4th grade children (9-10 year olds) in 3 highly endemic regions (~1,000,000 children)

Clinical Database (Phase 1,2 &3 trials)

		<9 years (not indicated)	9-16 years (indicated)	17-45 years (indicated)	46-60 years (indication varies)
Non-endemic settings	Safety	-	-	638	241
	Immunogenicity	-	-	632	241
	Efficacy	-	-	-	-
Endemic settings	Safety	5,689	19,120	668	-
	Immunogenicity	1,296	2,810	294	-
	Efficacy	5,166	18,262	-	-

Phase 3 Trials of CYD-TDV

CYD14 Asia

5 Countries, 11 Sites
2–14 years, 10, 275 volunteers

CYD15 Latin America

5 Countries, 22 sites
9–16 years, 20,869 volunteers

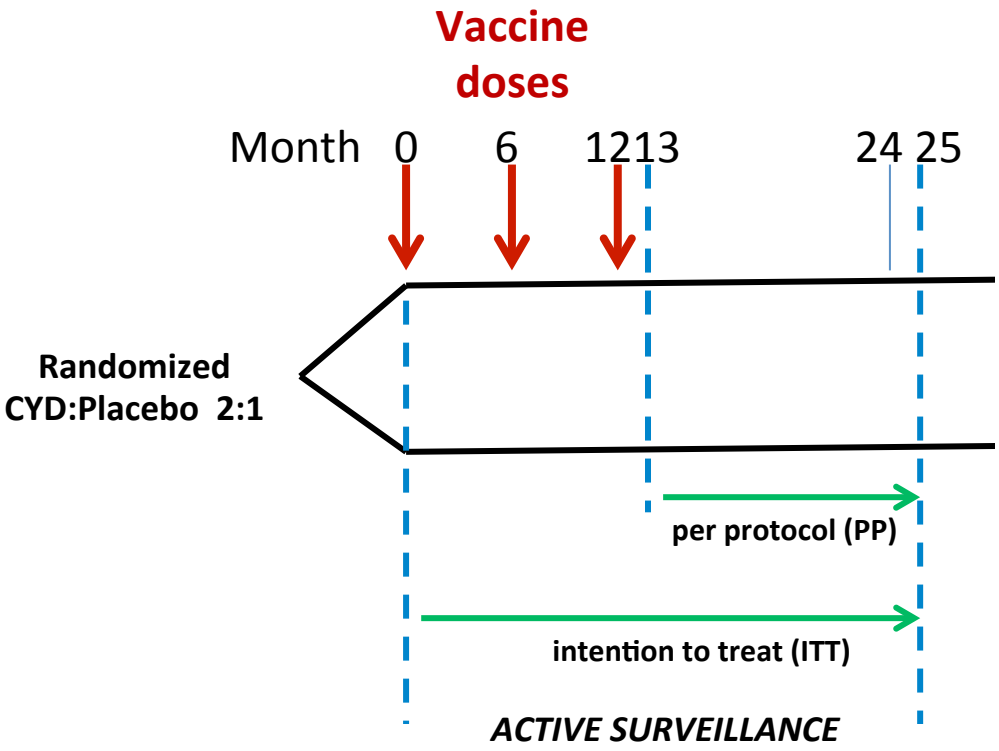
Adapted from *Guy (2015)*

Phase 3 Trials of CYD-TDV

	CYD14 (Asia)	CYD15 (Latin America)
Trial size (Immunogenicity subset)	10,275 (1,983)	20,869 (1,944)
Randomization CYD:Placebo	2:1	2:1
Ages included	2-14 years	9-16 years
Countries participating (no. of participants)	**Indonesia** (1870), **Malaysia** (1401), **Philippines** (3501), **Thailand** (1170), **Vietnam** (2333)	**Brazil** (3548), **Colombia** (9743), **Honduras** (2799), **Mexico** (3464), **Puerto Rico** (1315)
Study start date	June 2011	June 2011
End of Active Phase for primary endpoint	December 2013	April 2014
Estimated end date	November 2017	April 2018

Placebo=0.9% solution of sodium chloride.

Study design overview (CYD14 & 15)



Vaccine Efficacy (VE) measures

- **Primary Endpoint:** symptomatic, virologically-confirmed, dengue, of any severity, due to any of the four serotypes, from 1 month post dose 3 to 13 months post dose 3.
- **Exploratory/secondary analyses of VE:**
  - By serotype
  - By disease severity
  - By age
  - By sero-status prior to vaccination
  - Pooled across trials
- **Post hoc analyses:**
  - VE limited to 9-14 year age group in CYD14
  - Pooled VE from CYD14/CYD15 restricted to the 9-16 year age group

Per-Protocol (PP) Vaccine Efficacy (M13 to M25)

Outcome - Virologically confirmed dengue	CYD14 (2-14 years)	CYD15 (9-16 years)	Pooled (2-16 years)
DENV 1-4	**56.5%** (43.8-66.4)	**60.8%** (52.0-68.0)	**59.2%** (52.3-65.0)
DENV 1	**50.0%** (24.6-66.8)	**50.3%** (29.1-65.2)	**50.2%** (35.6-61.5)
DENV 2	**35.0%** (-9.2, 61.0)	**42.3%** (14.0-61.1)	**39.6%** (18.7-55.2)
DENV 3	**78.4%** (52.9-90.8)	**74.0%** (61.9-82.4)	**74.9%** (65.1-82.0)
DENV 4	**75.3%** (54.5-87.0)	**77.7%** (60.2-88.0)	**76.6%** (65.0-84.4)

Vaccine Efficacy after ≥1 Dose (ITT) (M0-M25)

