Société de Pharmacie de Lyon
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Sanofi Pasteur Dengue Vaccine, its development up to registration

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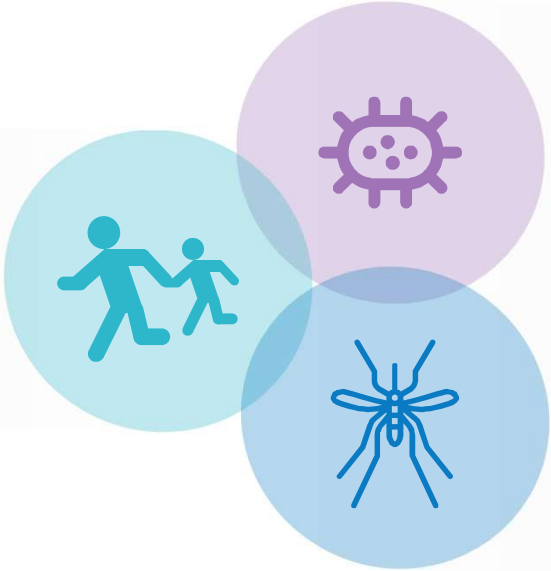
Sanofi Pasteur

Contents

Dengue is a complex disease with interactions among virus, vector and host

Host

- Anyone can be infected[1]
- Identified risk factors for more severe dengue: age, pregnancy near the term, chronic diseases, dengue immune status[4]



Virus

- Arbovirus of the Flaviviridae family[1]
- Four disease-causing viral serotypes: DENV-1, DENV-2, DENV-3 and DENV-4[1]

Vector

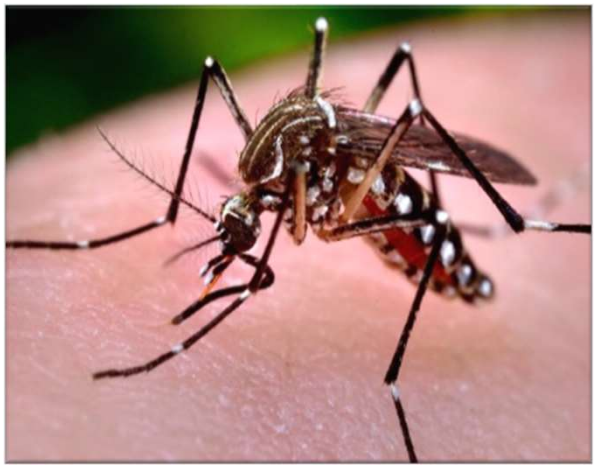
- Mosquito-borne virus[1]
  - Primary vector: *Aedes aegypti*
  - Secondary vector: *Aedes albopictus*
- Transmission is both endemic and epidemic in many countries[2,3]

DENV=dengue virus.

1. WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control, 2009; 2. Gubler DJ. Trop Med Health 2011;39:3–11;
3. Wang E, et al. J Virol 2000;74:3227–34; 4. Guzmán MG, Kouri G. Lancet Infect Dis 2002;2:33–42.

