Dengue Vaccine (CYD-TDV "Dengvaxia®")

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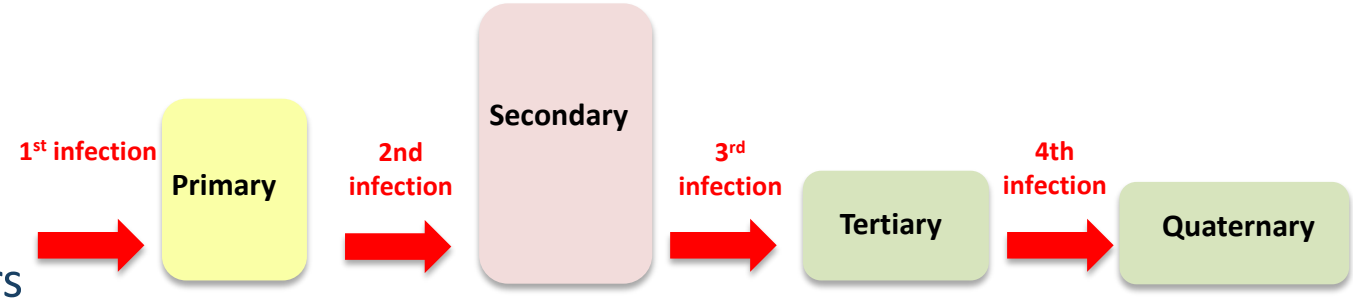
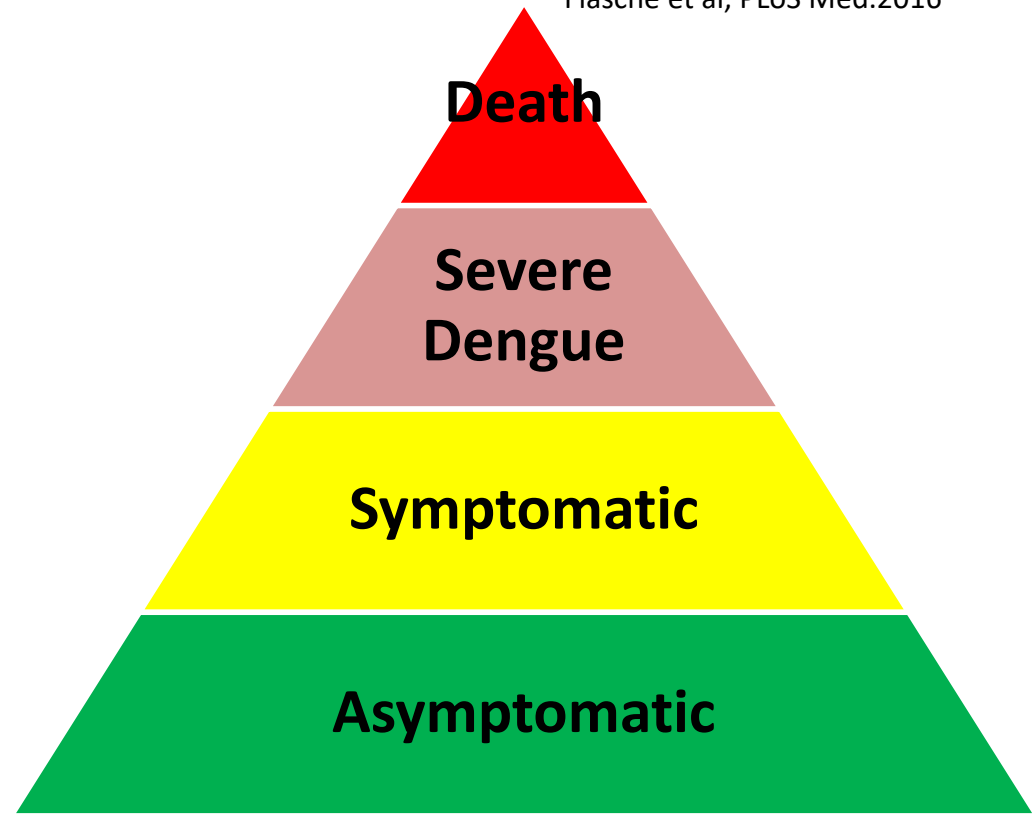
Dengue