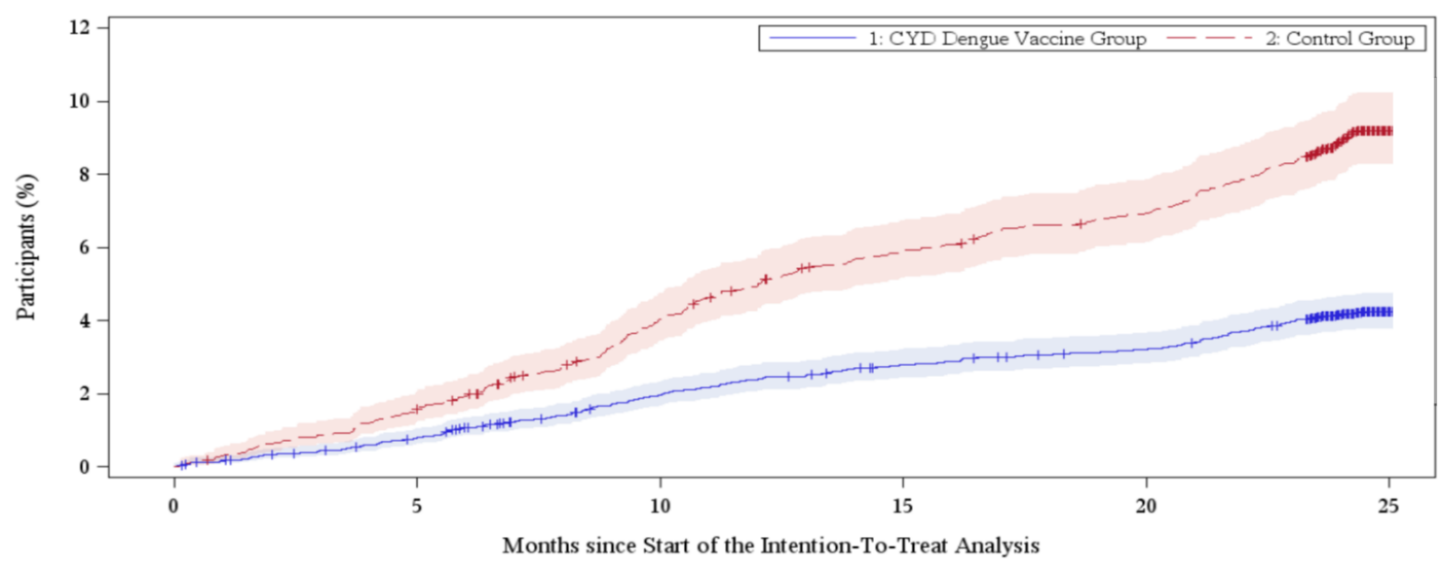
Outcome – Virologically confirmed dengue	CYD14 (2-14 years)	CYD15 (9-16 years)	Pooled (2-16 years)
DENV1-4	**54.8%** (46.8-61.7)	**64.7%** (58.7-69.8)	**60.3%** (55.7-64.5)
DENV 1	**54.5%** (40.9-64.9)	**54.8%** (40.2-65.9)	**54.7%** (45.4-62.3)
DENV 2	**34.7%** (10.4-52.3)	**50.2%** (31.8-63.6)	**43.0%** (29.3-53.9)
DENV 3	**65.2%** (43.3-78.9)	**74.2%** (63.9-81.7)	**71.6%** (63.0-78.3)
DENV 4	**72.4%** (58.5-81.7)	**80.9%** (70.9-87.7)	**76.9%** (69.5-82.6)

Vaccine Efficacy after ≥1 Dose (ITT) (M0-M25)

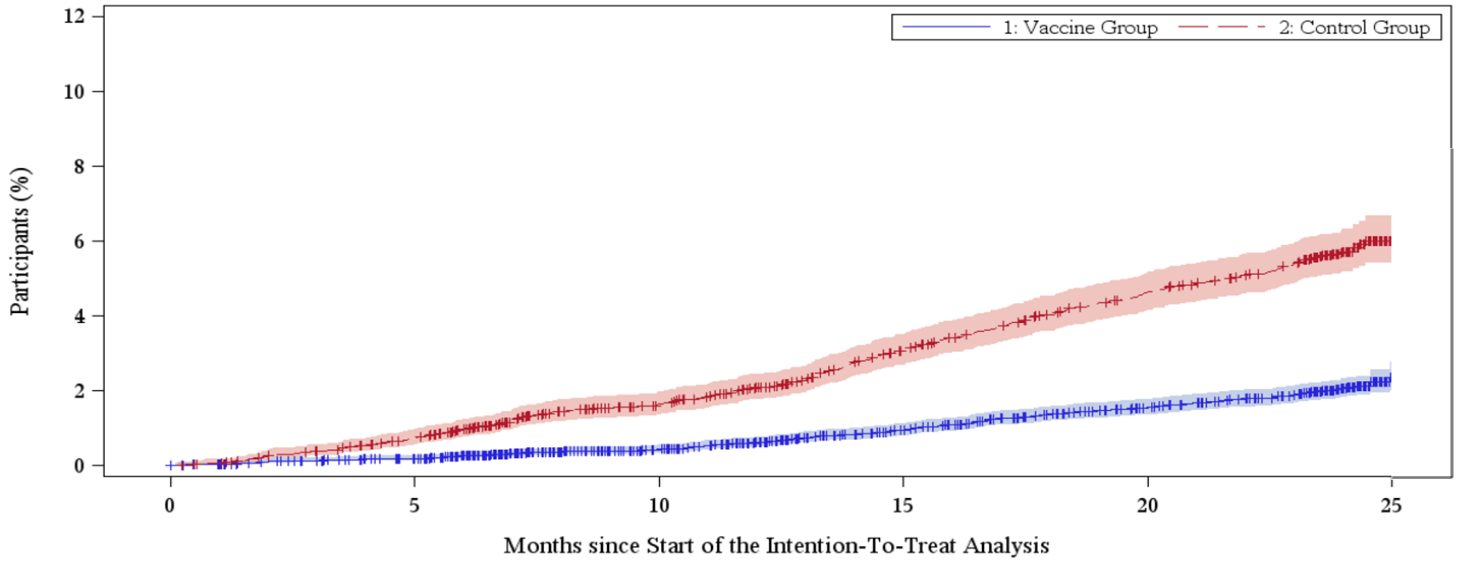
Outcome – Virologically confirmed dengue	CYD14 (2-14 years)	CYD15 (9-16 years)	Pooled (2-16 years)	Pooled (9-16 years)
DENV1-4	**54.8%** (46.8-61.7)	**64.7%** (58.7-69.8)	**60.3%** (55.7-64.5)	**65.6%** (60.7-69.9)
DENV 1	**54.5%** (40.9-64.9)	**54.8%** (40.2-65.9)	**54.7%** (45.4-62.3)	**58.4%** (47.7-66.9)
DENV 2	**34.7%** (10.4-52.3)	**50.2%** (31.8-63.6)	**43.0%** (29.3-53.9)	**47.1%** (31.3-59.2)
DENV 3	**65.2%** (43.3-78.9)	**74.2%** (63.9-81.7)	**71.6%** (63.0-78.3)	**73.6%** (64.4-80.4)
DENV 4	**72.4%** (58.5-81.7)	**80.9%** (70.9-87.7)	**76.9%** (69.5-82.6)	**83.2%** (76.2-88.2)

