# Potential impact of dengue vaccination in different endemic settings

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**DSABNS**
Evora, Portugal, February 2nd 2017

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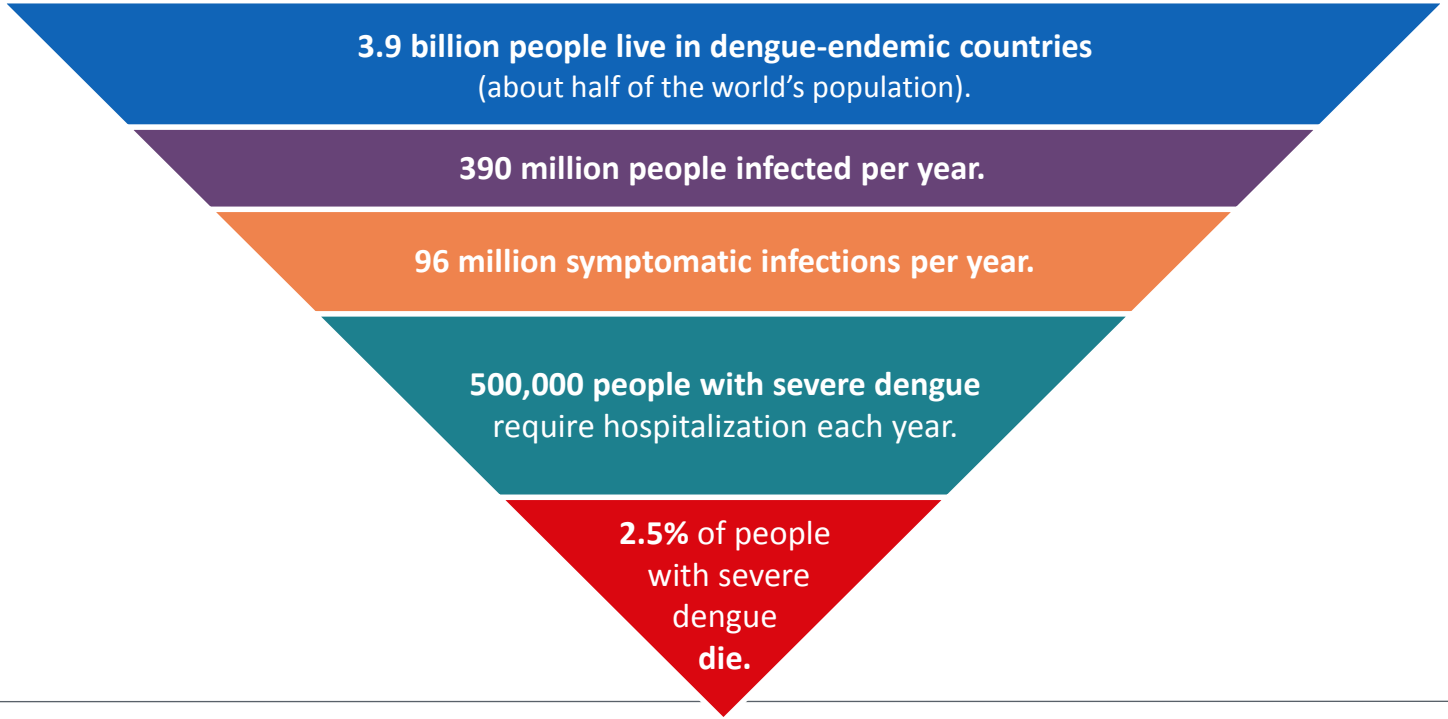
# Contents

# DESPITE PREVENTIVE MEASURES, DENGUE CONTINUES TO GROW

## WHO Estimates[1]




WHO=World Health Organization.

1. WHO, 2015, Dengue fact sheet.

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# VACCINATION IS ONE OF THE PILLARS OF THE WHO STRATEGY TOWARDS EFFECTIVELY FIGHTING DENGUE[1]

## WHO OBJECTIVES

**Reduce mortality** by ≥50% by 2020*

**Reduce morbidity** by ≥25% by 2020*

**Estimate true burden** of disease by 2015

## TECHNICAL ELEMENTS

- Diagnosis and case management
- Integrated surveillance and outbreak preparedness
- Sustainable vector control
- vaccine implementation [2]
- Basic operational and implementational research

*The baseline year is 2010.

WHO=World Health Organization.


1. WHO, 2012, Global Strategy for Dengue Prevention and Control.
2. Summary of the April 2016 meeting of the Strategic Advisory Group of Experts on immunization (SAGE).


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# OVERVIEW OF SANOFI PASTEUR'S CLINICAL DEVELOPMENT PROGRAM CLINICAL DATABASE

- **25 clinical studies**, in 15 countries, completed (23) or ongoing (2).[1]
- More than **40,000 subjects** included in clinical studies.[1]
- Nearly **29,000 individuals** **children, adolescent and adults** received the vaccine.[2,3]

**5 phase I trials[4]**
**in 3 countries**
**(USA, Mexico, Philippines)**
**N=400 CYD vaccinees**
**Ages: 2–45 years**

**14 phase II trials[5]**
**in 14 countries**
**(USA, Australia, Latin America, Asia)**
**N=5400 CYD vaccinees**
**Ages: 12 months–45 years**

**6 phase III trials[5]**
**in 12 countries**
**(Australia, Latin America, Asia)**
**N=23,000 CYD vaccinees**
**Ages: 9 months–60 years**

SP=Sanofi Pasteur.


1. Sanofi pasteur, 2015, Dengue fact sheet.
2. Capeding MR, et al. Lancet 2014;384:1358-65 8.
3. Villar L, et al. NEJM 2015; 372(2):113-23
4. Guy B et al. Vaccine 2011;29(42):7229-41.
5. ClinicalTrials.gov. Accessed February 10, 2016.


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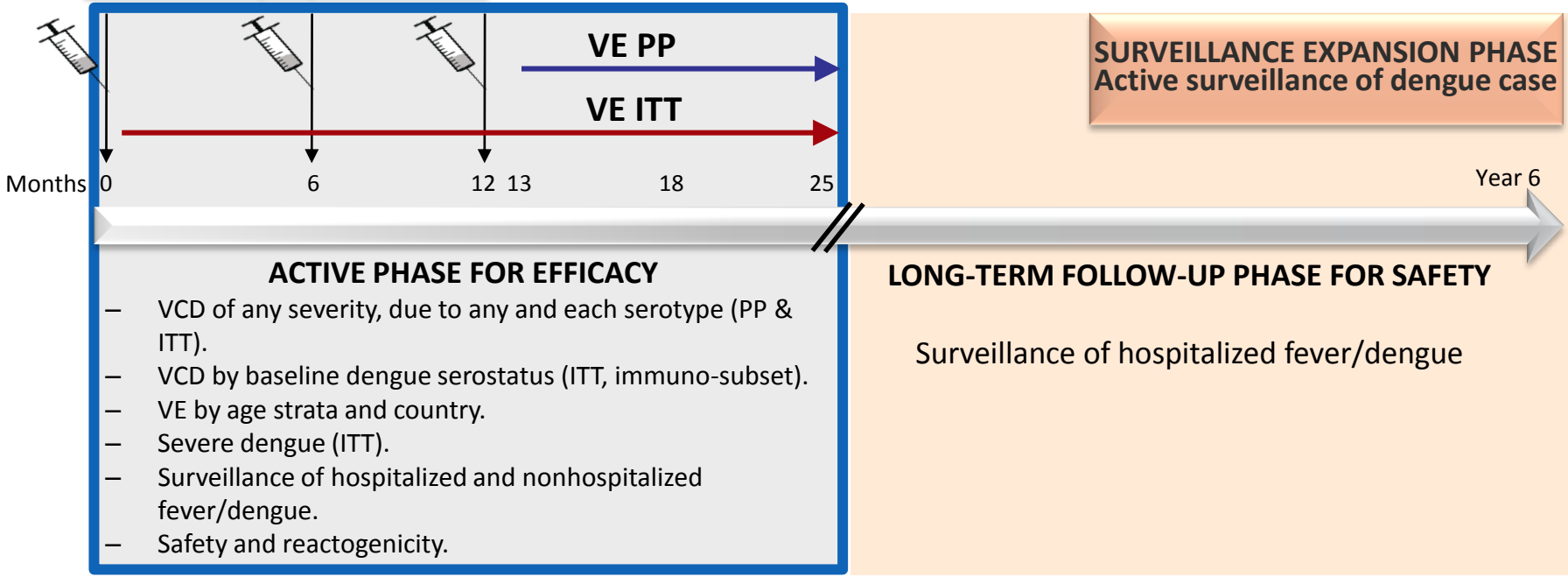
# PHASE III STUDIES: SIMILAR STUDY DESIGN WITH A 25-MONTH EFFICACY SURVEILLANCE PHASE AND A 4-YEAR LONG-TERM SAFETY FOLLOW-UP PHASE[1,2,3]