- Rapidly expanding arboviral disease transmitted by *Aedes* mosquitoes
- 50 fold increase in past 50 years
- Four antigenically distinct serotypes (DENV1-4)
- Clinical spectrum:
  - 80% asymptomatic
  - Self-limiting febrile illness
  - Severe dengue (~2-4% of symptomatic)
  - Secondary infections are associated with higher risk of more severe dengue
  - CFR 0.1—1%



Flasche et al, PLoS Med.2016



Dengue Vaccine

(http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/)

Phase I | **Phase II** | **Phase IIb** | **Phase III** | **Registration**

DPIV
GlaxoSmithKline, Biomanguinhos, WRAIR

DEN-80E
Merck

TVDV
Naval Medical Research Center

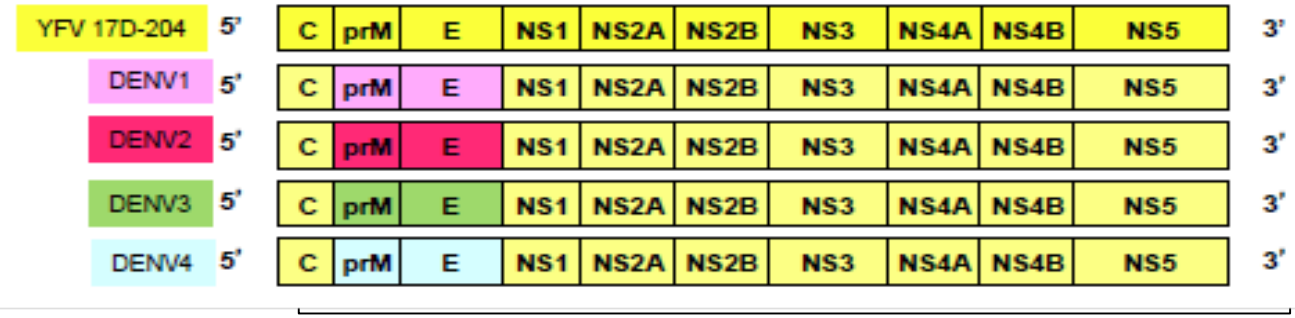
TLAV-TPIV
WRAIR

TV003/TV005
US National Institutes of Health[1] Butantan

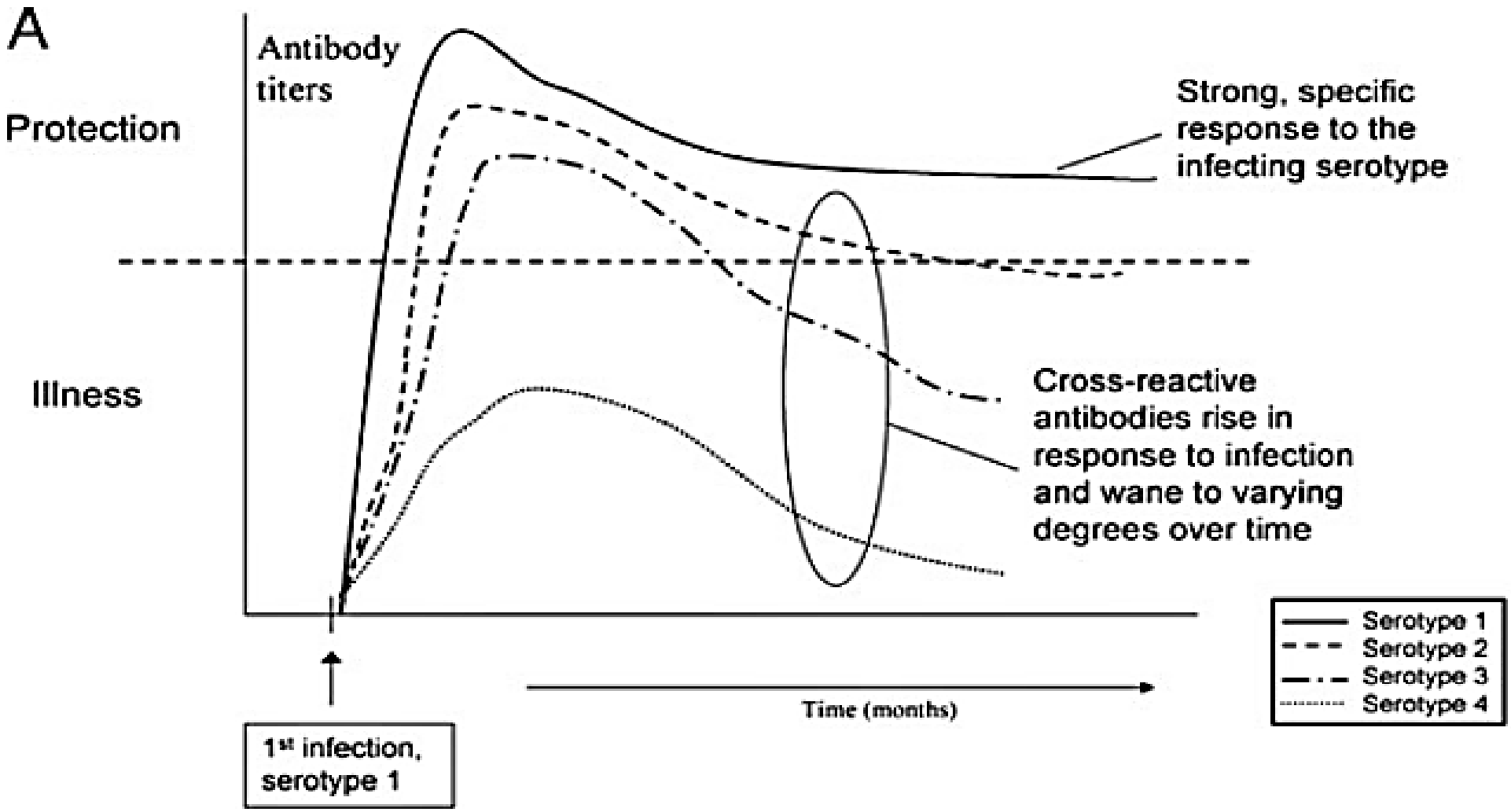
DENVax
Takeda

CYD-TDV
Dengvaxia™
Sanofi Pasteur

