VACCINATION CONTRE LA DENGUE : DE LA CONCEPTION À L'AMM

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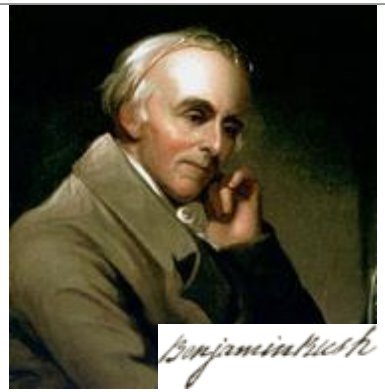
Dengue: Primeros brotes en las Américas 1600 - 1900



1635: Las primeras epidemias de dengue ocurrieron en Martinica y Guadalupe.

1780: Benjamin Rush describió un amplio brote en Filadelfia, Pensilvania, en los Estados Unidos.

1827: Primer brote multi-país (Islas Vírgenes, Cuba, Jamaica, Venezuela y ciudades en los EE.UU.).

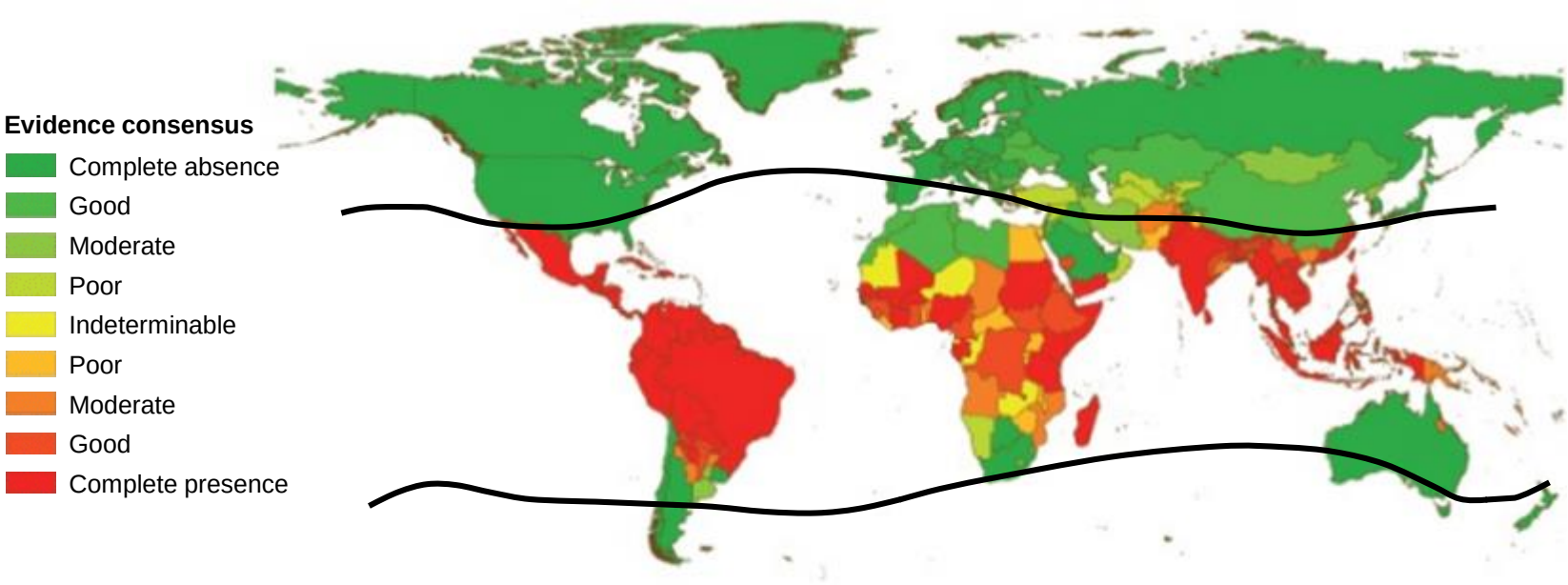
1912: Epidemia de dengue en Panamá, Puerto Rico, Chile y el norte de Argentina.

1600 1650 1700 1750 1800 1850 1900 1950

Pan American Health Organization
Regional Office of the World Health Organization

ABOUT HALF OF THE WORLD'S POPULATION LIVES IN DENGUE-ENDEMIC REGIONS[1]

GLOBAL EVIDENCE CONSENSUS: RISK AND BURDEN OF DENGUE IN 2010[2]



National and subnational evidence consensus on complete absence (green) through complete presence (red) of dengue.[3*]

- More than 100 endemic countries.[1]
- Dengue cases have been reported in several nonendemic countries and territories.[1]

*Black lines indicate areas at risk, defined by the geographic limits of the northern and southern hemispheres for year-round survival of *Aedes aegypti*.[3]

1. WHO, 2015, Dengue fact sheet.
2. Bhatt, 2013, Nature
3. WHO, 2012, Public Health Information and Geographic Information Systems.

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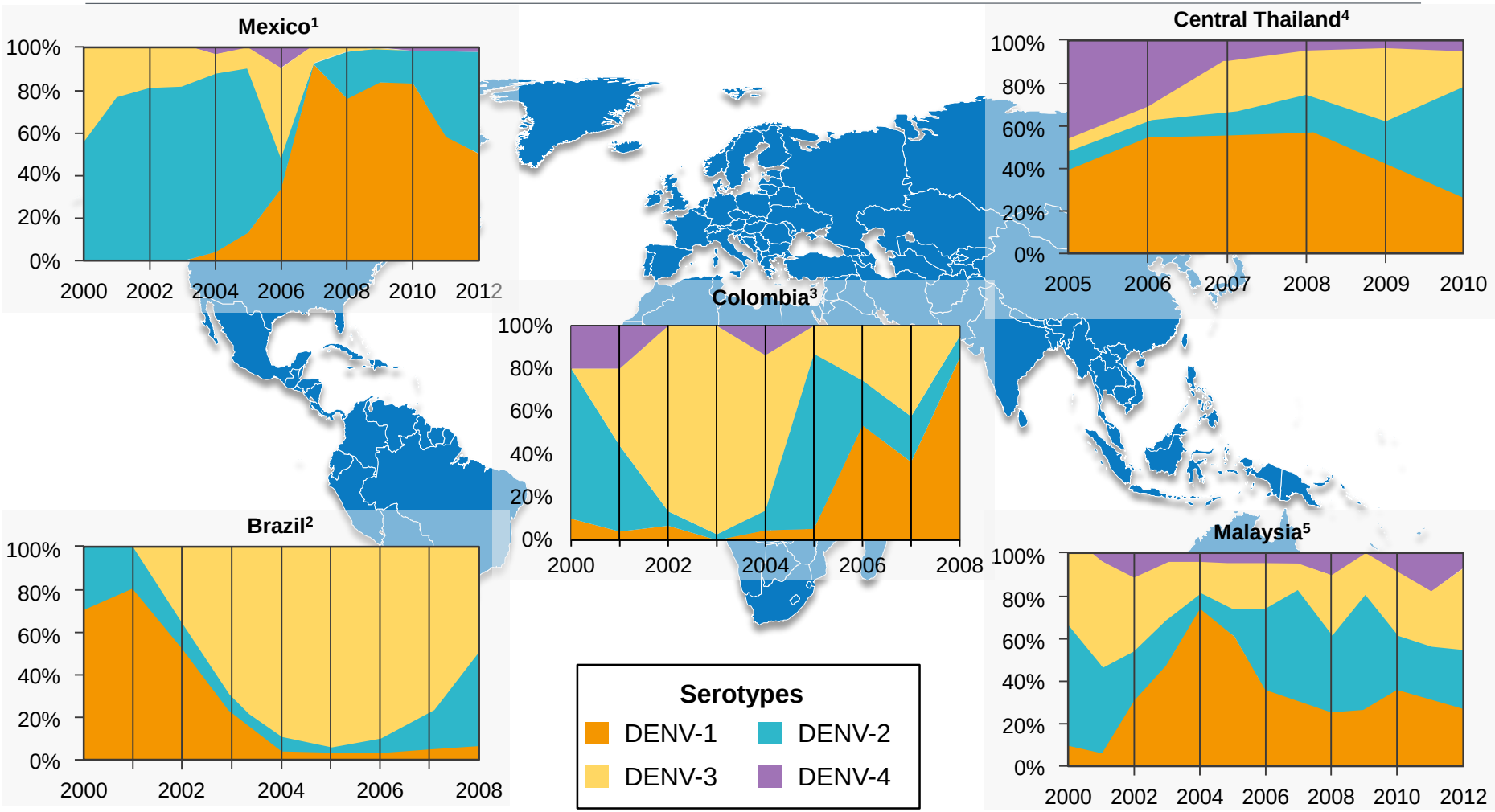
FOUR DENGUE SEROTYPES CAUSE DISEASE AND THEIR DISTRIBUTION VARIES UNPREDICTABLY



DENV=dengue virus.