**CYD-TDV group or Control (placebo) group (2:1)**

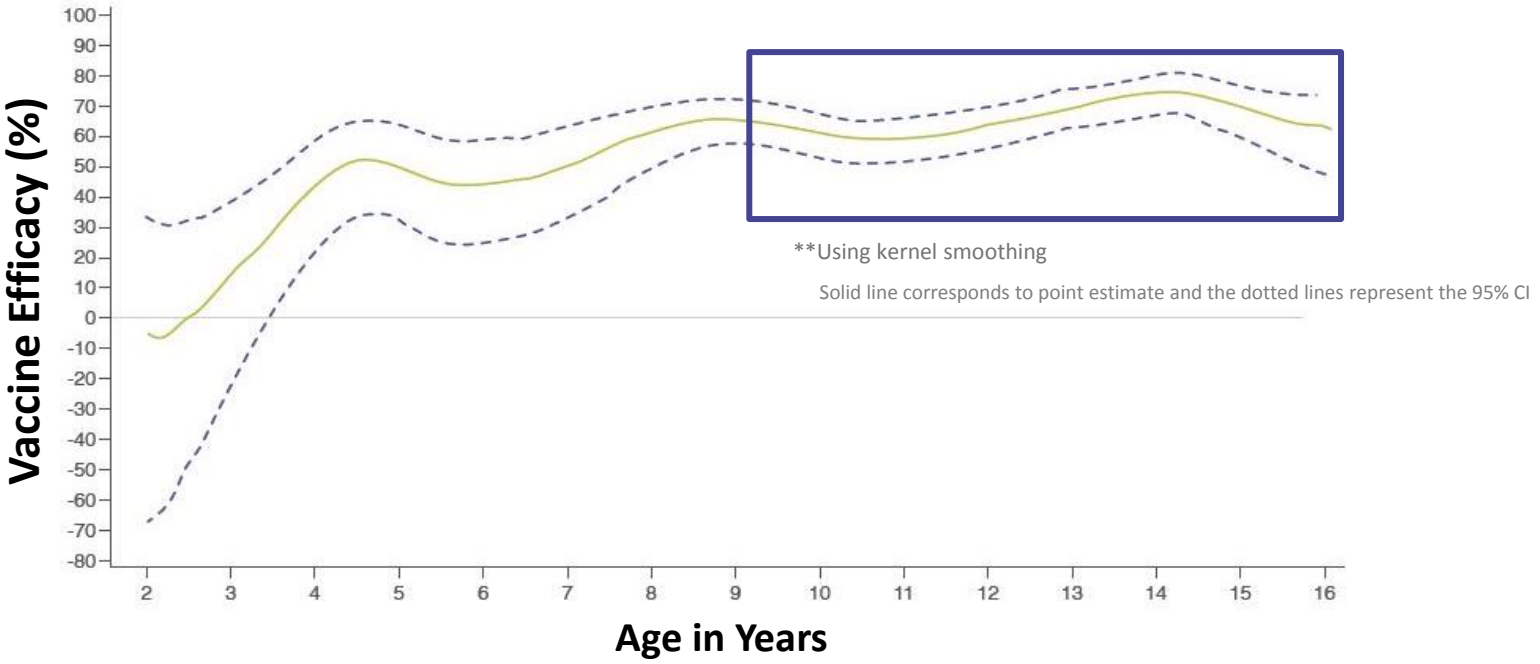



ITT=intent to treat; PP=per protocol; VCD=virologically confirmed dengue; VE=vaccine efficacy.


1. Capeding MR, et al. Lancet 2014;384:1358-65 8.
2. Villar L, et al. NEJM 2015; 372(2):113-23
3. Hadinegoro et al. NEJM 2015;373(13):1195-206.

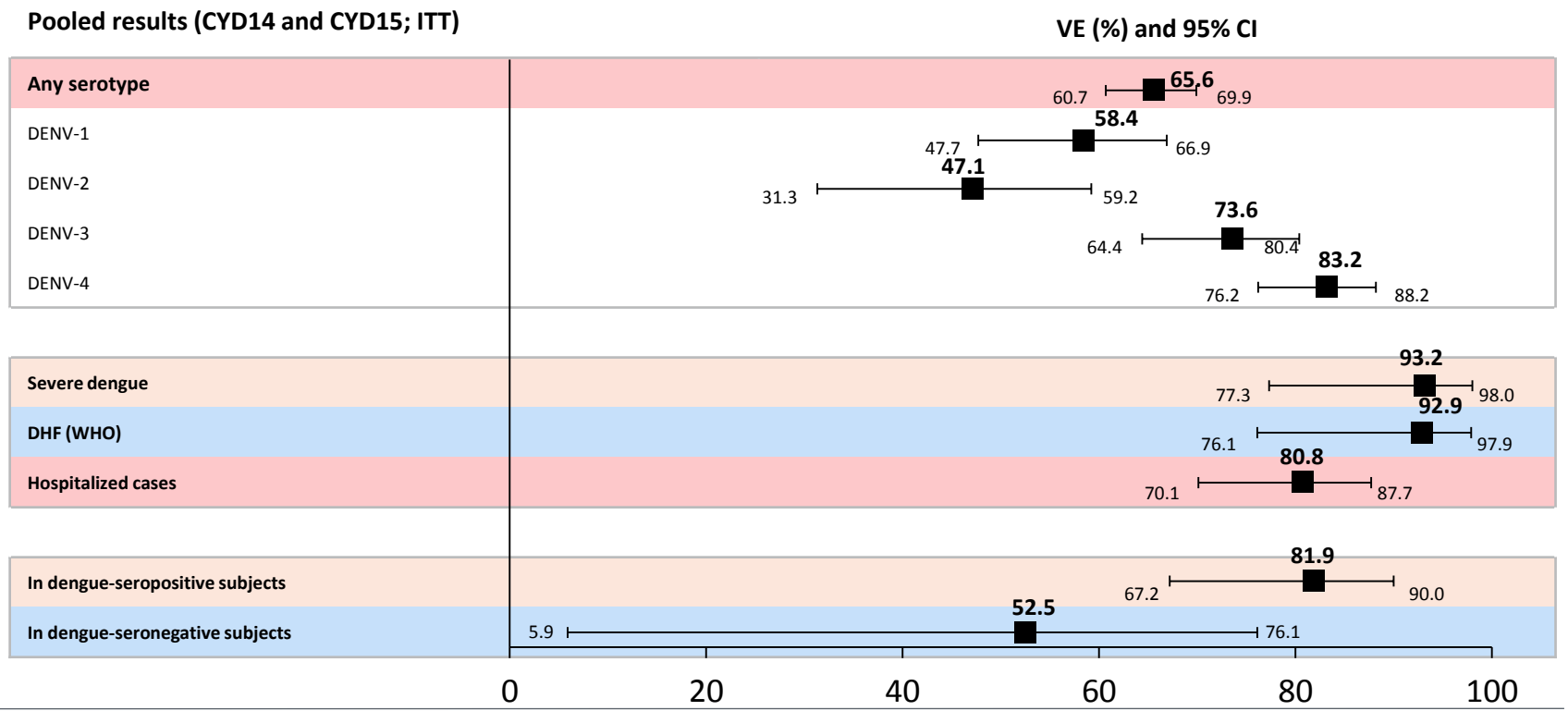
# VACCINE EFFICACY ACCORDING TO AGE AS A CONTINUOUS VARIABLE (ASIA CYD14 AND LATAM CYD15) *

**VE against symptomatic virologically-confirmed dengue cases during the whole Active Phase due to any of the 4 serotypes according to age using kernel smoothing - FASE - CYD14 & CYD15 (2-16 years)**




* 8th Asian Congress of Pediatric Infectious Diseases (ACPID), Poster Presentation- 7 -10 November 2016, Bangkok, Thailand.