CYD-TDV
SANOFI PASTEUR



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

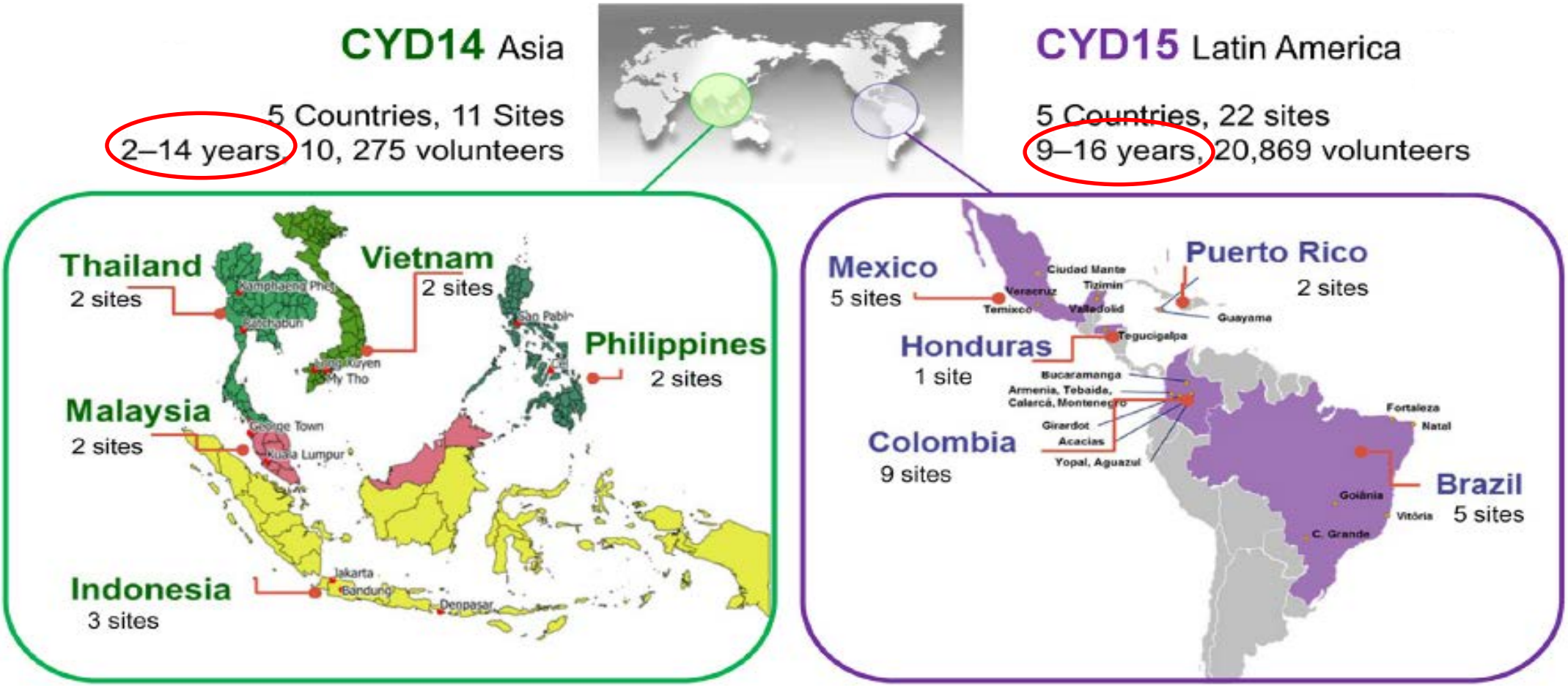
Status of CYD-TDV

(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.)

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)*

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)

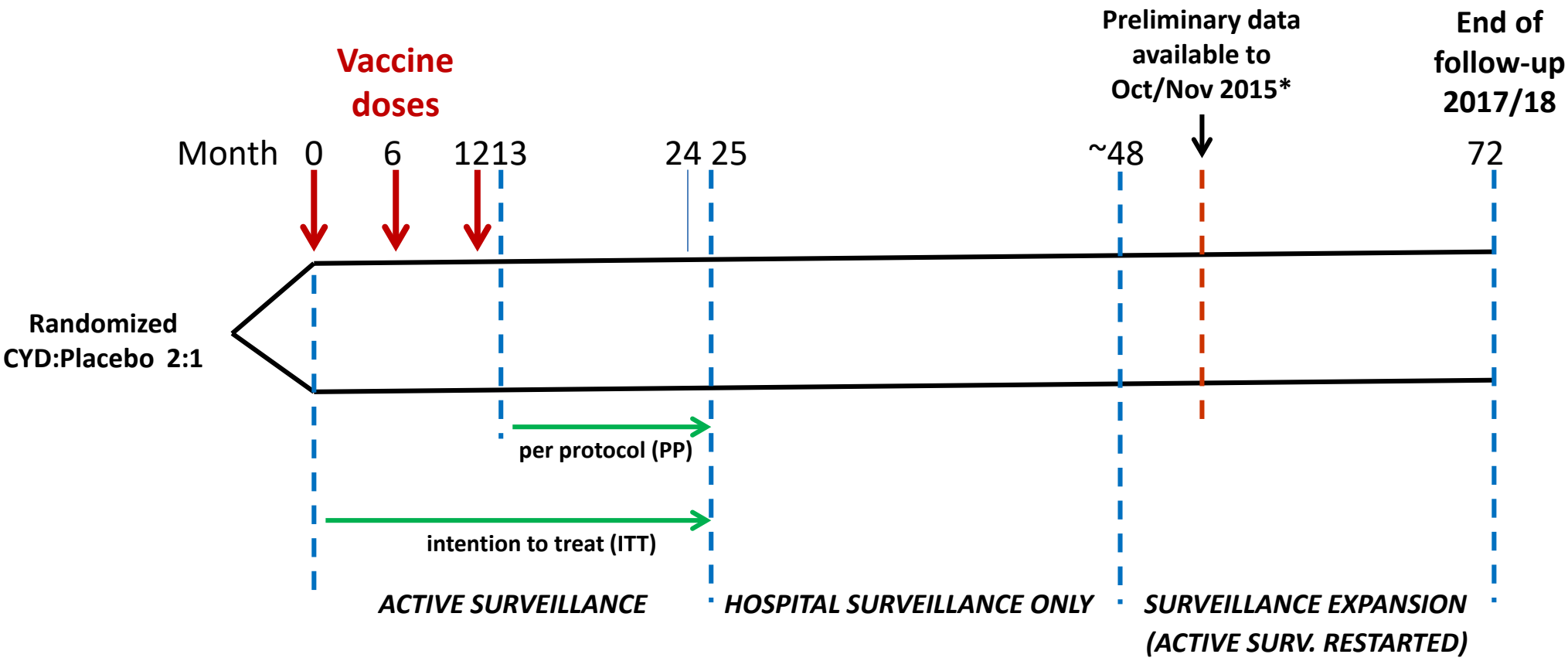
Longer-term Follow Up for Hospitalized Dengue: 2-5 year age group