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 DENV1-4 by serostatus before vaccination (ITT – M0-M25)

Study Population	CYD14 (2-14 years)	CYD15 (9-16 years)	Pooled (2-16 years)	Pooled (9-16 years)
Seropositive at baseline	**74.3%** (53.2-86.3)	**83.7%** (62.2-93.7)	**78.2%** (65.4-86.3)	**81.9%** (67.2-90.0)
Seronegative at baseline	**35.5%** (-27.0-66.6)	**43.2%** (-61.6-80.0)	**38.1%** (-3.4-62.9)	**52.5%** (5.9-76.1)

VE against DENV1-4 by age (ITT – M0-M25)

Study Population	CYD14 (2-14 years)	CYD15 (9-16 years)
All ages	**54.8%** (46.8-61.7)	**64.7%** (58.7-69.8)
2-5 years	**33.7%** (11.7-50.0)	NA
6-11 years	**59.5%** (48.9-68.0)	**61.7%** (52.3-69.3)
12-16 years	**74.4%** (59.2-84.3)	**67.6%** (59.3-74.3)

VE against DENV1-4 by age (ITT – M0-M25)

Study Population	CYD14 (2-14 years)	CYD15 (9-16 years)	% seropositive before vaccination	
			CYD 14	CYD15
All ages	**54.8%** (46.8-61.7)	**64.7%** (58.7-69.8)	68%	79%
2-5 years	**33.7%** (11.7-50.0)	NA	51%	NA
6-11 years	**59.5%** (48.9-68.0)	**61.7%** (52.3-69.3)	72%	75%
12-16 years	**74.4%** (59.2-84.3)	**67.6%** (59.3-74.3)	81%	84%

VE against DENV1-4 by country: CYD15 (9-16 years, ITT)

Country	N (% trial)	Baseline dengue seropositivity	Number of cases in placebo group				VE
			DENV-1	DENV-2	DENV-3	DENV-4	
Mexico	3464 (17%)	53.1%	25	30	0	1	**31.3%** (1.3-51.9)
Puerto Rico	1315 (6%)	56.2%	11	1	0	1	**57.6%** (-2.5-82.8)
Brazil	3548 (17%)	73.5%	9	0	0	72	**77.5%** (66.5-85.1)
Honduras	2799 (13%)	85.7%	6	20	39	0	**71.1%** (57.0-80.7)
Colombia	9743 (47%)	92.2%	58	33	67	9	**67.5%** (58.3-74.7)

VE against DENV1-4 by country: CYD14 (2-14 years, ITT)

Country	N (% trial)	Baseline dengue seropositivity	Number of cases in placebo group				VE
			DENV-1	DENV-2	DENV-3	DENV-4	
Malaysia	1401 (14%)	47.0%	5	5	3	2	**79.0%** (52.3-91.5)
Vietnam	2333 (23%)	54.2%	7	11	4	26	**51.1%** (26.1-67.6)
Thailand	1170 (11%)	67.7%	16	17	11	2	**51.8%** (25.3-68.9)
Philippines	3501 (34%)	78.1%	87	22	17	33	**53.9%** (41.7-63.6)
Indonesia	1870 (18%)	80.9%	11	19	8	4	**54.3%** (28.0-71.0)

VE against Severe or Hospitalized Dengue (ITT)

Outcome	CYD14 (2-14 years)	CYD15 (9-16 years)	Pooled (2-16 years)	Pooled (9-16 years)
Severe VCD	70.0% (35.7-86.6)	95.5% (68.8-99.9)	**79.1%** (60.0-89.0)	**93.2%** (77.3-98.0)
Hospitalized VCD	67.4% (50.6-78.7)	80.3% (64.7-89.5)	**72.7%** (62.3-80.3)	**80.8%** (70.1-87.7)
Hospitalised by serotype				
DENV1	71.5% (44.1-86.0)	73.2% (27.8-91.0)	**72.1%** (52.9-83.4)	-
DENV2	50.2% (-12.7-78.0)	80.1% (45.7-93.7)	**65.7%** (39.3-80.6)	-
DENV3	73.2% (27.6-90.9)	83.4% (33.6-97.1)	**77.4%** (52.2-89.3)	-
DENV4	77.9% (20.8-95.0)	91.7% (31.8-99.8)	**83.5%** (54.5-94.0)	-