Dengue is transmitted by Aedes mosquitoes

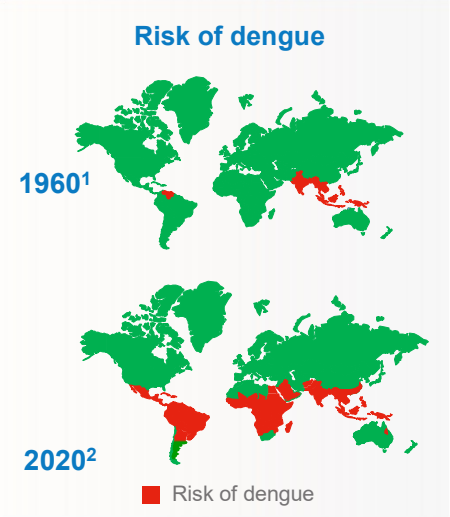
Aedes aegypti

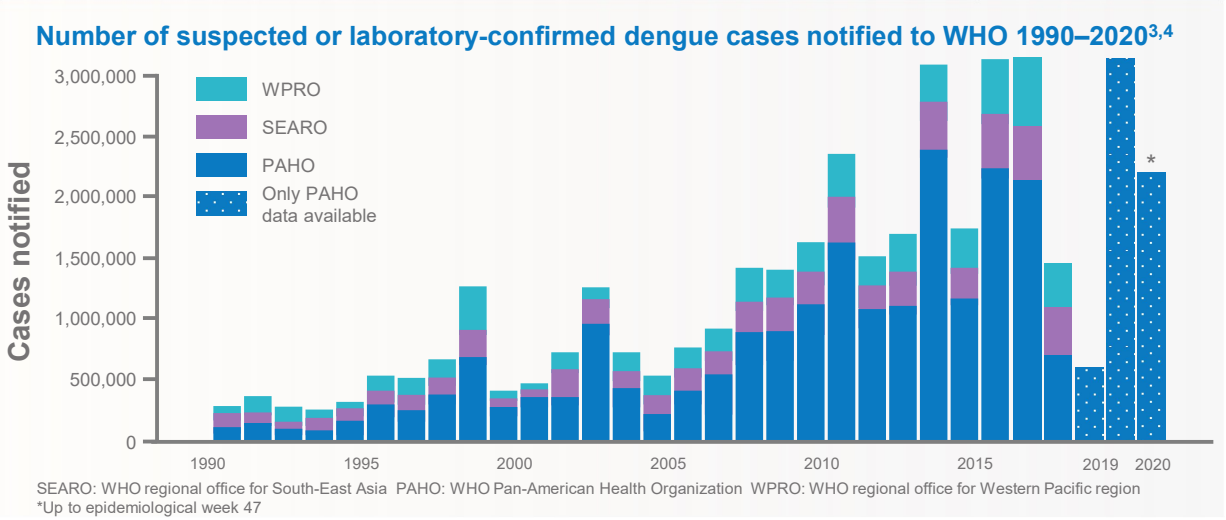


Aedes albopictus

WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control, 2009.

Dengue is a major public health concern, and its threat has grown dramatically in recent decades





SEARO: WHO regional office for South-East Asia PAHO: WHO Pan-American Health Organization WPRO: WHO regional office for Western Pacific region
*Up to epidemiological week 47

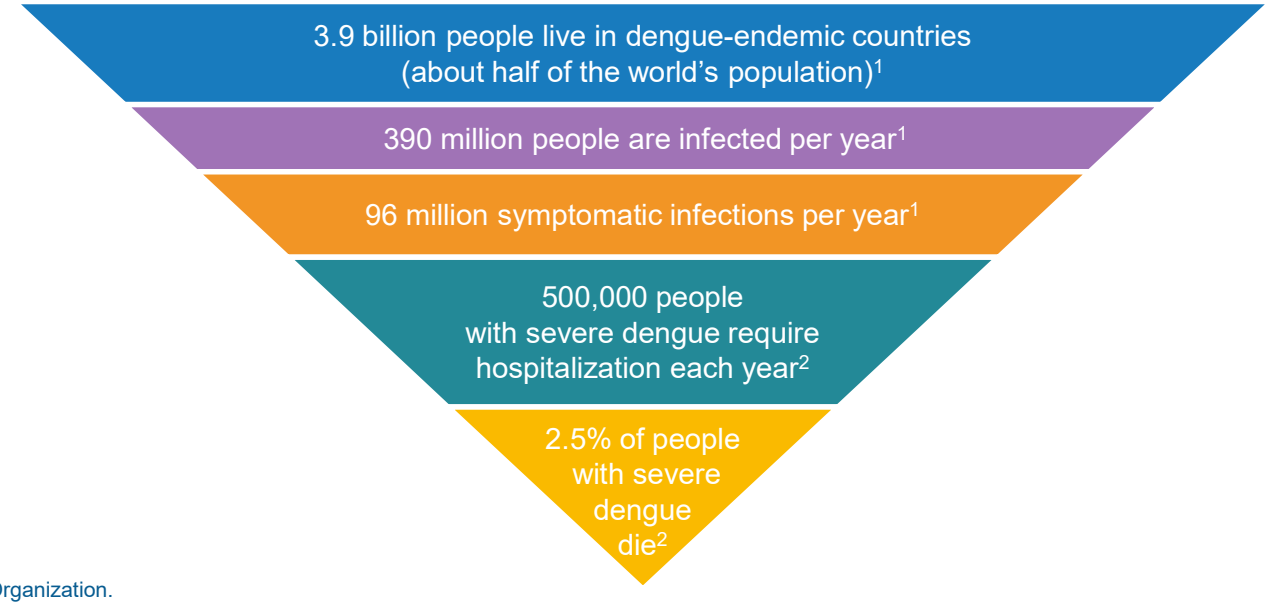
- The threat of dengue has grown dramatically in recent decades;[5] and its spread parallels the expanding range of mosquito vectors[6]
- The number of dengue cases reported to the WHO has increased by more than 8-fold since the turn of the century[5]
  - tropical and sub-tropical Americas now have the highest number of reported cases[7]
- About half of the world's population live with the daily risk of dengue infection[5]