	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)*

Conclusions and basis for SAGE recommendations in 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.
- Modelling of public health impact 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 an important unanswered question by both GACVS and SAGE.
- Long-term prospective studies were thought to be needed to address the safety question
- However, in 2017, 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).

Study design overview (CYD14 & 15)



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

(2-16 year-olds - MI method)

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

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

(2-16 year-olds - MI method)

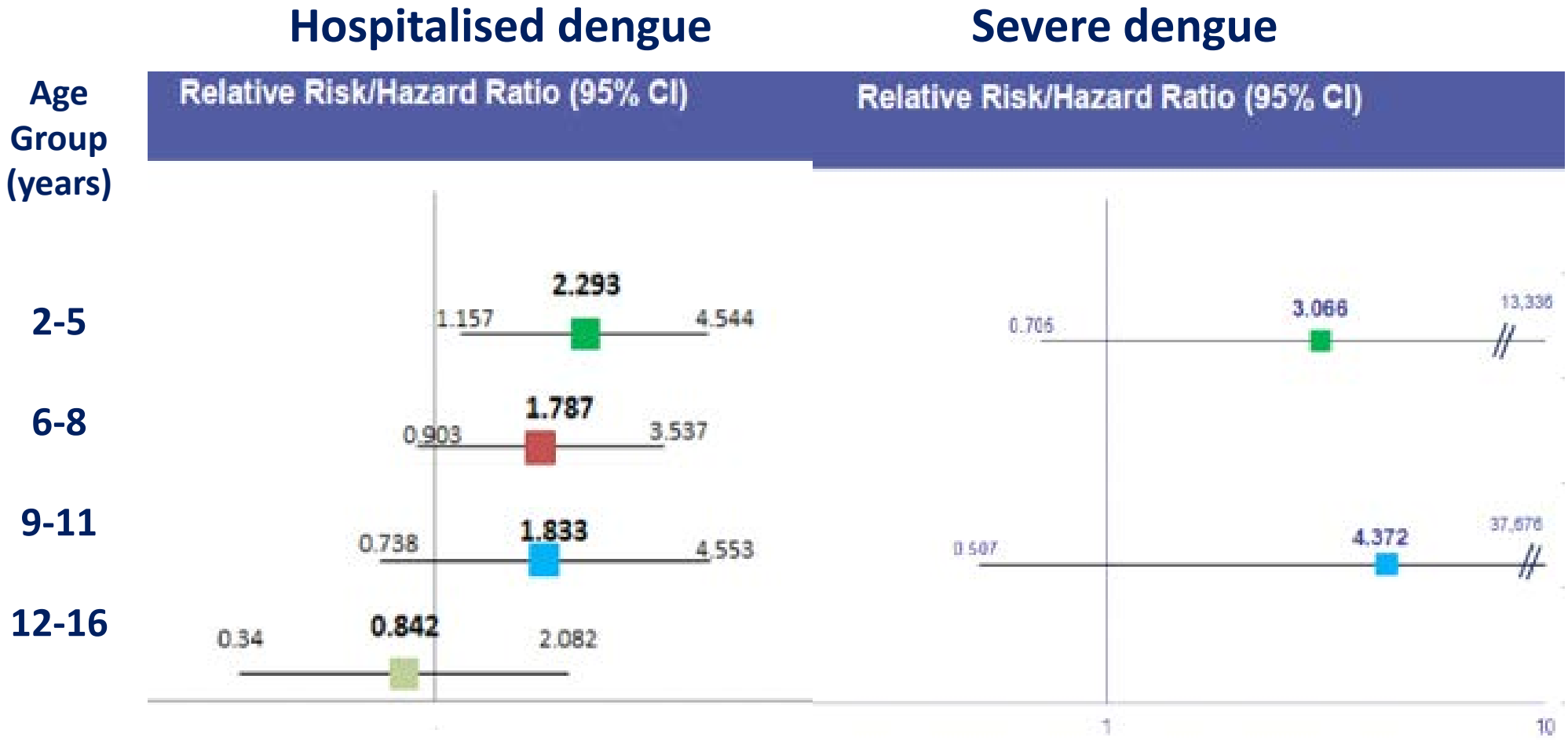
Sero-status at dose 1	Relative risk (CYD:Control)	95% confidence interval
Sero-positive	**0.29**	0.21, 0.42
Sero-negative	**1.65**	1.04, 2.61