# POOLED ANALYSIS OF THE 25-MONTH EFFICACY PHASE CONFIRMS CONSISTENT VE AGAINST VCD (ANY AND EACH SEROTYPE, ANY SEVERITY, INDEPENDENT OF PRIOR DENGUE EXPOSURE) IN SUBJECTS 9–16 YEARS OF AGE[1]




DENV=dengue virus; DHF=dengue hemorrhagic fever; ITT=intent to treat; VE=vaccine efficacy; WHO=World Health Organization.

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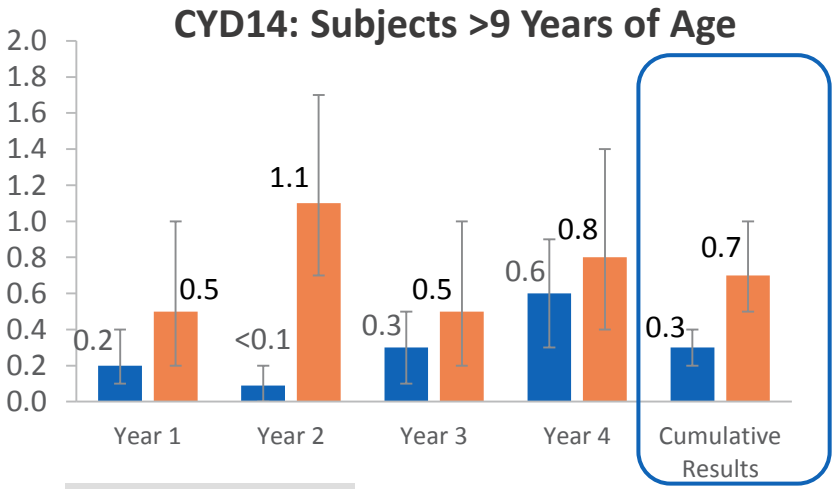
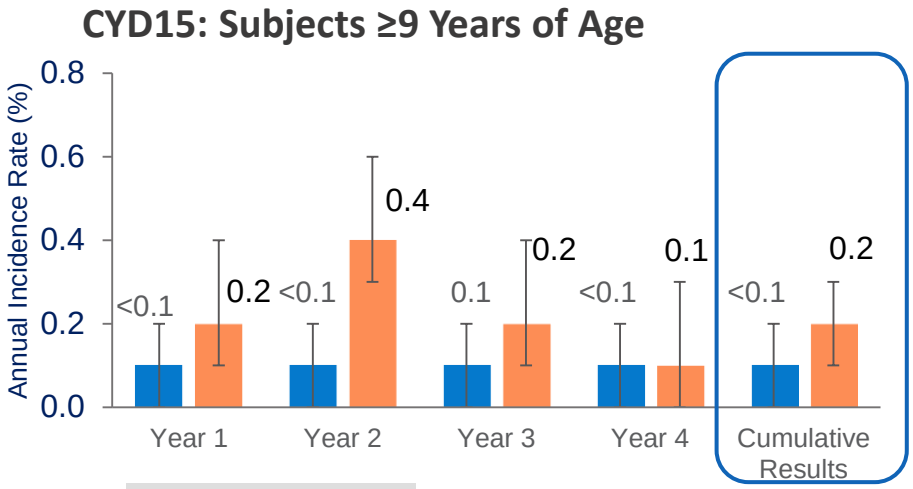
1. Hadinegoro et al. NEJM 2015;373(13):1195-206.

# OVERALL RESULTS BY STUDY YEAR - HOSPITALIZED VCD (ANY SEVERITY) IN SUBJECTS ≥ 9 YOA FOR ASIA CYD14 AND LATAM CYD15 STUDIES

## 25-Month Active Phase + Year 3 + Year 4 [1,2,3]




| | Efficacy Surveillance Phase† | | | | | Efficacy Surveillance Phase† | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **RR** (95% CI) | **0.44** (0.14, 1.38) | **0.08** (0.01, 0.25) | **0.57** (0.18, 1.86) | **0.73** (0.34, 1.61) | **0.39** (0.24, 0.60) | **0.166** (0.05, 0.48) | **0.214** (0.10, 0.43) | **0.533** (0.25, 1.16) | **0.334** (0.10, 1.05) | **0.291** (0.19, 0.44) |

Vaccine Group  Control Group

*CYD14 was conducted in Asia-Pacific in subjects 2–14 years of age.
†Efficacy surveillance phase year 1=day 0 to dose 3; year 2=dose 3 to month 25; cumulative results=day 0 to year 4.
RR=relative risk; VCD=virologically confirmed dengue.

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1. Hadinegoro et al. NEJM 2015;373(13):1195-206.
2. Hadinegoro SR et al. 5th Pan-American Dengue Research Meeting, Panama, Apr 20-23, 2016.
3. Cortez M et al. 65th ASTMH Annual Meeting Atlanta Nov 2016.

# NO IMPORTANT DIFFERENCES IN CLINICAL SIGNS, SYMPTOMS, VIROLOGICAL OR IMMUNOLOGICAL PATTERNS BETWEEN ONGOING LTFU VERSUS ACTIVE PHASE IN PLACEBO GROUP AND IN SUBJECTS 2–16 YEARS OF AGE[1]

**LENGTH OF HOSPITALIZATION**

Similar for both the 25-month efficacy phase and the ongoing LTFU phase in CYD14, CYD15, and CYD23/57

**DURATION OF FEVER AND CLINICAL SYMPTOMS**

Similar for both the 25-month efficacy phase and the ongoing LTFU phase in CYD14, CYD15, and CYD23/57

**FREQUENCY OF SIGNS AND SYMPTOMS**

No clinically important differences observed for the frequency of various signs and symptoms during the 25-month efficacy phase and the ongoing LTFU phase in CYD14, CYD15, and CYD23/57

**VIREMIA AND CYTOKINE PATTERN**

- Similar levels of viremia observed in vaccine vs control groups (CYD14 and CYD15)
- Similar cytokine pattern in the vaccine group compared to placebo

LTFU=long-term follow-up.

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1. Hadinegoro, 2015, N Engl J Med.

# CONCLUSION: FAVORABLE EFFICACY AND SAFETY PROFILE FOR SUBJECTS 9–16 YEARS OF AGE IN DENGUE-ENDEMIC AREAS

## Key Efficacy Results – 25-month efficacy phase[1]

Overall VE of 65.6% against symptomatic VCD.

VE against severe dengue and dengue leading to hospitalizations during the 25-month efficacy phase was consistently demonstrated.

VE against symptomatic VCD of each serotype and in both dengue-seropositive and dengue-seronegative subjects.

## Key Safety Results – 25-month efficacy phase and up to 2 years of LTFU

- Continued lower risk of hospitalization.[1,3]
- SAE profile similar between the vaccine group and the placebo group.[1]
- SAEs consistent with medical disorders in the age group.[2]
- No evidence of sensitization.[1]
- Reduction of severe VCD in vaccine group based on pooled analysis across CYD14, CYD15, and CYD23/57.[1]

LTFU=long-term follow-up; SAE=serious adverse event; VCD=virologically confirmed dengue; VE=vaccine efficacy.


1. Hadinegoro et al. NEJM 2015;373(13):1195-206.
2. Capeding MR, et al. Lancet 2014;384:1358-65 8.
3. Hadinegoro SR et al. 5th Pan-American Dengue Research Meeting, Panama, Apr 20-23, 2016.