The WHO has stated that preparing for epidemics such as dengue is one of the most urgent global health challenges of the new decade[8]

1. Halstead SB. World Health Stat 1992;45:292–8; 2. CDC. Dengue around the world. 2020. Available at: https://www.uptodate.com/contents/dengue-virus-infection-epidemiology/print; 3. WHO. Dengue control. Dengue data application, 2019. Available at: https://www.who.int/denguecontrol/epidemiology/dengue_data_application/en/; 4. PAHO. Reported cases of dengue in the Americas. Available at: https://www.paho.org/data/index.php/en/mnu-topics/indicadores-dengue-en/dengue-nacional-en/252-dengue-pais-ano-en.html; 5. WHO. Dengue and severe dengue fact sheet 2020; 6. WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control, 2009; 7. WHO. Dengue control. Epidemiology, 2020; 8. WHO. Urgent health challenges for the new decade. 2029. Available at: https://www.who.int/news-room/feature-stories/ten-threats-to-global-health-in-2019.

Dengue is a public health priority

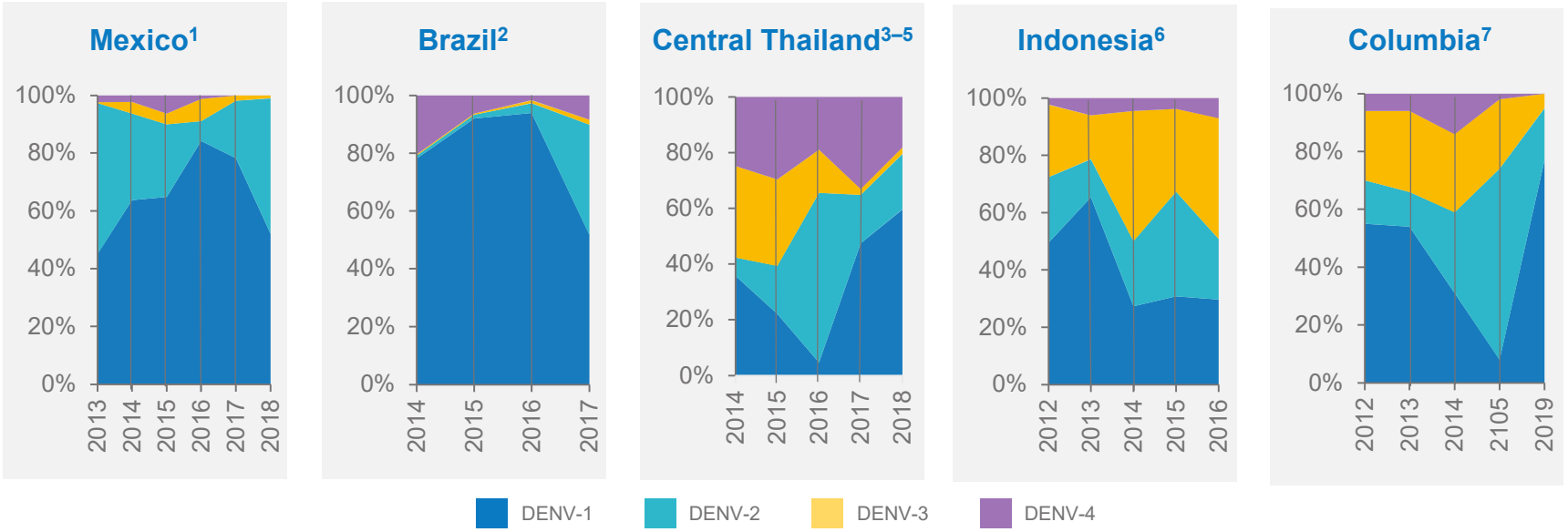
WHO estimates



WHO=World Health Organization.

1. WHO. Dengue Fact Sheet, 2020; 2. WHO. Dengue Fact Sheet, 2018

Four dengue virus serotypes can cause disease, and their distribution varies unpredictably



- In 2020 in the Americas, all four serotypes are currently circulating, including in Brazil, Colombia, Mexico and Guatemala[8]
- In Argentina and Paraguay, DENV 1, DENV 2, and DENV 4 have been circulating[8]

Graphs are plotted from yearly average serotype prevalence values. *Estimate for May–October 2016. DENV=dengue virus.