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

(2-16 year-olds - MI method)

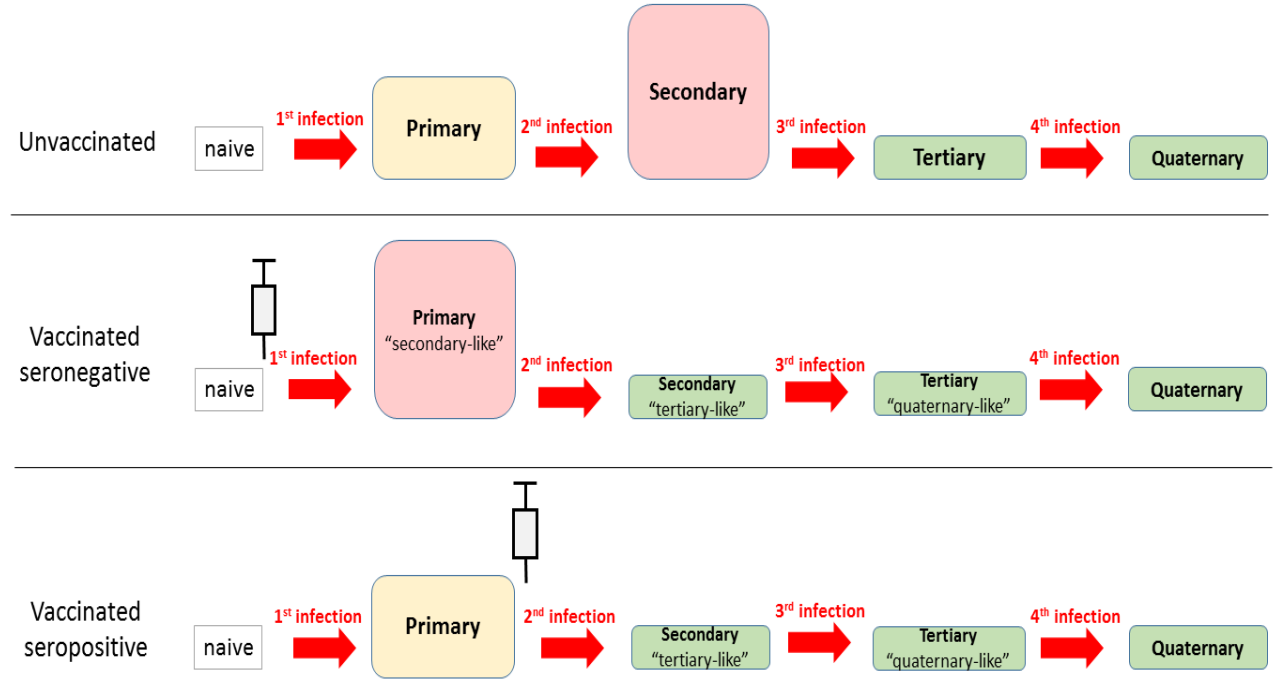
Sero-status at dose 1	Relative risk (CYD:Control)	95% confidence interval
Sero-positive	**0.28**	0.15, 0.52
Sero-negative	**3.00**	1.10, 8.15