2

# Model comparison: The CMDVI exercise

# Comparative modelling of dengue vaccine public health impact (CMDVI) exercise

| | GROUP | LEAD | MODEL TYPE |
|---|---|---|---|
| 1 | Johns Hopkins and University of Florida | D. Cummings, I. Rodriguez-Barraquer | Deterministic non-spatial |
| 2 | Imperial College London | N. Ferguson | Deterministic non-spatial |
| 3 | Duke University | K. Koelle | Deterministic non-spatial |
| 4 | University of Florida | I. Longini | Stochastic spatial |
| 5 | University of Western Australia | G. Milne | Stochastic spatial |
| 6 | Notre Dame University | A. Perkins | Stochastic spatial |
| 7 | Exeter University and Oxford University | J. Lourenco, M. Recker | Stochastic spatial |
| 8 | Sanofi Pasteur | L. Coudeville | Deterministic non-spatial |

- To assess the potential value of dengue vaccination in different settings to inform the SAGE recommendation[1,2]
- Publicly available data from the phase III efficacy trials were used for model validation[1,2]
- Similar assumptions for all groups regarding vaccine mode of action[1,2]

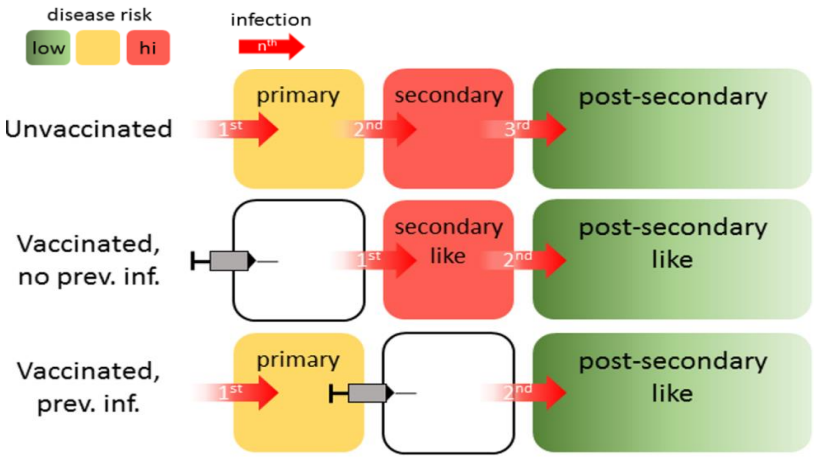
CMDVI, comparative modelling of dengue vaccine public health impact; SAGE, Strategic Advisory Group of Experts.

1. Flasche S, *et al*. Comparative modelling of dengue vaccine public health impact (CMDVI). Available at: http://www.who.int/immunization/sage/meetings/2016/april/2_CMDVI_Report_FINAL.pdf Accessed November 2016;
2. Flasche S, *et al. PLoS Med* 2016 (in press).

# Assumption regarding vaccine mode of action

**ASSUMPTION:**

Vaccination mimics a silent natural infection and modifies the probabilities of disease outcomes in the same manner as a natural infection[1,2]




**LIMITATIONS OF THIS ASSUMPTION[1,2]**

- Assumption that a 3-dose vaccination with a recombinant, tetravalent vaccine is equivalent to a primary wild-type infection with a single serotype
- Serostatus considered as the main driver of efficacy, age effect independent from seropositivity or differences according to serotype not considered in most models
- Data used for validation not accounting for differences in efficacy according to serotype or age-specific differences observed when controlling for serostatus

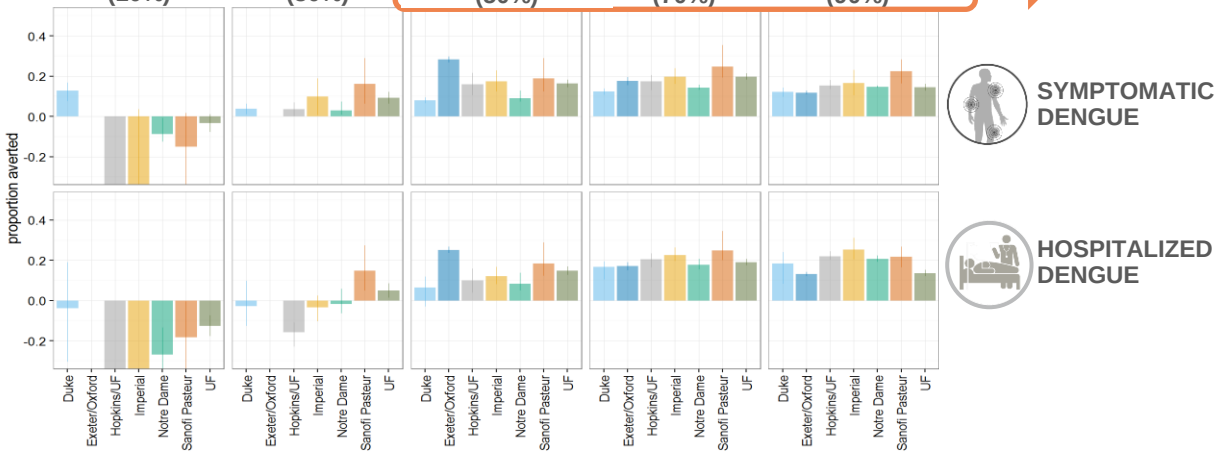

1. Flasche S, *et al*. Comparative modelling of dengue vaccine public health impact (CMDVI). Available at: http://www.who.int/immunization/sage/meetings/2016/april/2_CMDVI_Report_FINAL.pdf Accessed November 2016;
2. Flasche S, *et al. PLoS Med* 2016 (in press).

# Results on potential vaccination impact

**RESULT:**

**PROPORTION OF SYMPTOMATIC AND HOSPITALIZED DENV CASES AVERTED OVER 30 YEARS** (routine at 9 years, 80% coverage)[1,2]

Transmission intensity: VERY LOW (10%) | LOW (30%) | MODERATE (50%) | HIGH (70%) | VERY HIGH (90%) → Phase III data




- Vaccination benefits identified by all groups for moderate-to-high transmission settings ⇨
  Consistent with data observed during the trials for over 4 years in the indicated population (aged >9 years)
- Potential risk of increase in hospitalizations in very low-to-low transmission settings ⇨
  No direct evidence collected for these settings during Phase III efficacy trials

DENV, dengue virus.

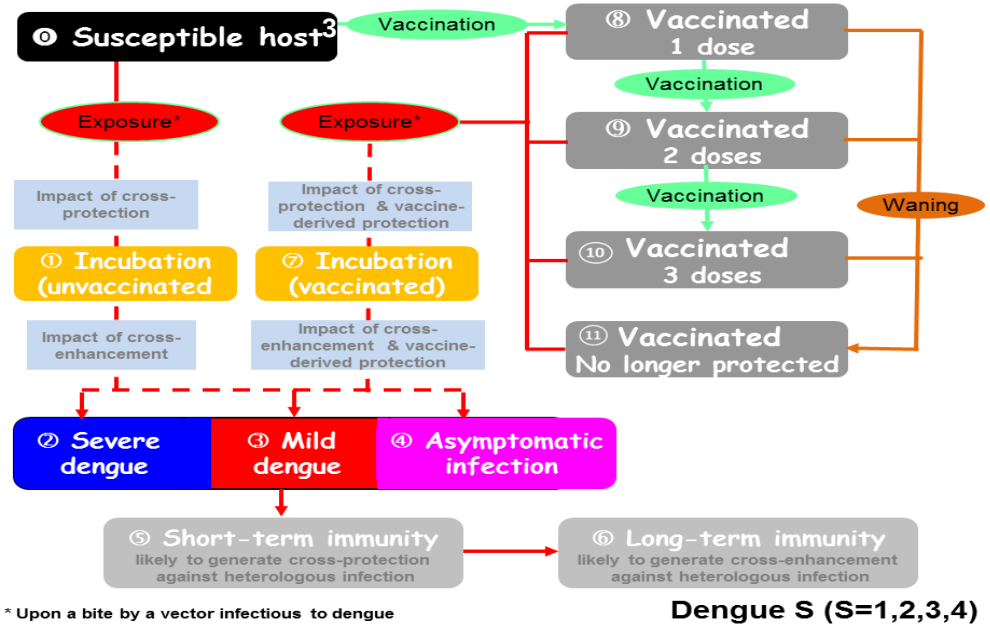
1. Flasche S, *et al*. Comparative modelling of dengue vaccine public health impact (CMDVI). Available at: http://www.who.int/immunization/sage/meetings/2016/april/2_CMDVI_Report_FINAL.pdf Accessed November 2016;
2. Flasche S, *et al. PLoS Med* 2016 (in press).

3

# The Sanofi Pasteur transmission model

# Model design

- Host-vector compartmental model accounting for interactions between the four dengue serotypes[1,2]
- Key model parameters estimated from **individual-level data collected in phase III efficacy studies**[1,2]
- Phase III data completed by country-specific routine surveillance and demographic data (10 countries)[1,2]



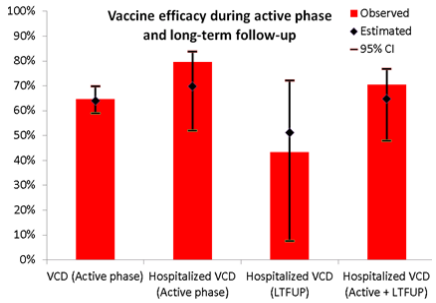

Adapted from: Coudeville L, *et al. PloS One* 2012;7(12):e51244.