1. Secretaría de Salud. Panorama Epidemiológico de Dengue, 2013–2018; 2. Ministry of Health / SVS - Notification Disease Information System - Sinan Net DENGUE; 3. Thai NIH Annual Report; 4. Suwanmanee S, et al. Acta Tropica 2018;188:244–50; 5. Dengue Fever Report 2019, Department of Disease Control, Ministry of Public Health; 6. Harapan H, et al. Rev Med Virol 2019;e2037; 7. Gutierrez-Barbosa H, et al. Trop Med Infect Dis 2020 Oct 3;5(4):156. 8. PAHO. Reported cases of dengue in the Americas. Available at: https://www.paho.org/data/index.php/en/mnu-topics/indicadores-dengue-en/dengue-nacional-en/252-dengue-pais-ano-en.html;

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Dengue epidemiology in EU Overseas Territories varies by region

- **EU dengue endemic areas include tropical Latin America, the Caribbean and Indian/Pacific oceans**
- Caribbean and Latin America: High-level transmission/endemicity demonstrated by incidence rates during epidemics, seroprevalence, 4-serotype circulation1–5
  - Widespread presence of the vector: *Aedes aegypti* (most competent)[1,5]
  - Reported seroprevalence among adults ≥18 years old >80%, and >90% in certain settings[2–5]
  - PAHO report that all 4 dengue serotypes are currently circulating increasing the risk of severe dengue[6]
  - Increasingly large epidemics in recent decades, with 2019 seeing the largest number of reported cases in the history of dengue in the Americas with >3 million cases of dengue reported, and >1500 deaths[6]
  - The French Caribbean islands are all experiencing an epidemic phase (October 2020)[7]

LS/2

EU=European Union; PAHO=Pan American Health Organization.

1. L'Azou M et al. PLoS Negl Trop Dis 2014;8:e3235; 2. L'Azou M, et al. Am J Trop Med Hyg. 2015;92:1137–1140; 3. Meynard J. Bull Épidémiologique Hebd 2009;33:357; 4. Wood H, et al. Am J Trop Med Hyg 2014;91:642–644; 5. Leslie T et al. PLoS One 2014;9:e95002; 6. PAHO. Reported cases of dengue in the Americas. Available at: https://www.paho.org/data/index.php/en/mnu-topics/indicadores-dengue-en/dengue-nacional-en/252-dengue-pais-ano-en.html.; 7. ECDC Dengue worldwide overview. Situation update, 20 October 2020.

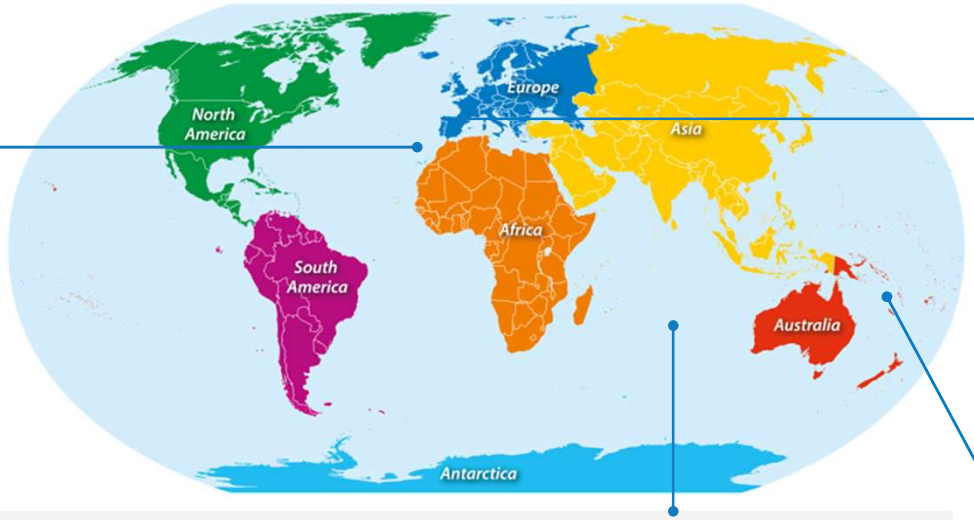
Diapositive 8

LS/2 This figure is confusing. The blue areas are not EU overseas territories. Why don't we point out these overseas territories, just like the next slide?