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



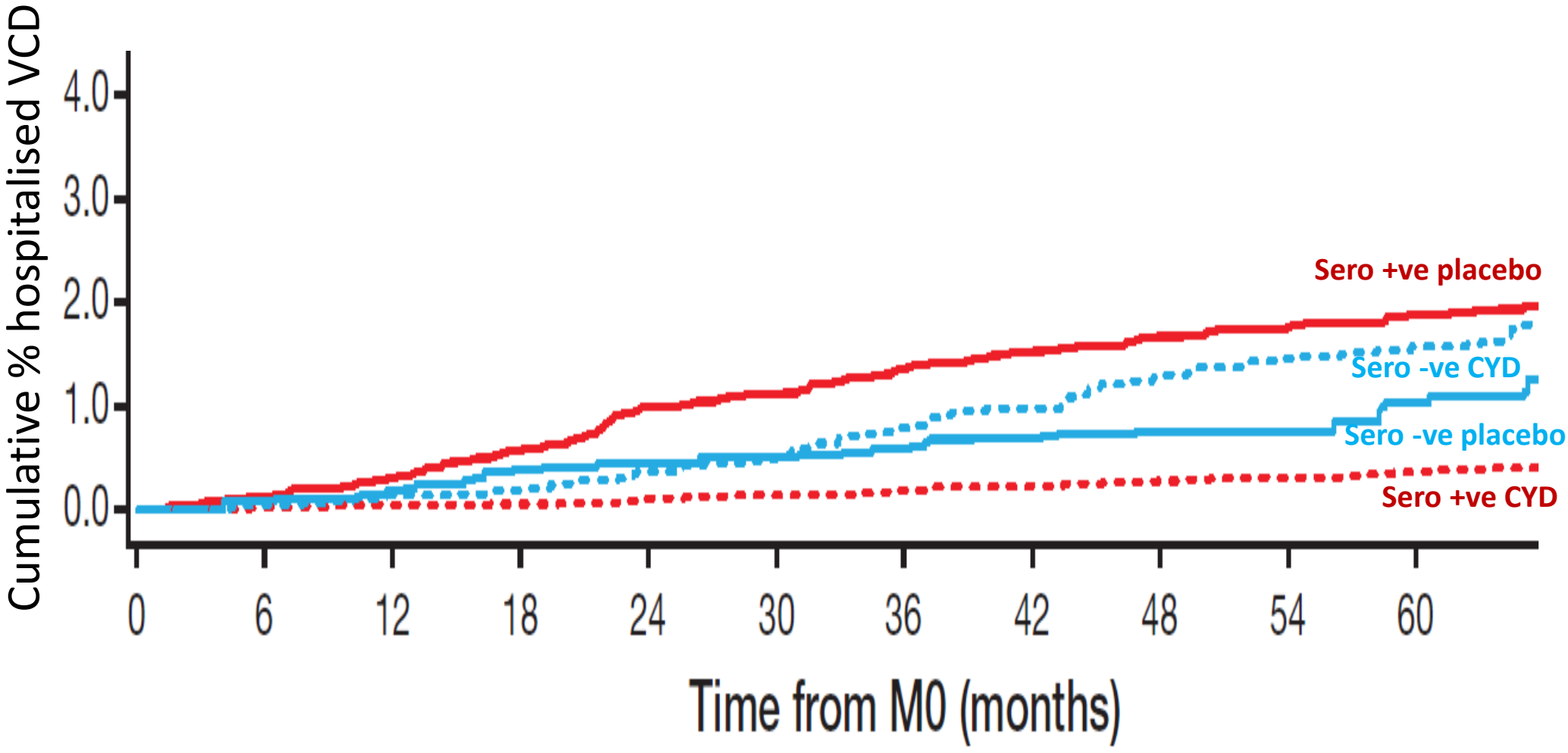
Explanatory hypothesis: "Silent infection" mode of action

- 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

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



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

Considerations

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.

3. Population eligible for vaccination

Population Seroprevalence Criteria without 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.

Pre-Vaccination Screening

- 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.

2. % vaccinated at increased risk of severe dengue

Population Seroprevalence Criteria without Screening	***Pre-Vaccination Screening***
• Dependent on seroprevalence criteria chosen • If vaccine is introduced in a setting with 80% seroprevalence, 20% of the vaccinated population will be put at risk.	• Dependent on the specificity of the screening test. • In a setting with 80% seroprevalence and a test with 80% specificity, 20% of true seronegatives will be unintentionally vaccinated. That is, 4% of the total population would be unintentionally vaccinated. • In a setting with 80% seroprevalence and a test with 98% specificity, 0.4% of the population would be unintentionally vaccinated.

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