1. Coudeville L, *et al, Vaccine* 2015
2. Coudeville L, *et al. Vaccine* 2016

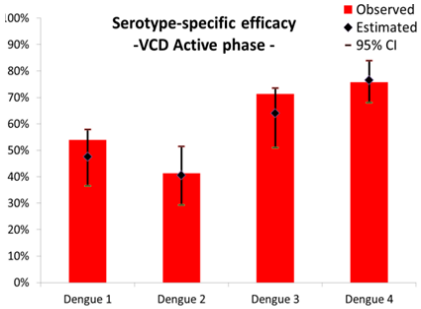
# Estimation from phase III data: Characteristics of the vaccine mode of action

| | Vaccine efficacy scenario[1] | |
|---|---|---|
| *Efficacy by serotype* | Serotype-specific | → Serotype |
| *Efficacy for seronegative subjects* | Lower efficacy than seropositive subjects | → Serostatus |
| *Efficacy against hospitalizations* | Higher for hospitalized cases | → Severity |
| *Increase in efficacy with doses* | Increase in efficacy with doses for naïve subjects | → Doses |
| *Waning of vaccine efficacy* | Waning dependent of serostatus | → Waning |
| *Accelerated exposure to secondary infection* | Yes | → Serostatus |
| *Age-specific differences not related to seropositivity* | Yes | → Age effect |

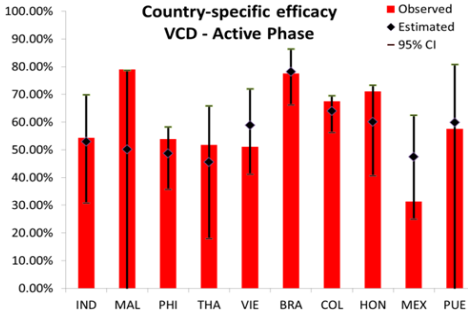
Indicated population[2]
(aged ≥9 years)




Serotype-specific[1,2]
(all ages)




Country-specific[1,2]
(all ages)





1. Coudeville L, *et al, Vaccine* 2015
2. Coudeville L, *et al. Vaccine* 2016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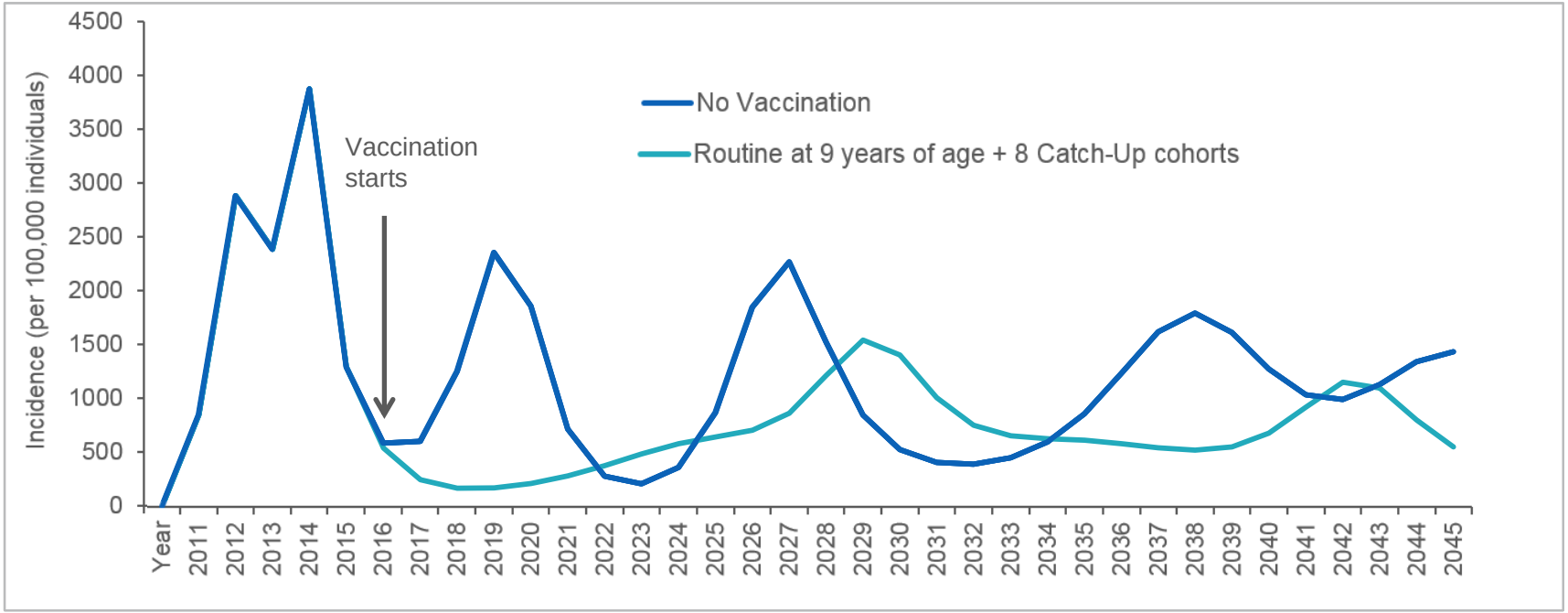
# Impact questions

- **What is the expected impact of vaccination over time?**

# Vaccination is expected to reduce the frequency and intensity of outbreaks

**SIMULATED EVOLUTION OF DENGUE INCIDENCE WITH AND WITHOUT VACCINATION IN MEXICO***




*Vaccination coverage in the targeted age groups 90%, first vaccination dose of the catch-up program administered in one year.

Coudeville L, *et al. Vaccine* 2016

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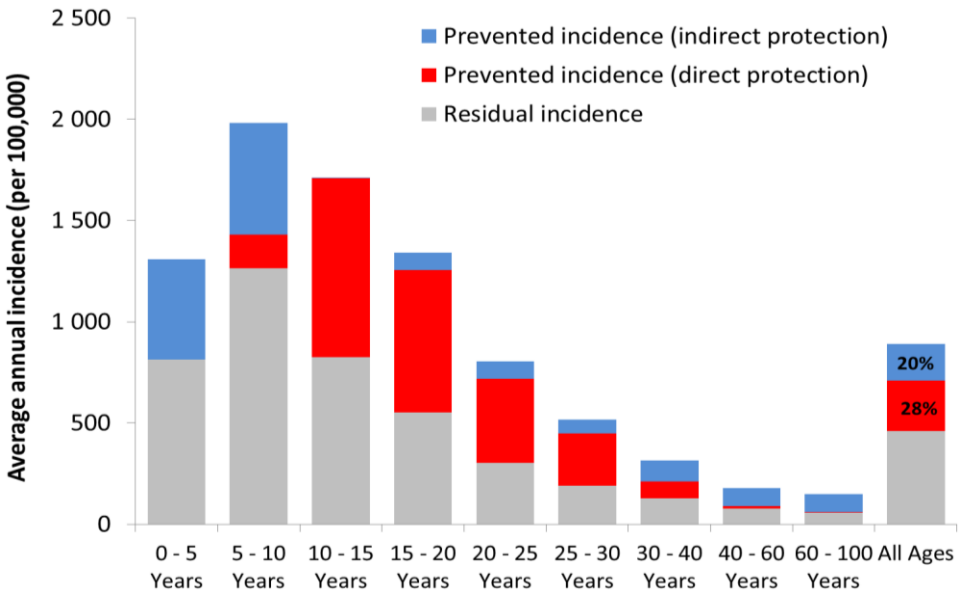
# Impact questions

- What is the expected impact of vaccination over time?
- **What is the contribution of indirect protection to vaccination impact?**

# Through indirect protection, vaccination can benefit the entire population

**PREVENTED CASES THROUGH DIRECT AND INDIRECT PROTECTION (VACCINATION IMPACT OVER 10 YEARS IN THE PHILIPPINES)**




The contribution of indirect protection to vaccination benefit varies with:

- Transmission intensity
- Vaccination program
- Time horizon considered

**By vaccinating 20% of the population, dengue cases could be reduced by 50% over 5 years**

Coudeville L, *et al. Vaccine,* 2016
Olivera-Botello G *et al.* J Infect Dis. Advance Access, 2016

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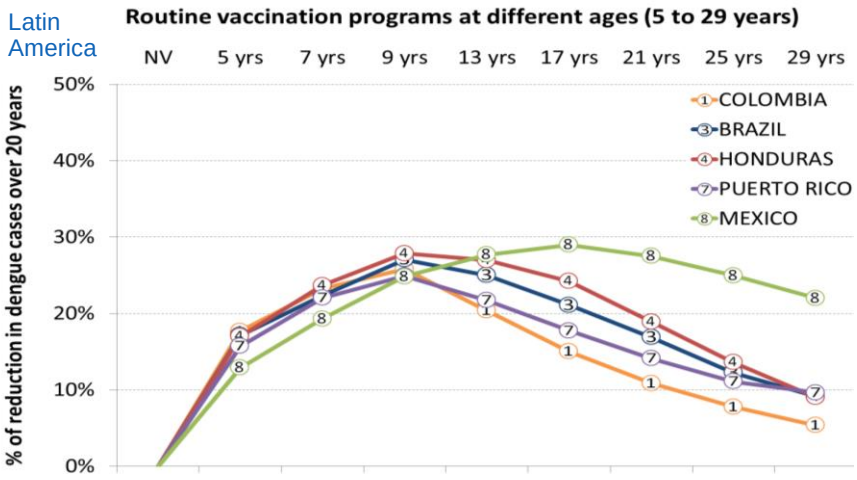
# Impact questions

- What is the expected impact of vaccination over time?
- What is the contribution of indirect protection to vaccination impact?
- **How does the value of vaccination vary with age?**

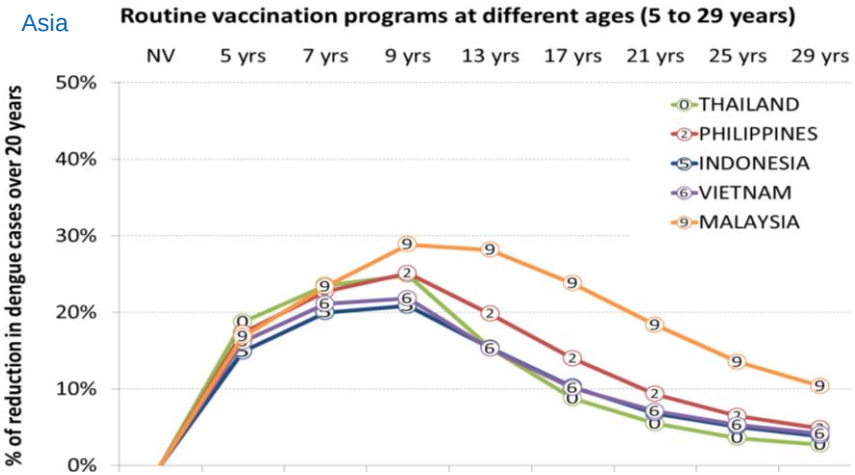
# Age groups to be targeted for vaccination are setting-dependent…

**CUMULATIVE REDUCTION IN NUMBER OF DENGUE CASES OVER 20 YEARS AT THE POPULATION LEVEL FOR ROUTINE VACCINATION PROGRAMS AT DIFFERENT AGES (5–29 YEARS)***

Latin America




Asia




…but 9 years of age is close to the most efficient age in most endemic countries

*Median reduction for a routine vaccination program with 90% coverage – parameters included in the sensitivity analysis: efficacy profile, relative efficacy versus asymptomatic cases, transmission intensity.

Coudeville L, *et al. Vaccine* 2016

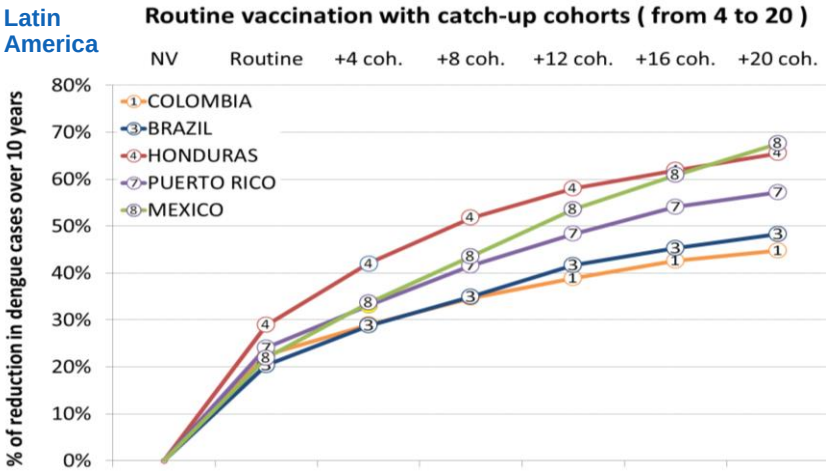
# Impact questions

- What is the expected impact of vaccination over time?
- What is the contribution of indirect protection to vaccination impact?
- How does the value of vaccination vary with age?
- **What type of vaccination program is likely to maximize the public health impact?**

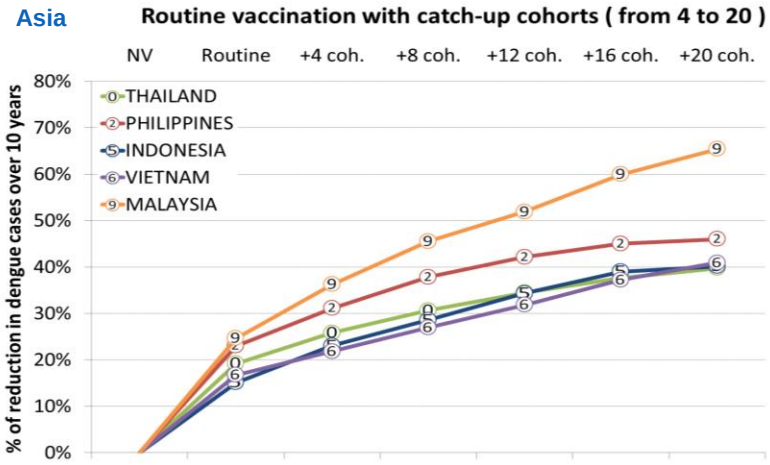
# Routine and catch-up programs can significantly impact dengue burden over the first 10 years following vaccine introduction…

**CUMULATIVE REDUCTION IN NUMBER OF DENGUE CASES OVER 10 YEARS AT THE POPULATION LEVEL, FOR ROUTINE VACCINATION AT 9 YEARS OF AGE + CATCH-UP CAMPAIGNS OF DIFFERENT MAGNITUDES (4–20 COHORTS)***

**Latin America**




**Asia**




…with an expected impact related to the magnitude of the catch-up program

*Median reduction for a vaccination program with 90% coverage, parameters included in the sensitivity analysis: efficacy profile, relative efficacy versus asymptomatic cases, transmission intensity.

Coudeville L, *et al. Vaccine* 2016

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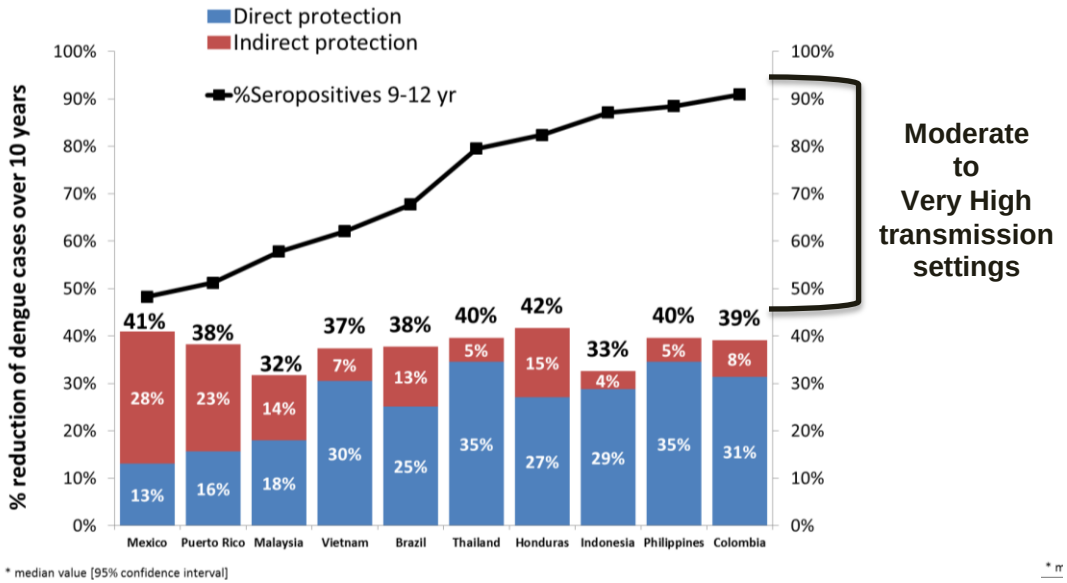
# Impact questions