Lai, Sherlock /SG; 18/01/2021

Dengue epidemiology in EU Overseas Territories: outside the Americas

Madeira: one reported outbreak in 2012–2013 (first sustained transmission of dengue in the EU since 1920s) with more than 1000 cases confirmed (no severe clinical forms reported, and no fatalities), with an estimated number of actual cases of >16,000[7,8]



France and Spain: 9 and 3 autochthonous dengue cases reported in 2019, respectively, sexual transmission also reported in Spain[9]
In 2020, France has reported eight autochthonous cases of dengue (to 20 October) and ten locally-acquired cases have been detected in Italy[4]

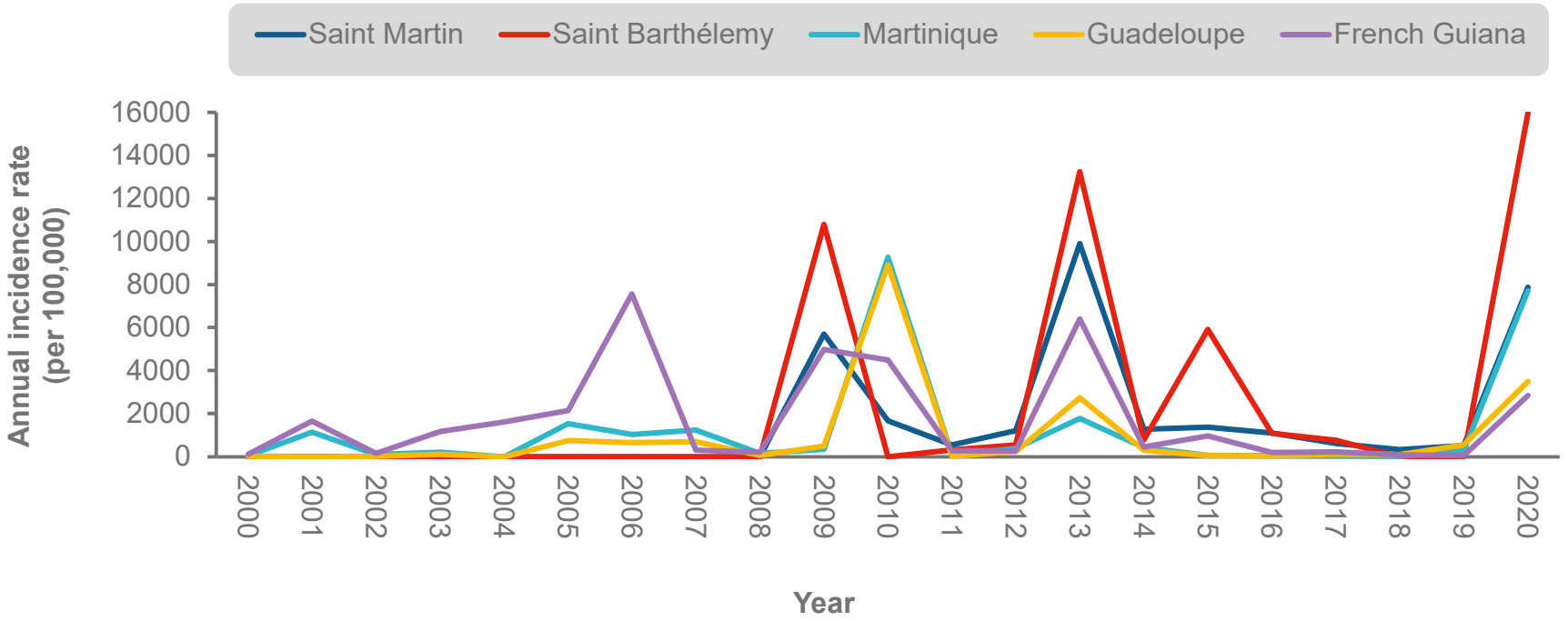
French Polynesia or New Caledonia: reported IR >100/100,000[5]
French Polynesia: Reported seroprevalence among general population >83%
French Polynesia 2020: 2,951 cases to 20 September[4]

La Réunion and Mayotte: seroprevalence among adults <50%[1,2]
La Réunion 2018–2019: unusual persistent circulation sign of changing epidemiology[3]
La Réunion 2020: 15,961 confirmed cases and 19 deaths (to 20 October)[4]

EU=European Union; EW=epidemiological week; IR=incidence rate.