1. Gomez Dantes, 2014, PLoS Negl Trop Dis.
2. Teixeira, 2013, PLoS Negl Trop Dis.
3. Villar, 2015, PLoS Negl Trop Dis.
4. Limkittikul, 2014, PLoS Negl Trop Dis.
5. Hamid, 2014, PLoS Negl Trop Dis.

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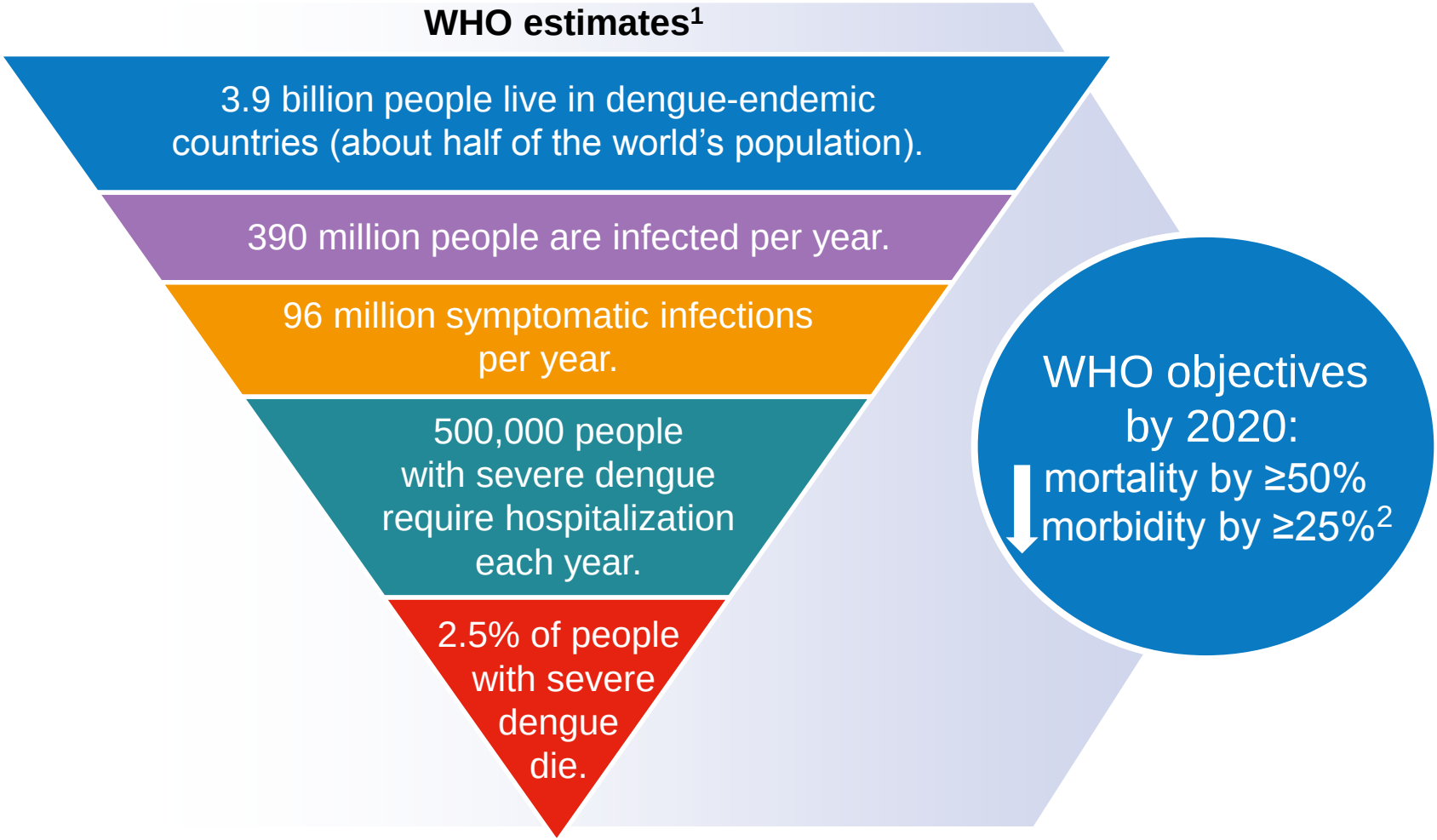
DENGUE IS A PUBLIC HEALTH PRIORITY WITH ALMOST 1 HOSPITALIZATION EVERY MINUTE

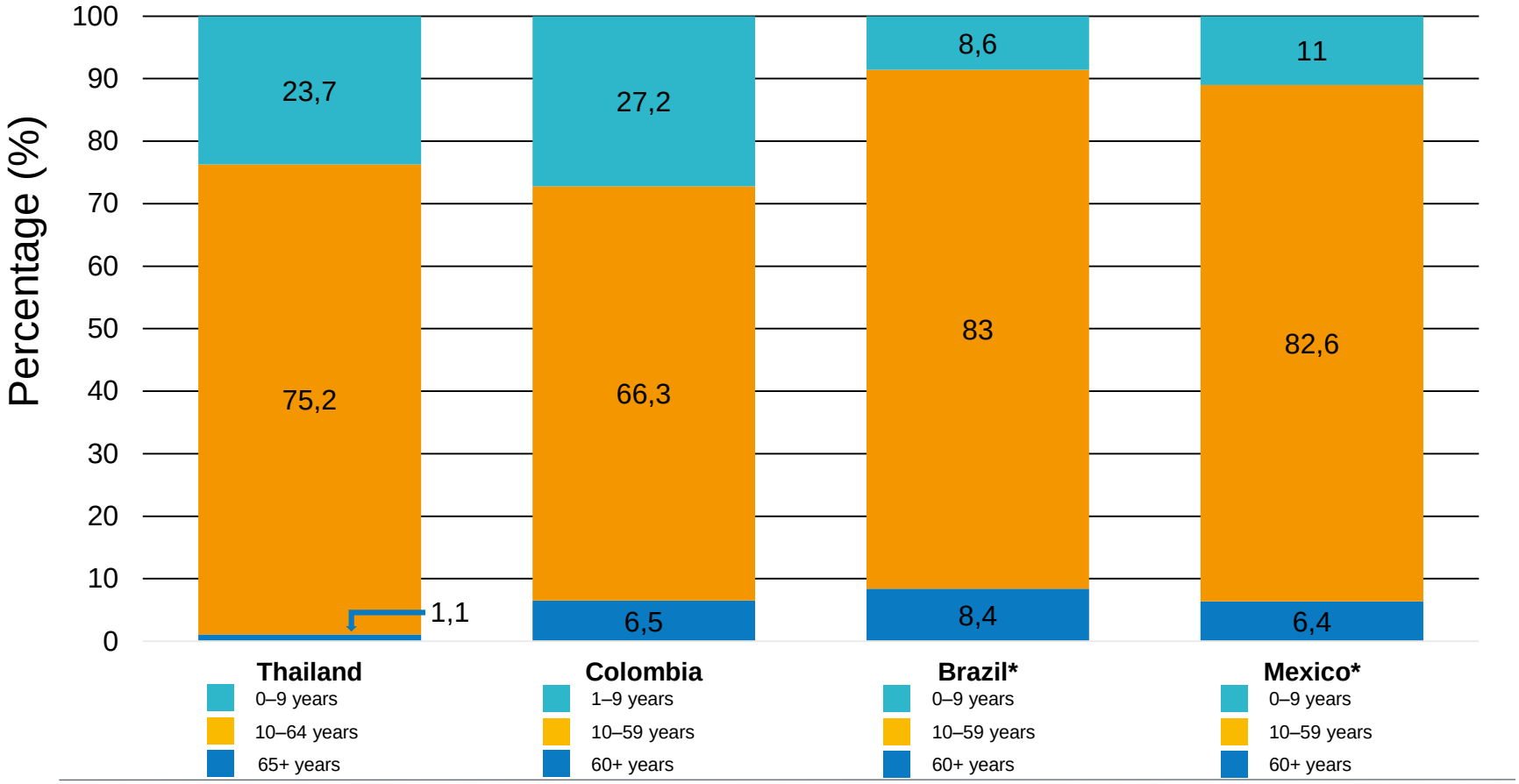


WHO=World Health Organization.