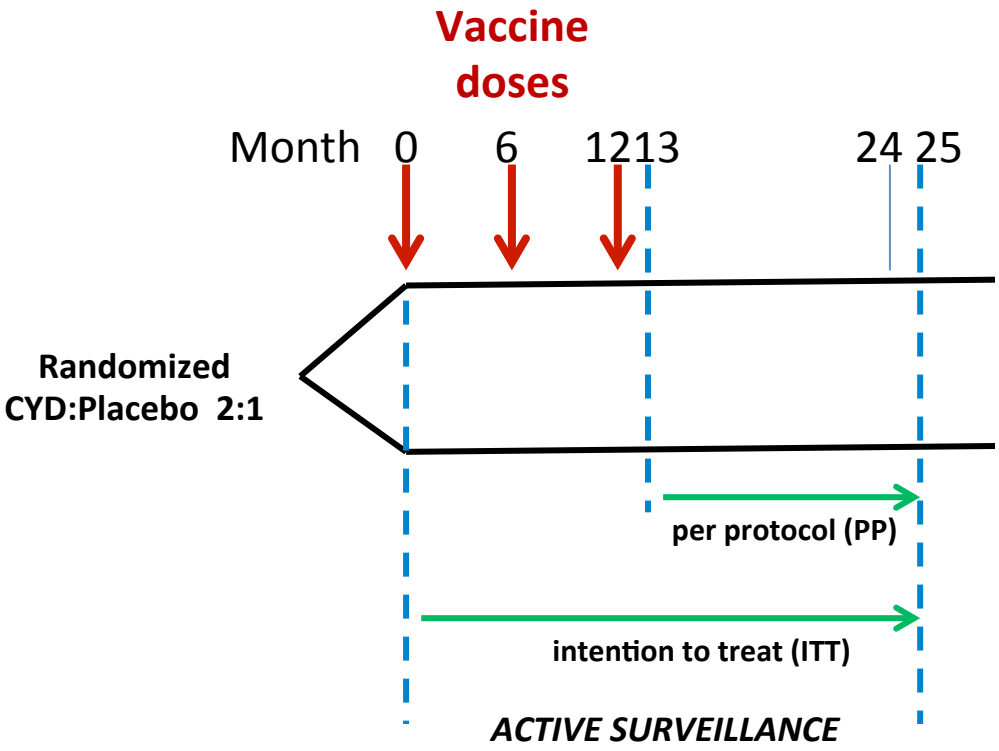
Summary of Vaccine Efficacy estimates from M0-M25

- Vaccine efficacy demonstrated against per protocol primary endpoint.
  - Pooled across CYD14 and CYD15 (ages 2-16 years) VE in the year following the 3rd dose was **59.2%** (95%CI 52.3-65.0).

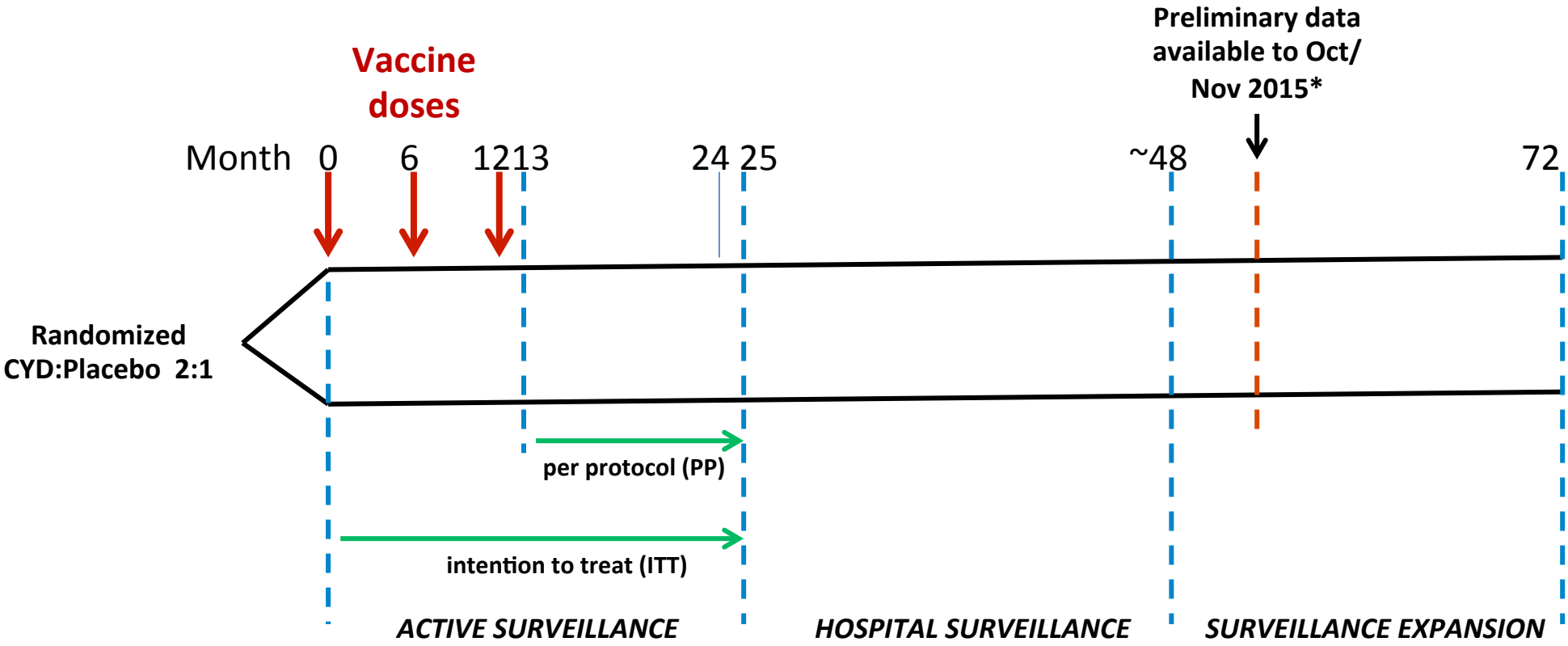
- Protection was seen from the first dose
  - Pooled 2-16 years VE in 2 years following first dose was **60.3%** (95%CI 55.7-64.5)
  - Post-hoc pooled 9-16 years VE in 2 years following first dose was **65.6%** (95%CI 60.7-69.9).

- VE varied by infecting serotype, serostatus, age, and severity of disease.
  - Variable efficacy by country, at least in part, due to these factors.