- What is the expected impact of vaccination over time?
- What is the contribution of indirect protection to vaccination impact?
- How does the value of vaccination vary with age?
- What type of vaccination program is likely to maximize the public health impact?
- **Does the vaccine provide benefits for both seropositive and seronegative individuals?**

# Dengue vaccination is expected to provide protection for both seronegative and seropositive subjects in all settings included in the phase III trials

**CUMULATIVE REDUCTION IN THE NUMBER OF DENGUE CASES OVER 10 YEARS FOR 9-YEAR-OLD SUBJECTS, ACCORDING TO THEIR SEROSTATUS AT BASELINE**

**Seronegative vaccinees**




**Moderate to Very High transmission settings**

* routine vaccination program at age 9 years combined with a catch-up campaign for those aged 10–17 years (8 catch-up cohorts). Vaccination coverage: 90%.

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Coudeville L, *et al. Vaccine* 2016
L'Azou *et al. NEJM* 2016

4

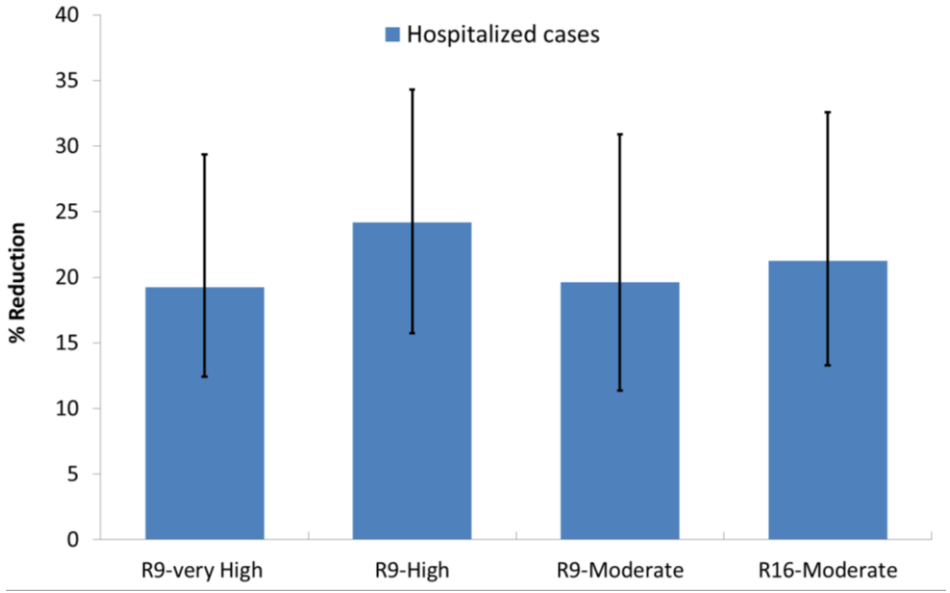
# Focus on Naïves, insights on how serotesting would affect impact

# Dengue vaccination* is expected to provide protection for both seronegative and seropositive subjects in all settings included in the phase III trials

**50-90% TRANSMISSION INTENSITY: CUMULATIVE REDUCTION** IN THE NUMBER OF HOSPITALIZED DENGUE CASES OVER 10 YEARS AT THE POPULATION LEVEL**

No serotesting:

- 100% of seropositives are vaccinated
- 100% of seronegatives are vaccinated




| | R9-very High | R9-High | R9-Moderate | R16-Moderate |
|---|---|---|---|---|
| Vaccinated subjects (M) | 35.8 | 35.8 | 35.8 | 35.8 |

* routine vaccination program at age 9 years. Vaccination coverage: 90%.

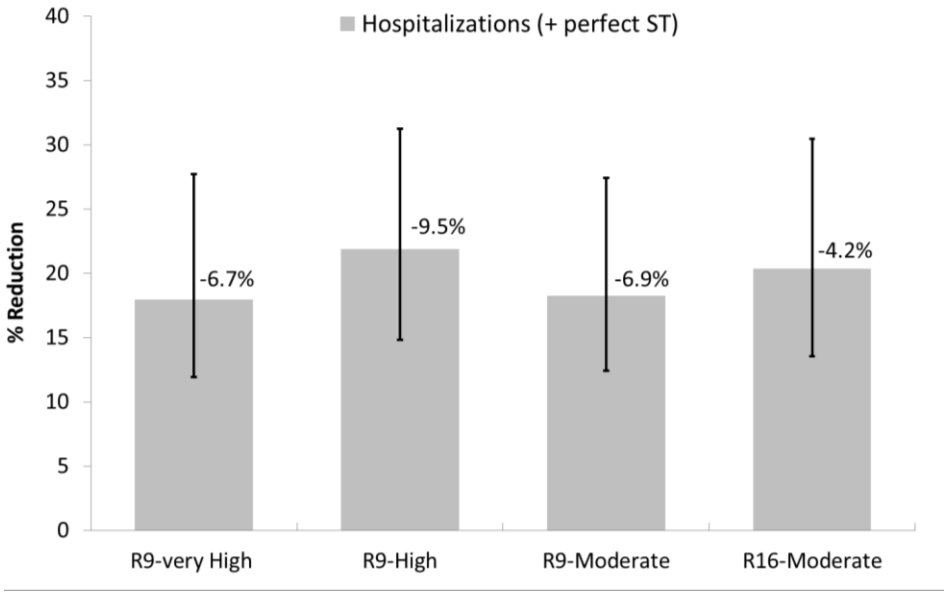
** median values [95 CI] based on 100 PSA samples (+/-10 % endemicity, [0-100%] relative efficacy, CYD14/15 vaccine efficacy, starting year of vaccination [0-8y.] )

# Use of serotesting in endemic settings would reduce the impact at the population level ( including seronegatives ! )

**50-90% TRANSMISSION INTENSITY: CUMULATIVE REDUCTION** IN THE NUMBER OF HOSPITALIZED DENGUE CASES OVER 10 YEARS AT THE POPULATION LEVEL**

Perfect serotest:

- 100% of seropositives are vaccinated
- 0% of seronegatives are vaccinated




| Vaccinated subjects (M) | R9-very High | R9-High | R9-Moderate | R16-Moderate |
|---|---|---|---|---|
| | 30.0 | 23.2 | 14.8 | 19.4 |

* routine vaccination program at age 9 years. Vaccination coverage: 90%.