1. WHO, 2015, Dengue Fact Sheet.
2. WHO, 2012, Global Strategy for Dengue Prevention and Control.

ALTHOUGH DENGUE AFFECTS PEOPLE OF ALL AGES, THE MAJORITY OF CASES IN ENDEMIC COUNTRIES OCCUR IN PREADOLESCENCE TO ADULTHOOD[1]

Proportion of dengue cases by age group, 2010–2014
(4- to 5-year average data)



*Laboratory-confirmed cases.

1. Jackson, 2015, WSPID.

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24 February 2016

SANOFI PASTEUR'S DENGUE VACCINE APPROVED FOR INDIVIDUALS 9 TO 45 YEARS OF AGE IN DENGUE-ENDEMIC AREAS

9–45 years

Indicated for the prevention of dengue disease caused by dengue virus **serotypes 1, 2, 3, and 4** in individuals **9–45 years of age** living in **endemic areas**.

3-dose schedule

The vaccination schedule consists of 3 injections of 0.5 mL to be administered at 6-month intervals.

Once the freeze-dried vaccine has been completely reconstituted using the solvent provided, it is administered via the subcutaneous route.

CHALLENGES IN VACCINE DEVELOPMENT

- No animal model for the disease
- Four different dengue virus serotypes
- Variable dengue epidemiology across regions and over time
- No known immune correlate of protection
- Theoretical risk of immunopotentiation caused by heterologous pre-immunity

- Need for a combined tetravalent vaccine
- Need for efficacy demonstration in the absence of widely accepted correlate of protection
- Need for large-scale safety studies and long-term follow-up
- Manufacturing process scale-up to supply large-scale phase III studies and subsequent broad vaccination programs

Guy, 2011, Vaccine.
WHO, 2011, Dengue Vaccine Guidelines.
Simmons 2012, New Engl J Med.
Halstead 1992 World Health Strat Q.
Sabchareon, 2012, Lancet..
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OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

- Clinical development program **initiated** in 2001.[1]
- Objectives are to **characterize the vaccine in terms of efficacy, safety and immunogenicity profiles**, when assessed in different **regions**, in different **age** groups and in **populations** with various degrees of endemicity.[4]

- Choice of controls: **no licensed vaccines to prevent dengue disease**. Clinical studies were either controlled with a placebo, or with an active vaccine conferring protection against another disease.[2,3]
- 2015: registration files submitted in different endemic countries.[5]

1. sanofi pasteur, 2015, Dengue fact sheet.
2. Sabchareon, 2012, Lancet.
3. Capeding, 2014, Lancet.
4. Guy, 2015, Vaccine.
5. Sagonowsky, 2015, FiercePharma.

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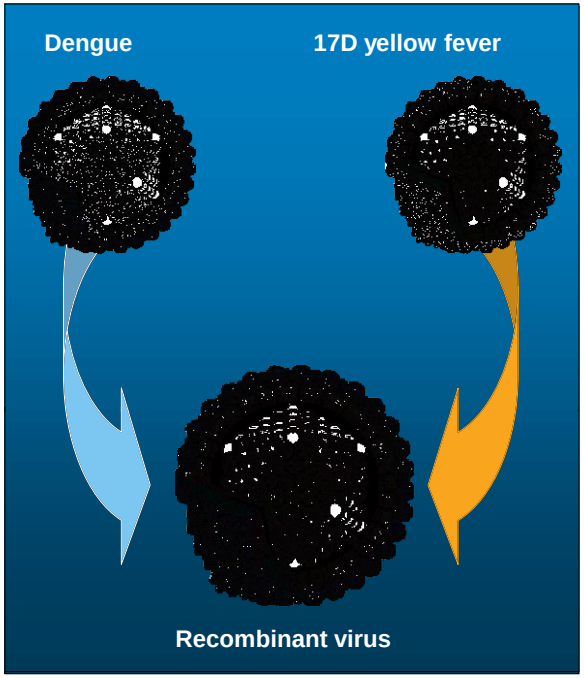
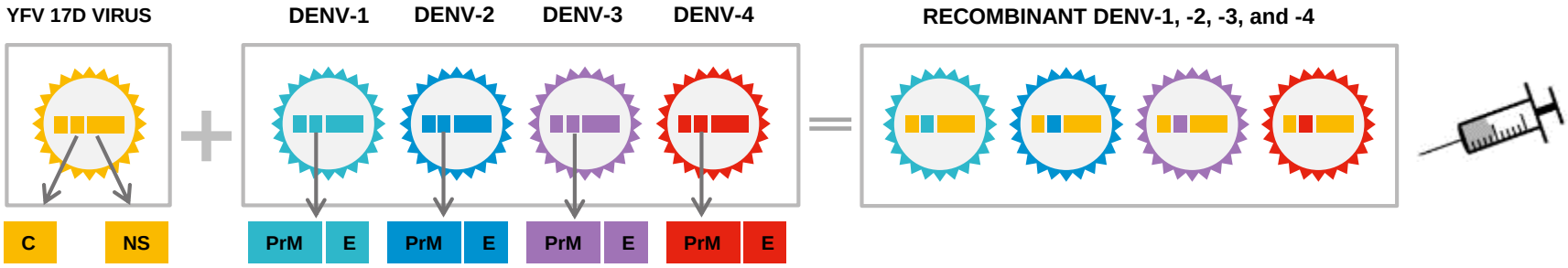
PRESENTATION AND COMPOSITION OF THE VACCINE

- A 4-serotype, recombinant, live, attenuated vaccine.[1-3]
  - **Four genetic constructs with 1 for each serotype.**
  - **Genes from each serotype combined with the genes encoding C and NS proteins from YFV 17D vaccine strain.**
- Combination into a single vaccine with ~5 $\log_{10}$ $CCID_{50}$ of each serotype.[1]
  - **Freeze-dried for reconstitution with 0.4% NaCl for single-dose (pre-filled syringe) or 0.9% NaCl for multidose (5 doses) presentations (vial).**
  - **Without adjuvant or preservatives.**
- After reconstitution, one 0.5 mL dose is to be administered by the SC route.[1]





C=capsid; DENV=dengue virus; $CCID_{50}$=cell-culture infectious dose 50%; CYD-TDV=chimeric yellow fever 17D-tetravalent dengue vaccine. E=envelope; NS=nonstructural; prM=precursor membrane; SC=subcutaneous; YFV 17D=Yellow fever vaccine 17D.

1. sanofi pasteur, 2015, data on file.
2. Guirakhoo 2000, J Virol
3. Guirakhoo, 2001, J Virol.
4. Guy, 2011, Vaccine.