Study design overview (CYD14 & 15)



Study design overview (CYD14 & 15)



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CYD14	Year 3	Year 4	Year 5 (incomplete)
CYD15	Year 3	Year 4 (incomplete)	Year 5 (incomplete)

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)*

Note - 2:1 randomisation

Longer-term Follow Up for Hospitalized Dengue: 6-8 year age group

	CYD14 (6-8 years)		
Time Period (Follow up)	**CYD group cases**	**Control group cases**	**RR (95%CI)**
Year 1 (Active)	5	12	**0.209** (0.06-0.64)
Year 2 (Active)	8	9	**0.446** (0.15-1.3)
Year 3 (Hospital)	4	5	**0.400** (0.08-1.86)
Year 4 (Hospital)	18	9	**1.000** (0.43-2.53)
Year 5 (Hospital/SEP)	5	3	**0.833** (0.16-5.37)
Cumulative Years 1-5	*40*	*37*	***0.541 (0.34-0.87)***

Note - 2:1 randomisation

Longer-term Follow Up for Hospitalized Dengue: 9-11 year age group

	CYD14			CYD15		
Time Period	**CYD (n)**	**Control (n)**	**RR (95%CI)**	**CYD (n)**	**Control (n)**	**RR (95%CI)**
Year 1 (Active)	5	5	**0.502** (0.12-2.18)	2	8	**0.125** **(0.01-0.63)**
Year 2 (Active)	2	13	**0.077** **(0.01-0.34)**	6	14	**0.214** **(0.07-0.59)**
Year 3 (Hospital)	6	3	**1.009** (0.22-6.23)	10	9	**0.554** (0.20-1.54)
Year 4 (Hospital)	12	3	**2.013** (0.54-11.11)	6	5	**0.601** (0.15-2.49)
Year 5 (Hospital/SEP)	3	2	**0.755** (0.09-9.04)	1	1	**0.498** (0.01-39.1)
Cumulative Years 1-5	***28***	***26***	***0.542*** ***(0.31-0.96)***	***25***	***37***	***0.337*** ***(0.19-0.58)***

Note - 2:1 randomisation

Longer-term Follow Up for Hospitalized Dengue: 12-16 year age group

	CYD14			CYD15		
Time Period (Follow up)	CYD (n)	Control (n)	RR (95%CI)	CYD (n)	Control (n)	RR (95%CI)
Year 1 (Active)	2	5	**0.139** (0.02-1.22)	3	7	**0.214** **(0.04-0.94)**
Year 2 (Active)	1	7	**0.071** **(0.00-0.55)**	7	14	**0.250** **(0.09-0.66)**
Year 3 (Hospital)	2	4	**0.249** (0.02-1.74)	6	6	**0.501** (0.13-1.87)
Year 4 (Hospital)	7	10	**0.348** (0.11-1.01)	0	2	**0.000** (0.00-2.67)
Year 5 Hospital/SEP)	1	2	**0.249** (0.00-4.79)	0	0	NC (NC)
Cumulative Years 1-5	***13***	***27***	***0.240*** **(0.11-0.48)**	***16***	***29***	***0.276*** **(0.14-0.52)**

Longer-term Follow Up for Severe Disease: 2-5 and 6-8 year age groups

Age Group	Time Period (follow-up)	CYD14			CYD15		
		CYD (n)	Control (n)	RR (95%CI)	CYD (n)	Control (n)	RR (95%CI)
2-5 Years	Year 1-2 (Active)	7	5	**0.697** (0.19-2.79)	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)*			
6-8 Years	Year 1-2 (Active)	3	4	**0.376** **(0.06-0.22)**	Not included in trial population		
	Year 3-5 (Hospital/SEP)	8	5	**0.800** (0.23-3.11)			
	Cumulative Years 1-5	*11*	*9*	**0.612** *(0.23-1.67)*			

Note - 2:1 randomisation

Longer-term Follow Up for Severe Disease: 9-11 and 12-16 year age groups

Age Group	Time Period	CYD14			CYD15		
		CYD (n)	Control (n)	RR (95%CI)	CYD (n)	Control (n)	RR (95%CI)
9-11 Years	Year 1-2 (Active)	2	8	**0.126 (0.01-0.63)**	0	3	**0.000** (0.00-1.21)
	Year 3-5 (Hospital/SEP)	7	1	**3.525** (0.45-158.86)	5	3	**0.832** (0.16-5.36)
	Cumulative Years 1-5	*9*	*9*	***0.503*** *(0.18-1.43)*	*5*	*6*	***0.416*** *(0.10-1.64)*
12-16 Years	Year 1-2 (Active)	0	3	**0.000** (0.00-1.20)	1	8	**0.062 (0.00-0.47)**
	Year 3-5 (Hospital/SEP)	1	3	**0.166** (0.00-2.07)	1	2	**0.250** (0.00-4.81)
	Cumulative Years 1-5	*1*	*6*	***0.083*** ***(0.00-0.68)***	*2*	*10*	***0.100*** ***(0.01-0.47)***

Note - 2:1 randomisation

Summary of Longer-Term Follow Up for Hospitalized and Severe Dengue

- Elevated risk among vaccinated primarily seen in 2-5 year-old age group in Year 3.
  - Risk diminishes in Years 4 and 5.
  - Overall excess of cases among vaccinated in 2-5 year age group, but not statistically significant

    [58 vs 23 RR=1.26 (95% CI 0.76-2.13)]
- VE against VCD of any severity is not evaluable after M25
- Trends in the relative risk against dengue hospitalization with time since vaccination suggest waning protection.