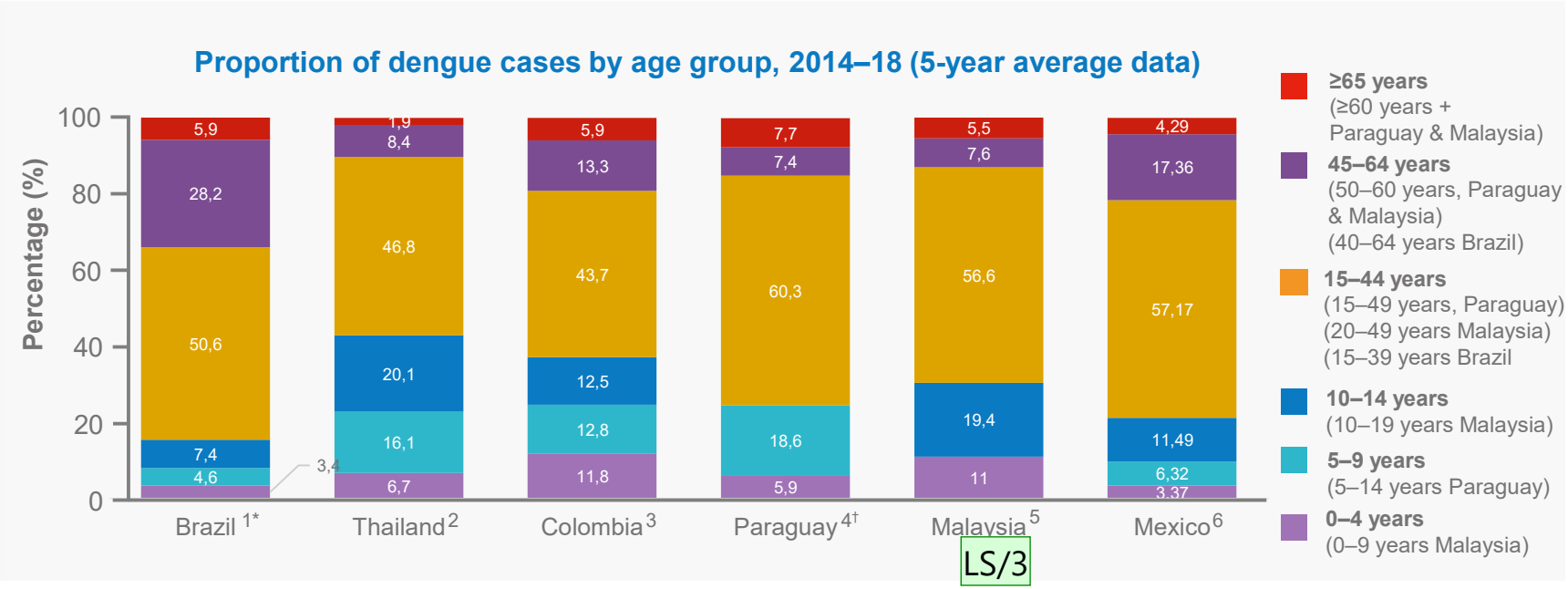
1. Larrieu S, *et al. Trans R Soc Trop Med Hyg* 2014;108:57–59; 2. Sissoko D, *et al. PLoS One* 2010;5:e14141; 3. WHO. Dengue fever – Réunion, France. 20 May 2019; 4. ECDC Dengue worldwide overview. Situation update, 20 October 2020; 5.Arima Y, *et al. Western Pac Surveill Response J* 2011;2:4–8; 6. Aubry M, *et al. Emerg Infect Dis* 2018;24:558–561; 7. ECDC. Dengue outbreak in Madeira (2012-2013); 8. Auerswald H, *et al. Parasites Vectors* 2019;12:103; 9. ECDC. Dengue worldwide overview. Situation update, 20 December 2019.

Annual incidence rate per 100,000 population, 2000–20, in selected French overseas territories



PAHO. PLISA Health Information Platform for the Americas. Dengue incidence. Available at: https://www.paho.org/data/index.php/en/mnu-topics/indicadores-dengue-en/dengue-nacional-en/254-dengue-incidencia-en.html?start=2.

Although dengue affects people of all ages, the majority of symptomatic cases in endemic countries occur in preadolescence to adulthood



LS/3

*4-year average data, from 2014 to 2017.
†2-year average data between 2016 and 2018.