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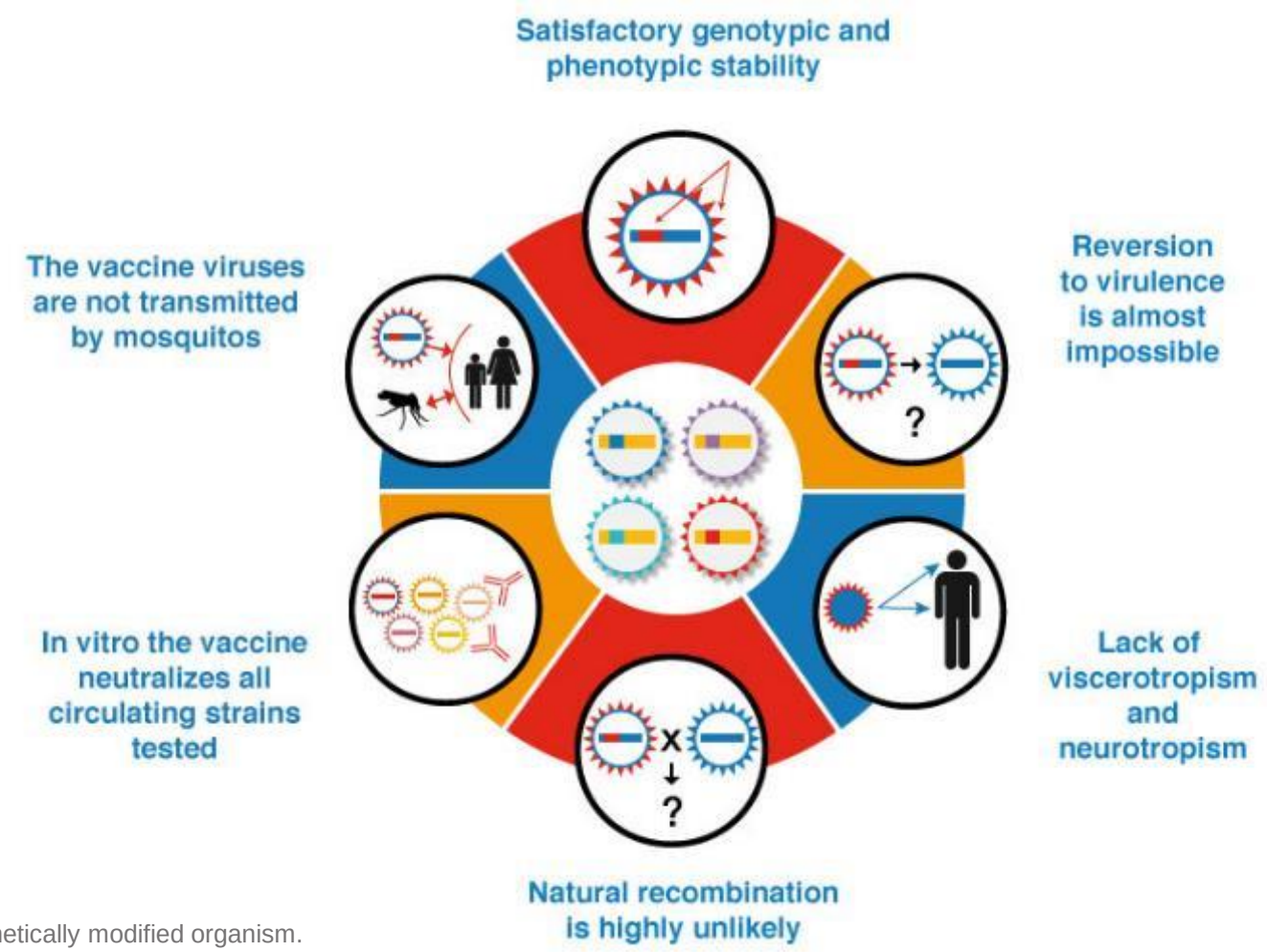
KEY ELEMENTS OF THE NON-CLINICAL DEVELOPMENT:
CHARACTERIZATION AND GMO ASPECTS



GMO=genetically modified organism.

Guirakhoo, 2001, J Virol.
Guirakhoo, 2000, J Virol.
McGee, 2008, J Infect Dis (1).
McGee, 2008, J Infect Dis (2).
Mantel, 2011, Vaccine.
.

Johnson, 2004, Am J Trop Med Hyg
Higgs, 2006, Am J Trop Med Hyg.
Barban, 2012, Virol.
Guirakhoo, 2004, J Virol.
Brandler, 2005, Am J Trop Med Hyg.

OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM CLINICAL DATABASE

- **25 clinical studies**, in 15 countries, completed (20) or ongoing (5).[1]
- More than **40,000 subjects** included in clinical studies.[1]
- Nearly **29,000 individuals** **children, adolescent and adults** received the vaccine.[2]

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

14 phase II trials[4]
in 14 countries
(USA, Australia, Latin America, Asia)
N=5400 CYD vaccinees
Ages: 12 months–45 years

6 phase III trials[4]
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. Monath, 2015, Vaccine.
3. Guy, 2011, Vaccine.
4. ClinicalTrials.gov, 2015, Accessed November 5, 2015.

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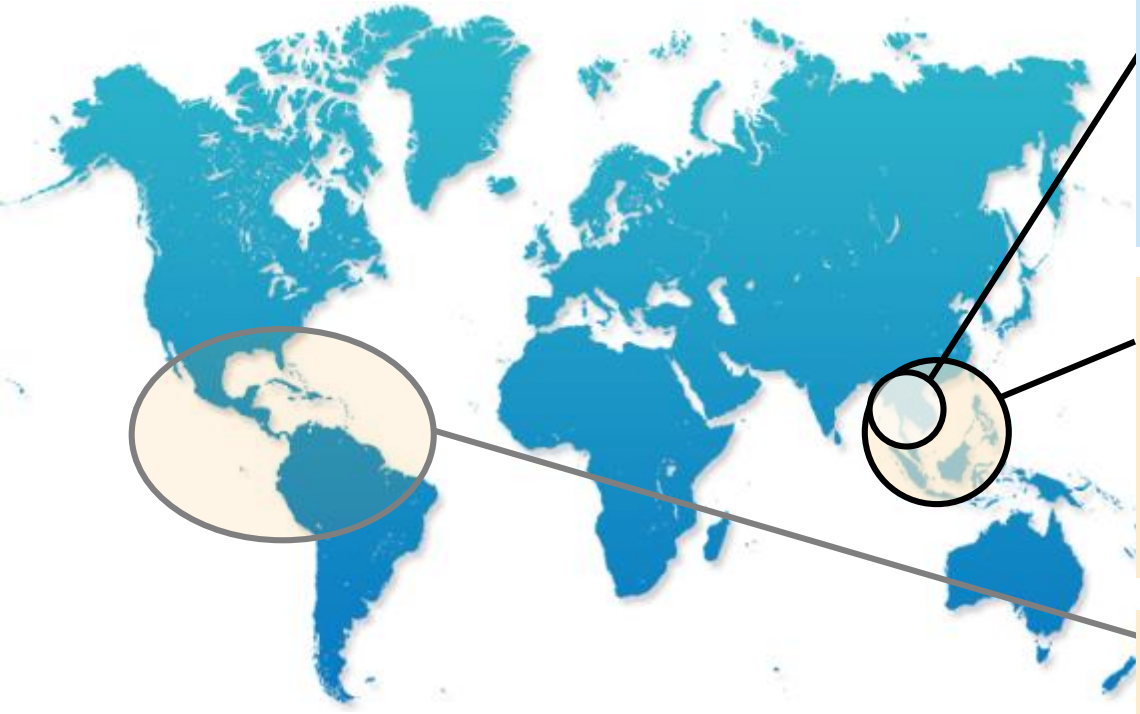
TWO PHASE III LARGE-SCALE RANDOMIZED EFFICACY STUDIES AND ONE PHASE IIb EFFICACY STUDY OF THE CANDIDATE DENGUE VACCINE INCLUDED >35,000 PARTICIPANTS IN ENDEMIC COUNTRIES

- **2009: first proof-of-concept phase IIb efficacy study; results published September 2012.[1]**
- **2011: 2 large-scale efficacy studies in Asia-Pacific and Latin America; results published in 2014.[2,3]**



*CYD57 is the long-term follow–up of CYD23.