Explanation of the excess risk of hospitalised cases in 2-5 year olds from year 3 in CYD14

- Chance is an unlikely explanation
- Reason unknown, but several hypotheses put forward
- Could be related to age, serostatus or both
- Plausible hypothesis is that vaccination primes the immune system similarly to natural infection
- After a period of cross-protection following vaccination, immunity wanes. After this
  - in seronegatives, the response to the first natural infection following vaccination is as if it was a 2nd infection (associated with a higher risk of serious disease)
  - In seropositives, the response to the first natural infection following vaccination is as if it was a 3rd or later infection (not associated with a higher risk of serious disease)
- Note that the excess risk is greatest in year 3 and diminishes in years 4 & 5. In the total follow-up period (from dose 1) there is an excess of hospitalised and severe cases in the vaccinated group but the excesses are not statistically significant.

Implications

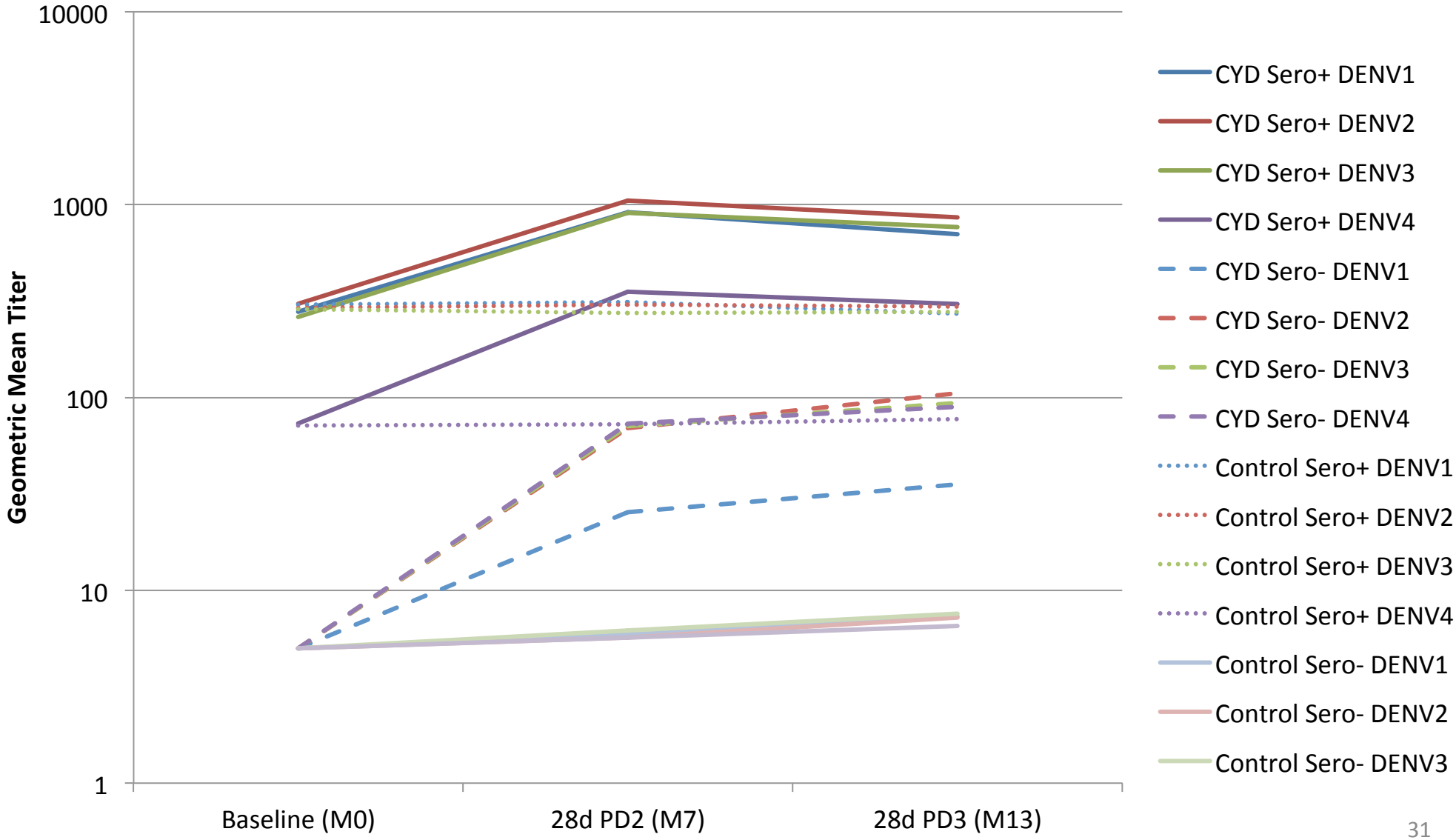
- If the increased risk of hospitalized and severe dengue at later follow-up periods is a result of both serostatus at baseline and age of vaccination younger than 6 years, the effect may be limited to younger children who are not included in the indication.

- If the increased risk is independent of age, children ≥9 years old who are vaccinated when seronegative could be at an increased risk.