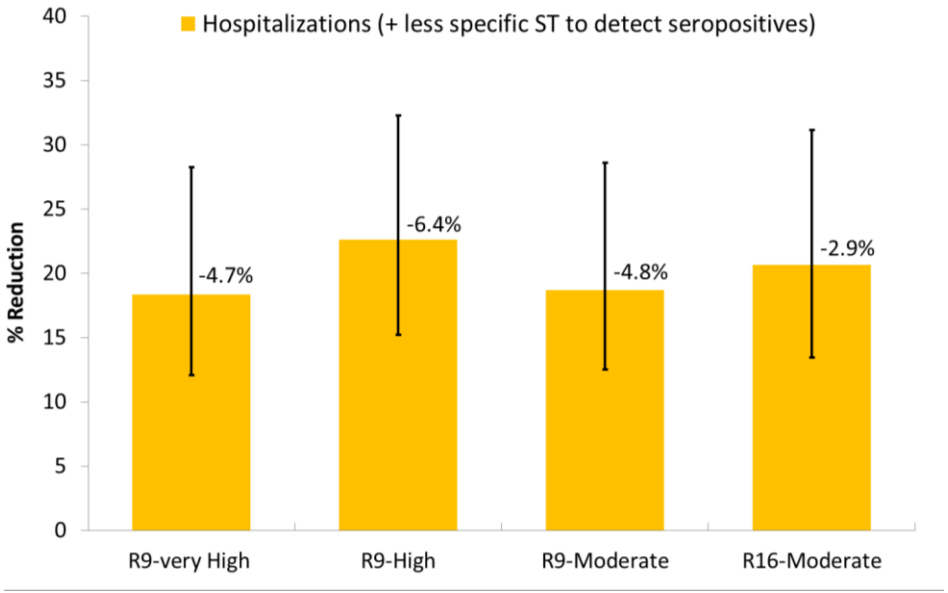
** median values [95 CI] based on 100 PSA samples (+/-10 % endemicity, [0-100%] relative efficacy, CYD14/15 vaccine efficacy, starting year of vaccination [0-8y.] )

# Use of serotesting in endemic settings would reduce the impact at the population level ( including seronegatives ! )

**50-90% TRANSMISSION INTENSITY: CUMULATIVE REDUCTION** IN THE NUMBER OF HOSPITALIZED DENGUE CASES OVER 10 YEARS AT THE POPULATION LEVEL**

Lack of specificity :

- 100% of seropositives are vaccinated
- 30% of seronegatives are vaccinated




| Vaccinated subjects (M) | R9-very High | R9-High | R9-Moderate | R16-Moderate |
|---|---|---|---|---|
| | 31.7 | 26.9 | 21.0 | 23.4 |

* routine vaccination program at age 9 years. Vaccination coverage: 90%.

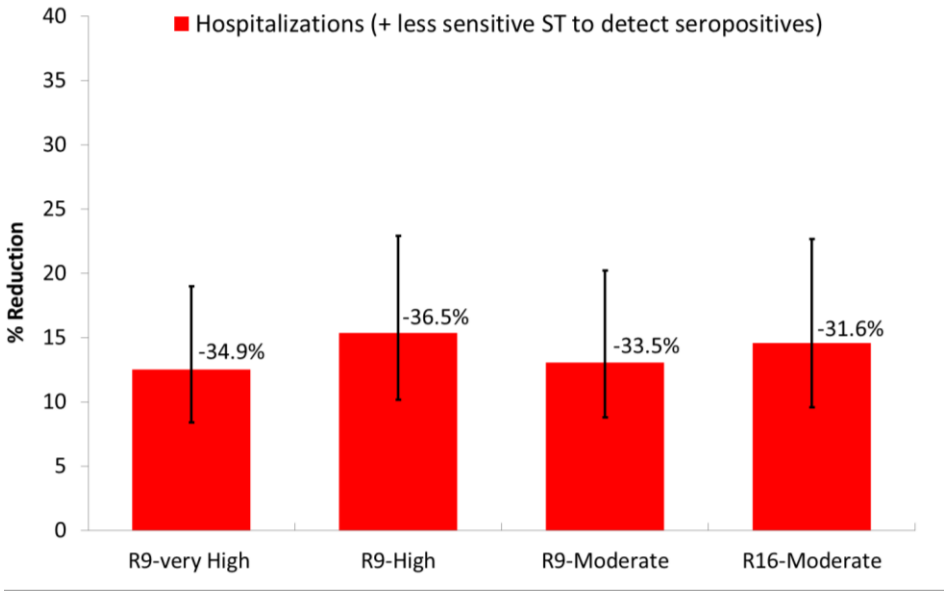
** median values [95 CI] based on 100 PSA samples (+/-10 % endemicity, [0-100%] relative efficacy, CYD14/15 vaccine efficacy, starting year of vaccination [0-8y.] )

# Use of serotesting in endemic settings would reduce the impact at the population level ( including seronegatives ! )

**50-90% TRANSMISSION INTENSITY: CUMULATIVE REDUCTION** IN THE NUMBER OF HOSPITALIZED DENGUE CASES OVER 10 YEARS AT THE POPULATION LEVEL**

Lack of sensitivity :

- 70% of seropositives are vaccinated
- 0% of seronegatives are vaccinated




| Vaccinated subjects (M) | R9-very High | R9-High | R9-Moderate | R16-Moderate |
|---|---|---|---|---|
| | 21.2 | 16.45 | 10.53 | 13.74 |

* routine vaccination program at age 9 years. Vaccination coverage: 90%.

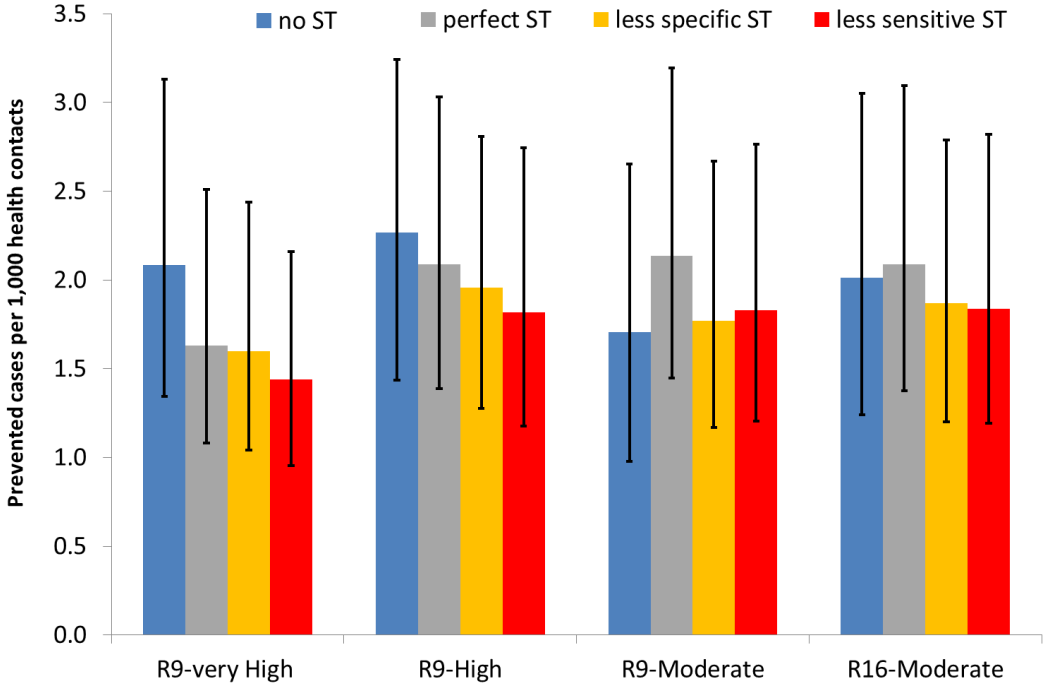
** median values [95 CI] based on 100 PSA samples (+/-10 % endemicity, [0-100%] relative efficacy, CYD14/15 vaccine efficacy, starting year of vaccination [0-8y.] )

# Use of serotesting in endemic settings would reduce the efficiency of the intervention, notably with less sensitivity to detect seropositives

**50-90% TRANSMISSION INTENSITY: NUMBER OF PREVENTED DENGUE HOSPITALIZATIONS** PER 1,000 HEALTH CONTACTS OVER 10 YEARS AT THE POPULATION LEVEL**

$$Efficiency = \left( \frac{\#\ prevented\ cases}{\#\ health\ contacts^{\perp}} \right) x1{,}000$$

⊥ Prevention contact = vaccination, serotesting




* routine vaccination program at age 9 years. Vaccination coverage: 90%.

** median values [95 CI] based on 100 PSA samples (+/-10 % endemicity, [0-100%] relative efficacy, CYD14/15 vaccine efficacy, starting year of vaccination [0-8y.] )

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# Conclusions

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- Efficacy has been demonstrated in the indicated population (aged 9 years and above) regardless of serostatus
- Safety profile is favorable up to 4 years after the 1st dose in the indicated population
- All modeling analyses performed in the context of CMDVI confirm vaccination benefits in moderate to high transmission settings in agreement with phase III results ⇒ positive WHO recommendation *
- Our analysis indicates that vaccination should reduce dengue risk for the whole population including seronegatives
- In this context, the use of serotesting would reduce the overall impact without improving efficiency, notably if the test used lacks sensitivity in detecting seropositives ( not considering feasibility issues )

* WHO position paper 2016. http://www.who.int/wer/2016/wer9130.pdf?ua=1

# THANK YOU