Phase IIb Efficacy Asia-Pacific (CYD23/57*) Proof-of-concept study[1,4]

- **Country: Thailand**
- **Age group: 4–11 years**
- **Sample size: 4,002**
- **Long-term follow-up: 5 years postdose 3**
- **Year of completion: 2016**

Phase III Efficacy Asia-Pacific (CYD14)[3]

- **Countries: Thailand, Indonesia, Malaysia, Vietnam, Philippines**
- **Age group: 2–14 years**
- **Sample size: 10,275**
- **Long-term follow-up: 5 years postdose 3**
- **Year of completion: 2017**

Phase III Efficacy Latin America (CYD15)[2]

- **Countries: Colombia, Mexico, Honduras, Puerto Rico, Brazil**
- **Age group: 9–16 years**
- **Sample size: 20,869**
- **Long-term follow-up: 5 years postdose 3**
- **Year of completion: 2017**

1. Sabchareon, 2012, Lancet.
2. Villar, 2015, N Engl J Med.
3. Capeding, 2014, Lancet.
4. sanofi pasteur, 2015, data on file.

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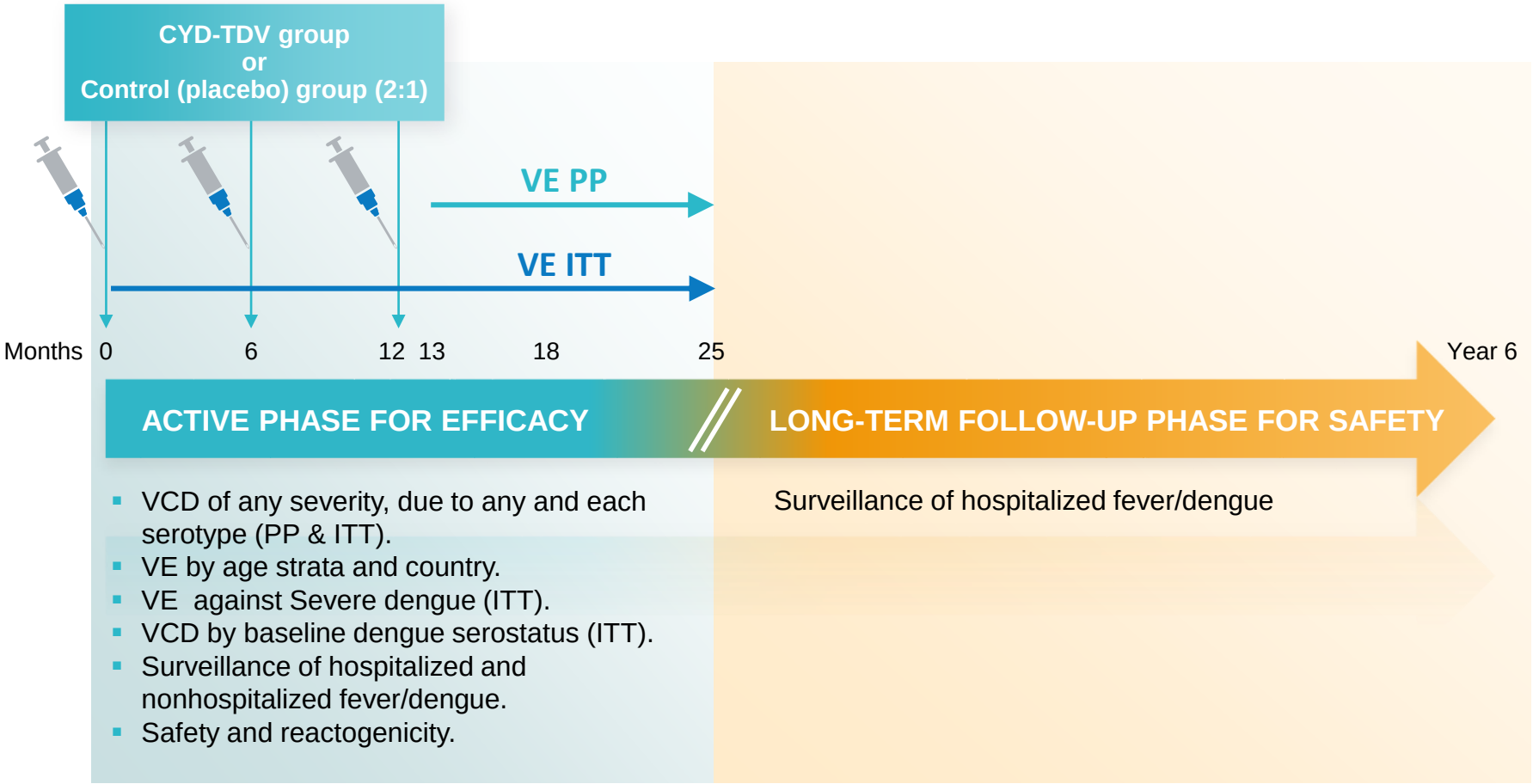
PHASE IIb AND PHASE III STUDIES: SIMILAR STUDY DESIGN WITH A 25-MONTH EFFICACY SURVEILLANCE PHASE AND A 4-YEAR LONG-TERM SAFETY FOLLOW-UP PHASE[1]



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

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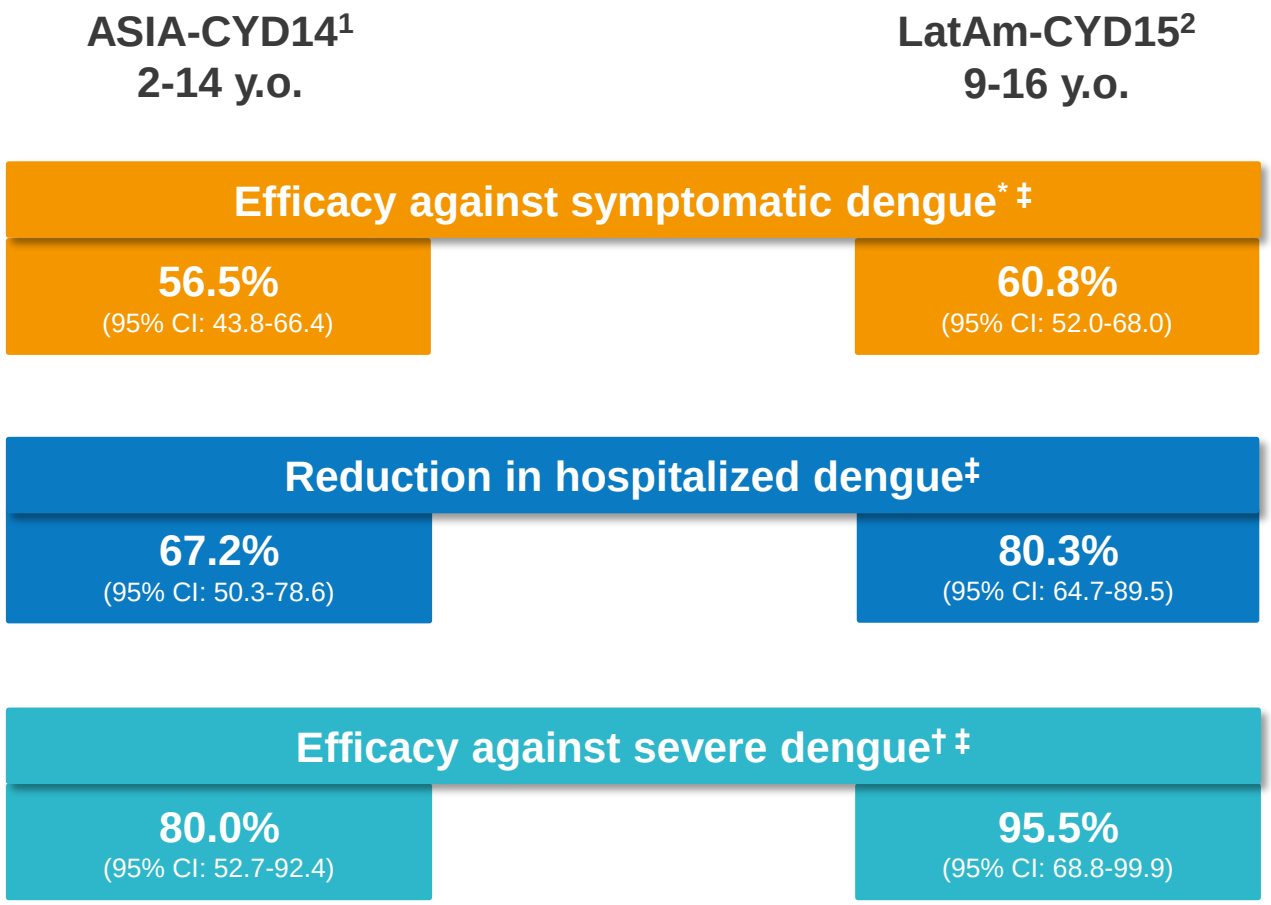
1.Hadinegoro, 2015, N Engl J Med.