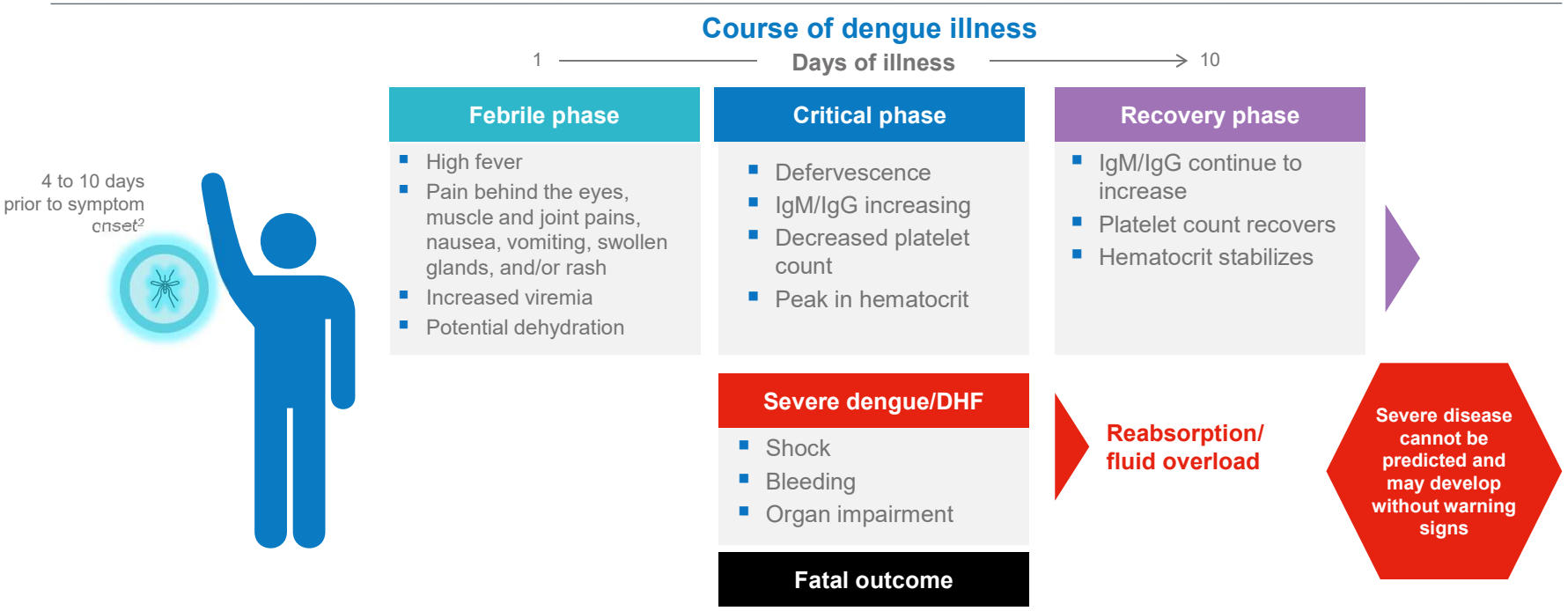
1. Ministry of Health / SVS - Brazil Information System for Notifiable Diseases (SINAN), Net DENGUE, years 2014-2017; 2. Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health. Dengue fever. Surveillance Report 506, years 2014-2018 3. Sivigila. Instituto Nacional de Salud, Colombia, INFORME DEL EVENTO DENGUE, years 2014-2018. 4. DGVS, Ministry of Public Health and Social Welfare, Boletines de Vigilancia Epidemiologica, SE1 A LA SE52, 2016 & 2018; 5. Primary research with Deputy General at Ministry of Health, Malaysia [data due to be published next year]; 6. FUENTE: SUIVE/DGE/Secretaría de Salud/Estados Unidos Mexicanos 2014-2018

Diapositive 11

LS/3 Consider to use Singapore data instead of Malaysia. You can find age distribution of dengue cases in Singapore here: https://doi.org/10.1371/journal.pntd.0007389.s002

Lai, Sherlock /SG; 18/01/2021

Dengue infection results in a spectrum of disease[1]



DHF=dengue hemorrhagic fever; IgG=immunoglobulin G; IgM=immunoglobulin M.