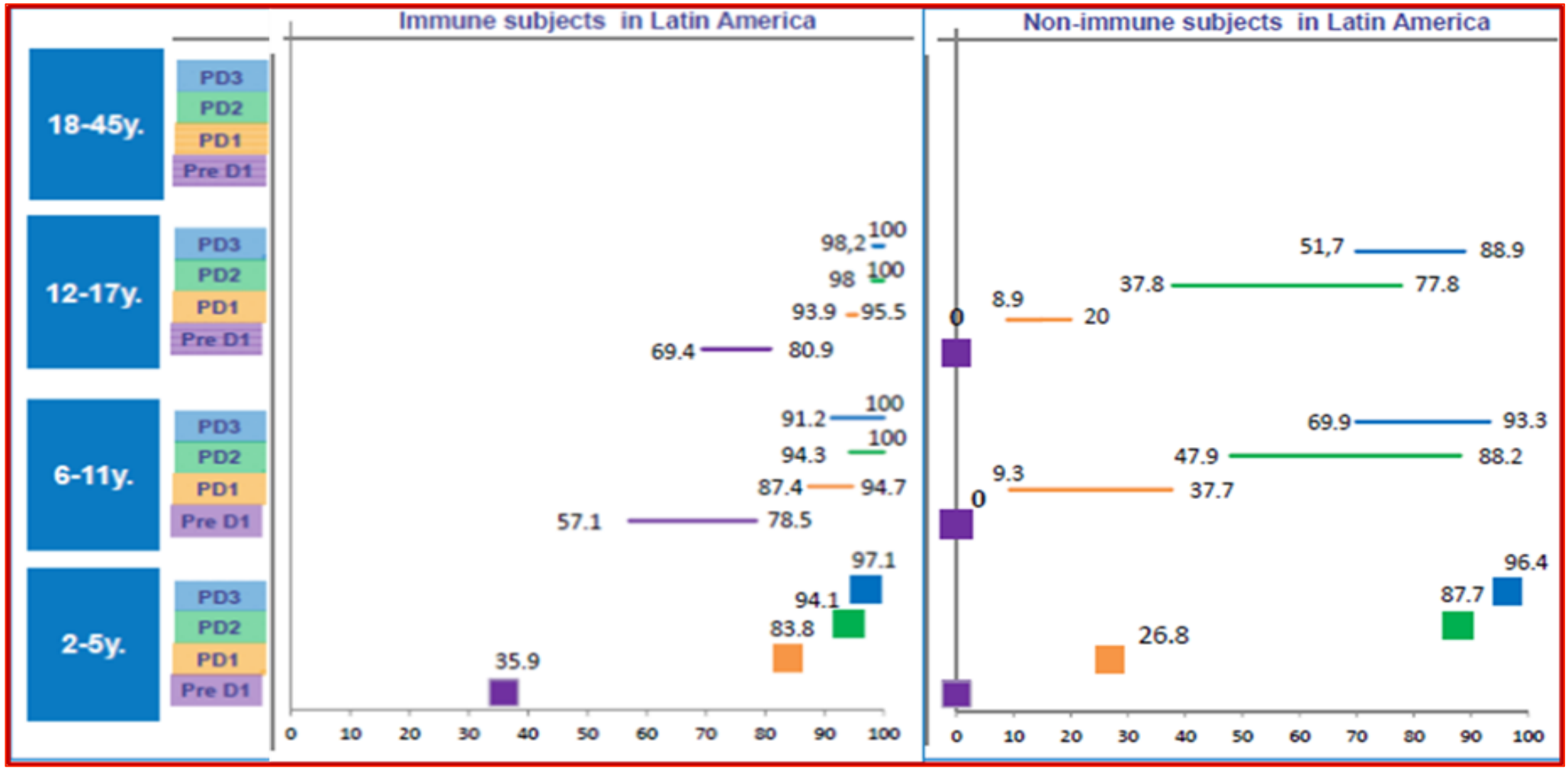
  - Data to inform this are very limited from the trial. The immunogenicity subset, for which serostatus at vaccination is known, is small, and there were few children included who were ≥ 9 years of age and seronegative.

- *There is a theoretical possibility that vaccination may be ineffective or may even increase risk of hospitalized and severe dengue in those who are seronegative at the time of first vaccination, regardless of age. However, there are few trial data available on older seronegative participants to address this.*

Immunogenicity - CYD15 (9-16 years)



Tetravalent seroconversion in Latin America



Immunogenicity Summary

- CYD-TDV is immunogenic
  - Greater immunogenicity in vaccinees seropositive at baseline.
  - 3 doses increases the proportion of vaccinees, especially seronegatives, who seroconvert to all four serotypes.
  - In vaccinees who are seropositive at baseline, the 3rd dose does not increase titres over the 2nd dose.

CYD-TDV Safety Assessment by GACVS

Reviewed by GACVS in December 2012, December 2014, and June 2015

- Based on data generated during the Active Phase, safety data from the clinical studies indicate that local and systemic adverse reactions are comparable to those recorded for other available live attenuated vaccines. No safety concerns had been identified.
- Following review of Year 3 data generated during the Hospital Phase, GACVS acknowledged the increased relative risk of hospitalized dengue in Year 3 the 2-5 year old vaccinated population.
- GACVS highlighted the importance of understanding the potential factors associated with this increased relative risk.
  - Until this is better understood and characterized GACVS was unable to fully assess the risk in this age group.
  - Current data indicate that the risk of dengue has been lower among vaccine recipients in all other age groups studied up to 2 years post dose 3 (without distinguishing prior exposure to dengue virus).

CYD-TDV Safety Assessment by GACVS

- GACVS also emphasized the importance of further monitoring the risk of dengue requiring hospitalization (particularly severe dengue) in older individuals who are serologically naive at the time of vaccination.

- GACVS supported the sponsors plans for post-licensure studies to monitor potential risk of increase in the severity of dengue disease in the vaccinated population.

- GACVS also noted that, as the company proposes to use the product in a broad age range, additional safety data should be generated for older age groups, (in particular among those aged ≥45 years) as currently the number of subjects evaluated is limited.

Safety in CYD14 and CYD15

Adverse Health Outcome	CYD14 % (95%CI)		CYD15 % (95%CI)	
	CYD	Control	CYD	Control
SAE	5% (4.7-5.7)	6% (5.6-7.3)	4.1% (3.7-4.4)	4.4% (4.0-4.9)
Death	<1% (0.0-0.1)	0% (0.0-0.1)	<1% (TBC)	<1% (TBC)
Immediate unsolicited non-serious AEs	0% (0.0-0.3)	0% (0.0-0.6)	0.2% (0.0-0.7)	0.2% (0.0-0.8)
Solicited injection-site reaction	47% (44.8-50.2)	43% (39.2-46.9)	50.8% (48.1-53.6)	42.4% (38.6-46.3)
Solicited systemic reaction	57% (54.3-59.7)	55% (51.5-59.2)	68.4% (65.9-70.9)	69.5% (65.8-73.0)
Unsolicited non-serious AE	37% (34.1-39.3)	40% (36.7-44.3)	44.6% (41.9-47.4)	44.0% (40.2-47.8)
Unsolicited non-serious AR	1% (0.9-2.2)	<1% (0.3-2.0)	1.2% (0.7-1.9)	0.8% (0.2-1.7)
Unsolicited non-serious injection site AR	<1% (0.3-1.3)	<1% (0.0-1.1)	0.7% (0.3-1.3)	0.5% (0.1-1.3)
Unsolicited non-serious systemic AE	37% (34.1-39.3)	40% (36.7-44.3)	44.6% (41.9-47.4)	44.0% (40.2-47.8)
Unsolicited non-serious systemic AR	<1% (0.4-1.4)	<1% (0.2-1.5)	0.5% (0.2-1.1)	0.3% (0.0-1.1)