TWO PHASE III EFFICACY TRIALS DEMONSTRATED A CONSISTENT EFFICACY PROFILE DURING THE 25 MONTH-ACTIVE PHASE

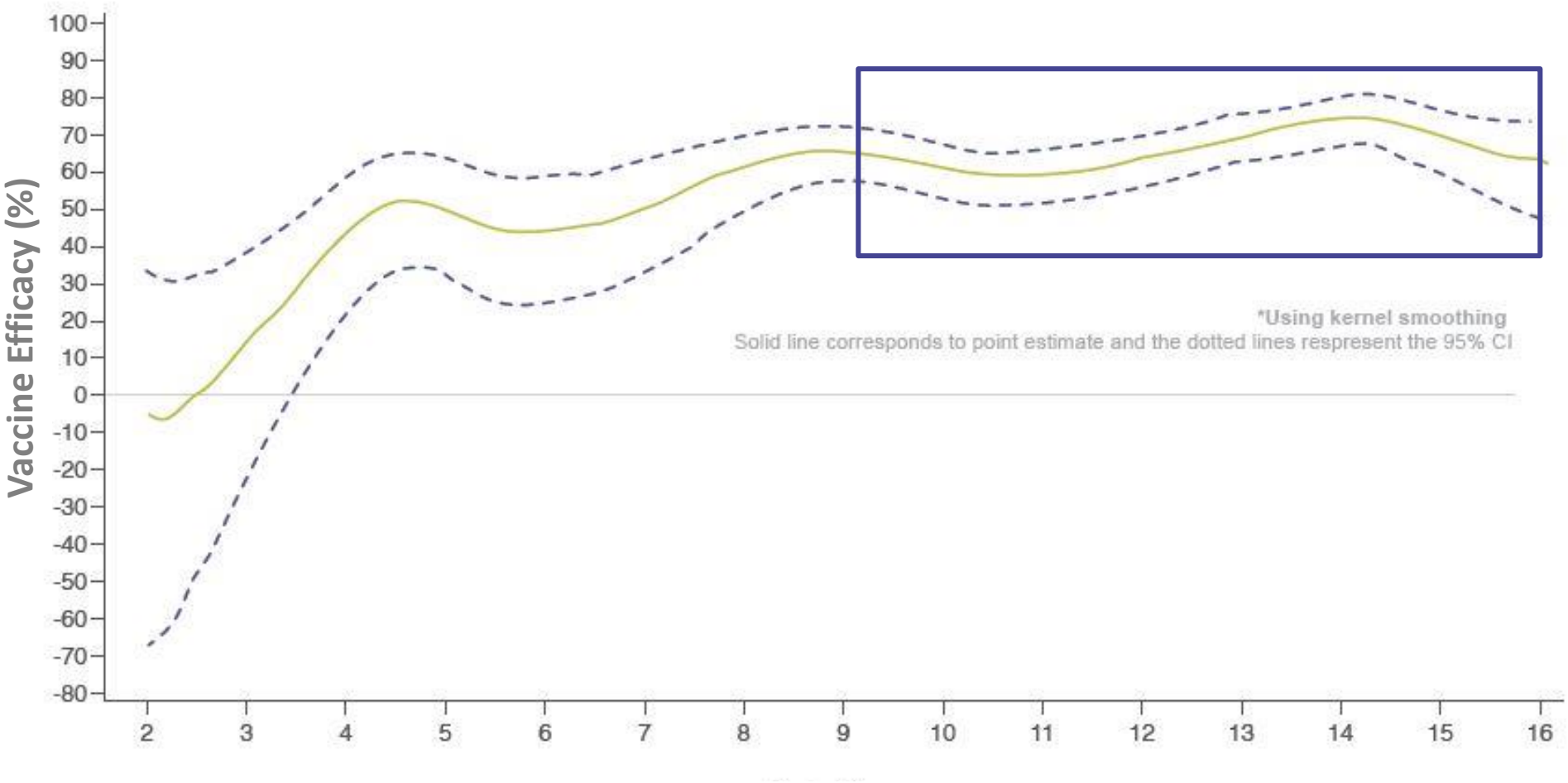


**Per protocol, 12 months post-dose 3 for CYD14 and CYD15 individual studies ; †Dengue hemorrhagic fever, World Health Organization (WHO) 1997 criteria, intent to treat; ‡Intent to treat, 25 months post dose 1 for hospitalized dengue, severe dengue*

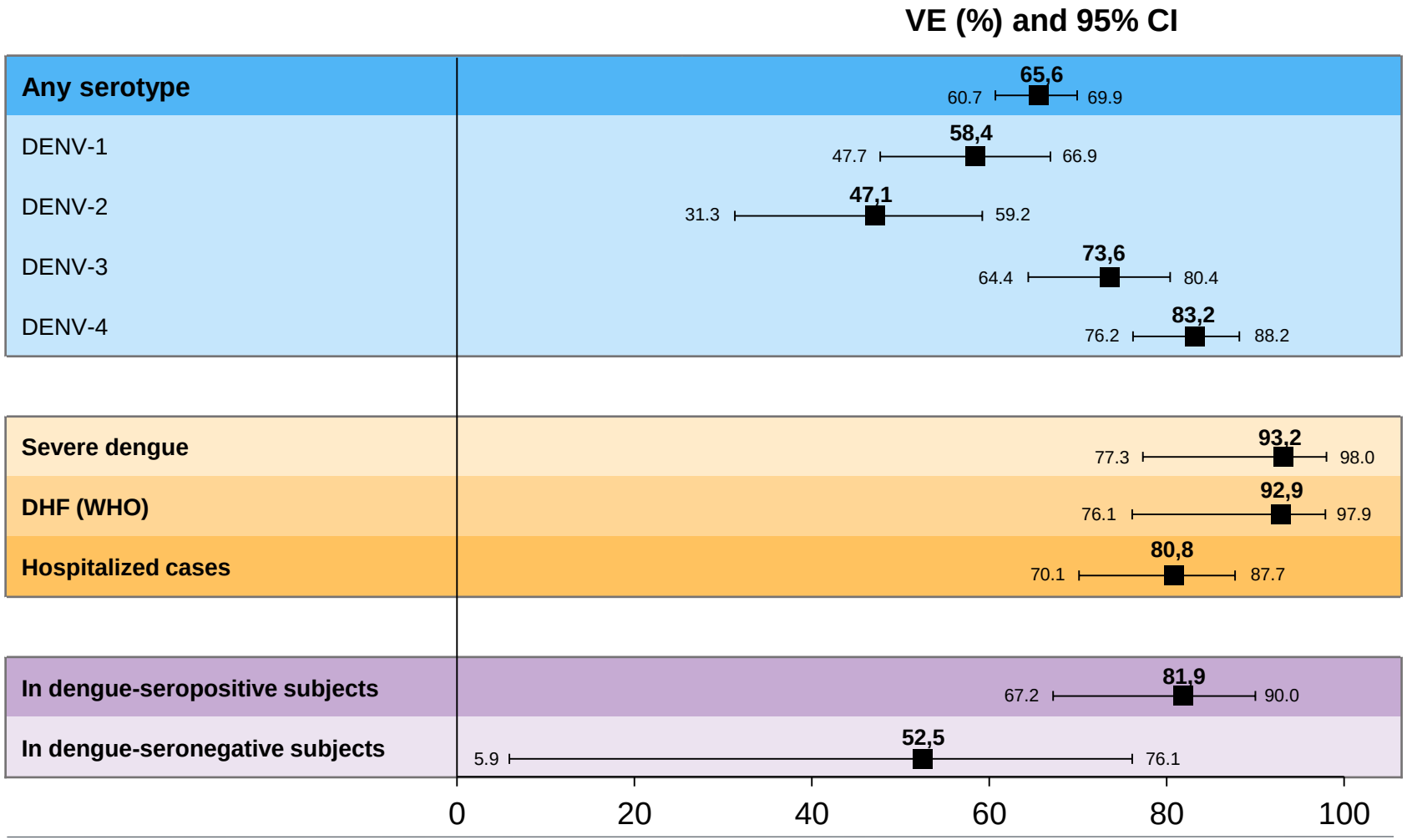
1. *Capeding, 2014, Lancet*
2. *Villar, 2015, N Engl J Med.*

VACCINE EFFICACY ACCORDING TO AGE AS A CONTINIOUS VARIABLE (CYD14 AND CYD15) 25 MONTH OF THE ACTIVE PHASE

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)



CONSISTENT VACCINE EFFICACY FOR VIROLOGICALLY CONFIRMED DISEASE DUE TO ANY & EACH SEROTYPE, SEVERITY, AND PRIOR DENGUE EXPOSURE IN SUBJECTS AGED 9–16 YEARS DURING THE ACTIVE PHASE (25 MONTHS)[1]



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

Hadinegoro et al., 2015, N Engl J Med. http://www.ncbi.nlm.nih.gov/pubmed/26214039

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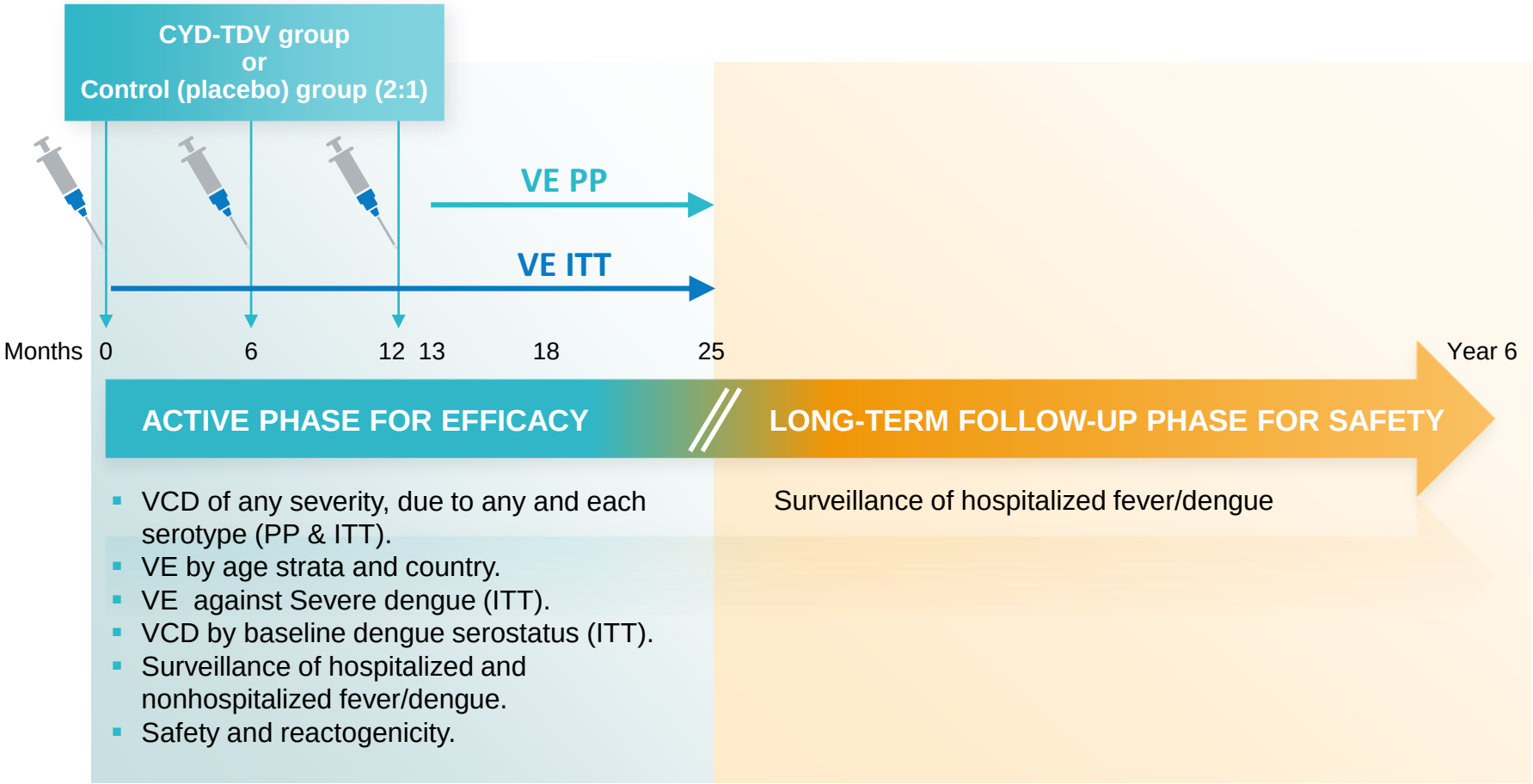
PHASE IIb AND PHASE III STUDIES: SIMILAR STUDY DESIGN WITH A 25-MONTH EFFICACY SURVEILLANCE PHASE AND A 4-YEAR LONG-TERM SAFETY FOLLOW-UP PHASE[1]



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

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1.Hadinegoro, 2015, N Engl J Med.

NO IMPORTANT DIFFERENCE IN CLINICAL SIGNS, SYMPTOMS & BIOLOGY DURING ONGOING LTFU VS. ACTIVE PHASE & PLACEBO[1]

LENGTH OF HOSPITALIZATION

Similar for both the 25-month active 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.

FREQUENCIES OF SIGNS AND SYMPTOMS

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

VIREMIA AND IMMUNE PROFILE PATTERN

- Similar levels of viremia observed in vaccine vs control groups (CYD14 and CYD15).
- No cytokine/chemokine pattern associated with increased disease enhancement in vaccine *vs* placebo.

LTFU=long-term follow-up; VCD=virologically confirmed dengue.

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 (93%) and dengue leading to hospitalizations (80%) 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

- **Acceptable safety profile: Similar AE rates between vaccine and control groups**
- Continued lower risk of hospitalization.[1]
- SAE profile similar between the vaccine group and the placebo group[1], 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 from efficacy trials (CYD14, CYD15, and CYD23/57) will provide additional evidence in **individuals <9 years of age**.

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

1. Hadinegoro, 2015, N Engl J Med.
2. Capeding, 2014, Lancet.

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OBJECTIVES OF THE POSTLICENSURE PLAN

Allow Benefit/Risk assessment through Risk Management Plan execution

Approved indication[1]
9–60 years of age
3 doses (0–6–12 months)
Preventive vaccine in endemic areas

- LONG-TERM EFFICACY AND SAFETY[2]
  - Surveillance expansion*
- EVALUATE VACCINE PROFILE IN REAL WORLD[3]
  - Routine and enhanced PV activities
  - PAES and PASS
- LIFECYCLE VACCINE PROFILE EXPANSION[4,5]
  - Booster and alternative dose schedule
  - Studies in specific populations
  - Coadministration studies
  - Support further licensures

*Active surveillance/detection of symptomatic (in addition to hospitalized) dengue cases.
PAES=postauthorization effectiveness studies; PASS=postauthorization safety studies; PV=pharmacovigilance.