Sponsor's proposed post-licensure risk management plan

Type	Activities
Post-marketing pharmacovigilance activities	• Routine pharmacovigilance monitoring • Enhanced safety surveillance
Long-term monitoring of ongoing efficacy studies	• Surveillance expansion in CYD14 and CYD15 (return to active surveillance currently in progress) • 5 year follow-up post-dose 3
Safety studies	• Background rates of viscerotropic and neurotropic like disease • Cohort event monitoring • Pregnancy registry
Effectiveness studies	• Community-based studies to evaluate impact on disease transmission • Facility-based studies to evaluate impact on hospitalization and severe dengue (with annual bleeding) • Monitor potential waning immunity over time
Additional clinical studies	• Booster studies • Clinical stable HIV+ subjects • Co-administration studies (HPV, Tdap)
Risk minimization	• Product information / labelling and packaging

Safety Assessment

- CYD-TDV is well-tolerated.
- SAEs similar across CYD/Placebo in Phase 3 trials.
- No non-dengue safety signals identified.
- Hypothetical vaccine-associated viscerotropic and neurotropic disease risk (under study by sponsor).
- Limited experience with vaccination in pregnancy (contraindication).
- Understanding the potential factors associated with the increased relative risk of hospitalized and severe dengue among some trial participants is a priority.

Thank you!

Inter-dose Vaccine Efficacy

	VE (95%CI)		
Interval between injections	**CYD14 ≥9 years**	**CYD15 ≥9 years**	**Pooled ≥9 years**
Between dose 1 and dose 2 (M0-M6)	61.5% (24.1-80.8)	74.3% (59.4-84.0)	**70.8%** (58.1-79.6)
Between dose 2 and dose 3 (M6-M12)	69.7% (49.0-82.4)	64.5% (46.3-76.7)	**66.6%** (54.5-75.5)
Between dose 3 and 6 months post-dose 3 (PD3) (M12-M18)	55.5% (9.5-78.3)	63.6% (51.4-72.8)	**62.4%** (51.4-70.9)
Between 6 months PD3 and end of active phase (M18-M25)	76.5% (57.1-87.6)	58.6% (45.5-68.5)	**62.7%** (52.6-70.7)
Full active phase (M0-M25)	67.8% (57.7-75.6)	64.7% (58.7-69.8)	**65.6%** (60.7-69.9)

Source: Sanofi Pasteur, unpublished data.

Longer-term Follow Up for Hospitalized Dengue: 9-11 year age group (incl. CYD 23/57)

	CYD14 (9-11 years)			CYD15 (9-11 years)			CYD23/57 (9-11 years)		
Time Period	CYD cases	Control cases	RR (95%CI)	CYD cases	Control cases	RR (95%CI)	CYD cases	Control cases	RR (95%CI)
Year 1 (Active)	5	5	0.502 (0.12-2.18)	2	8	**0.125 (0.01-0.63)**	3	2	0.759 (0.09-9.08)
Year 2 (Active)	2	13	**0.077 (0.01-0.34)**	6	14	**0.214 (0.07-0.59)**	3	9	**0.169 (0.03-0.68)**
Year 3 (Hospital)	6	3	1.009 (0.22-6.23)	10	9	0.554 (0.20-1.54)	3	5	0.308 (0.05-1.58)
Year 4 (Hospital)	12	3	2.013 (0.54-11.11)	6	5	0.601 (0.15-2.49)	3	5	0.308 (0.05-1.58)
Year 5 (Hospital/ SEP)	3	2	0.755 (0.09-9.04)	1	1	0.498 (0.01-39.1)	1	3	0.171 (0.00-2.13)
Year 6 (Hospital)	NA	NA	NA	NA	NA	NA	11	5	1.126 (0.36-4.14)
Cumulative to date	*28*	*26*	***0.542 (0.31-0.96)***	*25*	*37*	***0.337 (0.19-0.58)***	*24*	*29*	***0.422 (0.24-0.75)***

CYD14 N=2618, CYD15 N=8436, CYD23/57 N=1311. **Bold**=statistically significant.

Number of Hospitalized and/or severe VCD cases by age group and dengue immune status at baseline

		Active phase cases/N (%)		Hospital phase-SEP† cases/N (%)		Cumulative cases/N (%)	
Age group	**Serostatus**	**CYD group**	**Control group**	**CYD group**	**Control group**	**CYD group**	**Control group**
2-8 years	Seropositive*	2/493 (0.4)	8/240 (3.3)	7/476 (1.5)	3/234 (1.3)	9/481 (1.9)	11/236 (4.7)
	Seronegative*	2/337 (0.6)	2/178 (1.1)	15/326 (4.6)	3/170 (1.8)	17/330 (5.2)	5/173 (2.9)
9-16 years	Seropositive*	0/1605 (0.0)	6/777 (0.8)	7/1508 (0.5)	9/736 (1.2)	7/1546 (0.5)	15/752 (2.0)
	Seronegative*	0/398 (0.0)	2/214 (0.9)	7/372 (1.9)	3/197 (1.5)	7/382 (1.8)	4/204 (2.0)

Pool of CYD14, CYD15, and CYD57. *Includes only subjects from the Full Analysis Set for Immunogenicity; † Includes all subjects from the Safety Analysis Set for Efficacy; SEP: Surveillance Expansion Phase

Source: Sanofi Pasteur, unpublished data.