1. sanofi pasteur, 2015, data on file.
2. Hadinegoro, 2015, N Engl J Med.
3. Guy, 2015, Vaccine.
4. WHO, 2011, Guidelines on the quality, safety, and efficacy of dengue tetravalent vaccines (live, attenuated).
5. Global Vaccine Safety Initiative (GVSI), 2015, fourth meeting report.

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SIGNIFICANT INDUSTRIAL COMMITMENT TO ENSURE ACCESS AND CONSISTENT SUPPLY

Ready to produce >1 billion doses over the next 10 years[1]

- Investment towards **state-of-the-art facilities**, developed specifically for production of dengue vaccine.[1]
- Designed to produce **100 million doses of vaccine per year** and respond to public vaccination needs.[1]
- Vaccine supplied as early as end of **2015**.[1,2]

Manufacturing Site, Neuville-sur-Saône, France

1. sanofi pasteur, 2015, Dengue Fact Sheet.
2. sanofi pasteur, 2015, From Research to Production: A Quest to Make Dengue Preventable.

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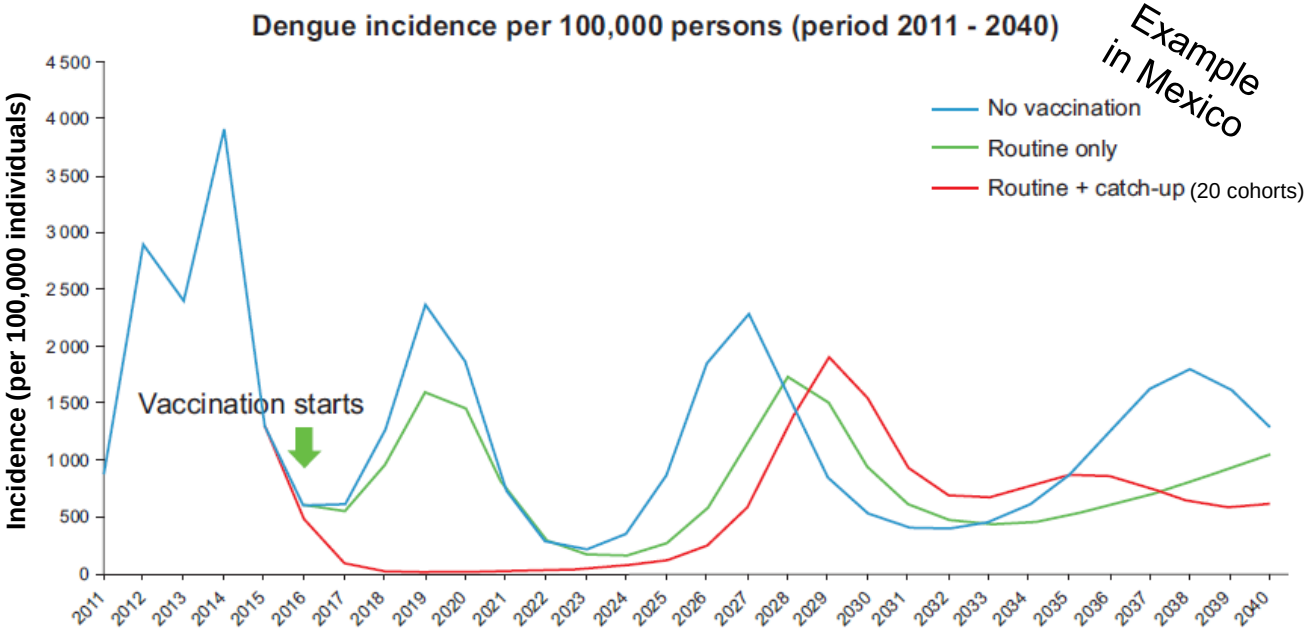
LARGE VACCINATION PROGRAM IS EXPECTED TO DECREASE THE FREQUENCY AND INTENSITY OF OUTBREAKS, REDUCING ASSOCIATED HEALTH CARE SYSTEM CONGESTION[1]*

Vaccination can moderate peaks in number of cases and reduce overall level of incidence.

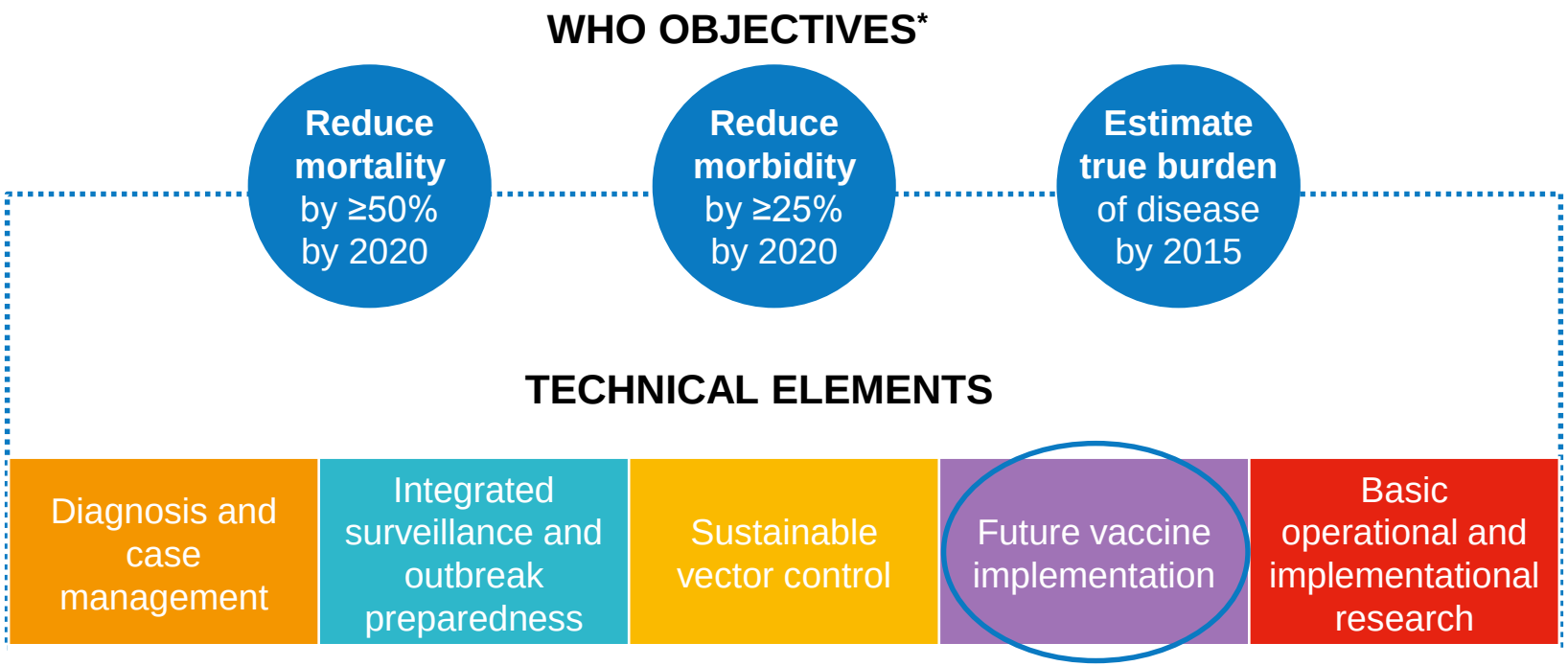


- Unpredictable variability of dengue incidence over time causes **distress in the health care infrastructure.**
- Vaccination does not stop year-to-year variations in dengue incidence but, rather, **limits the frequency and intensity of these variations.**
- Introducing large **catch-up programs limits the risk of outbreaks** during the first years.

*Based on Sanofi Pasteur phase III study results, with 10 countries included, and considering homogeneous parameters among countries.

1. Coudeville, 2015, SLIPE.

DENGUE VACCINATION PROGRAM: A MAJOR ADVANCE FOR DISEASE CONTROL THAT COULD HELP ACHIEVE WHO OBJECTIVES[1]



- Vaccination is a critical pillar of the WHO's strategy towards effectively fighting dengue.

*The baseline year is 2010.
WHO=World Health Organization.

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1. WHO, 2012, Global Strategy for Dengue Prevention and Control.

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