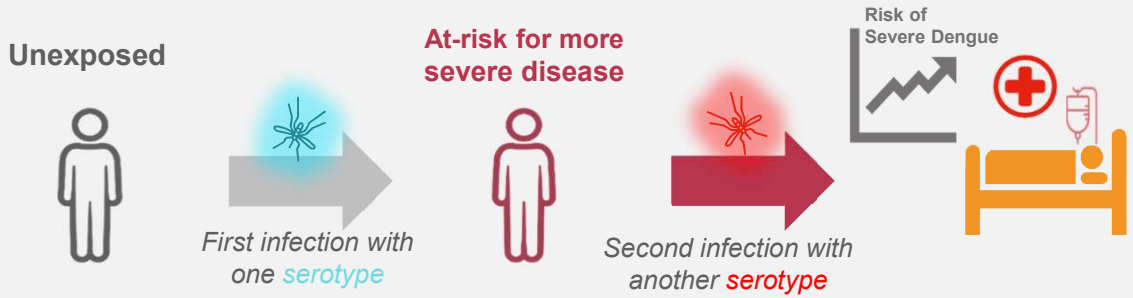
1. WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control, 2009; 2. WHO. Dengue and Severe Dengue Fact Sheet, 2020.

Risks for severe dengue disease

Although severe dengue may occur at first infection, the risk of severe dengue is higher at second infection

Individuals acquiring second dengue infection with a different serotype are at increased risk for severe dengue[1-2]

- Waning of cross protection after first infection[3]
- Time interval between the first and second infections[3]
- Pre-existing antibody titer level at the time of second infection? [4]



Other risk factors associated with severe dengue:

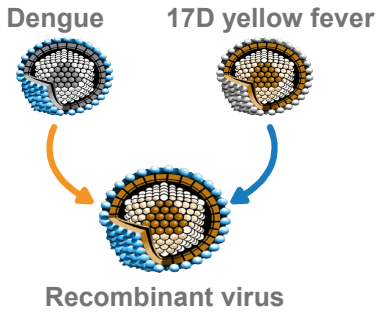
- Infecting dengue serotype and genotype[6]
- Host characteristics (age, sex, genetic background…) [2,5]

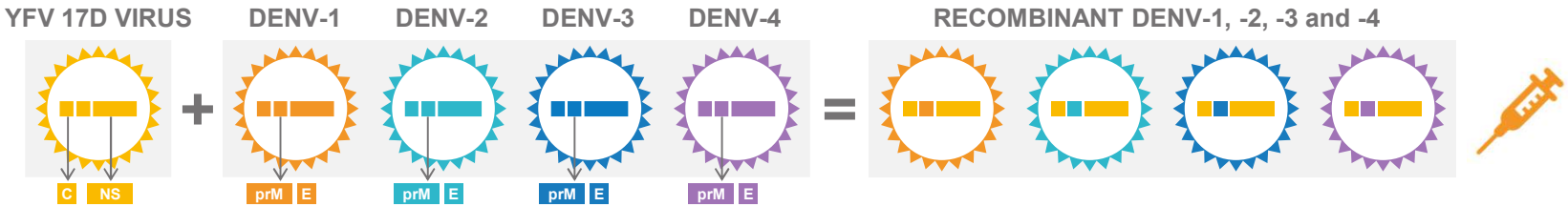
1. Guzmán MG, Kouri G. Lancet Infect Dis 2002;2:33–42. 2. 2. WHO. Dengue Vaccine WHO position paper - September 2018. 3. Anderson KB et al., J Infect Dis 2014; 209(3):360–8. 4. Salje H, et al. Nature 2018;557:719−23. 5. Huy NT et al. PLoS Negl Trop Dis 2013; 7(9). 6. Suppiah J. PLoS Negl Trop Dis. 2018;12(9).

Contents

Sanofi Pasteur dengue vaccine, a technological advance*

- The Sanofi Pasteur dengue vaccine is a 4-serotype, recombinant, live, attenuated vaccine[1,2]:
  - Four genetic constructs with one for each serotype
  - Genes encoding prM/E structural proteins from each dengue serotype combined with genes encoding C and NS proteins from YFV 17D vaccine strain
- Combination into a single vaccine[3]:
  - Freeze-dried
  - Without adjuvant or preservatives





*Vaccine referred to in the literature as chimeric yellow fever 17D-tetravalent dengue vaccine (CYD-TDV).
C=capsid; DENV=dengue virus; E=envelope; NS=nonstructural; prM=precursor membrane; YFV 17D=yellow fever vaccine 17D.

1. Guirakhoo F, et al. J Virol 2004;78:4761–75; 2. Guirakhoo F, et al. J Virol 2001;75:7290–304; 3. Guy B, et al. Vaccine 2011;29:7229–41.

Contents

Overview of the clinical program[1–4]

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

17 Phase II trials
in 13 countries
(USA, Australia, Latin America, Asia)
N=5400 CYD vaccinees
Ages: 12 months–50 years

9 Phase III trials
in 12 countries
(Australia, Latin America, Asia)
N=23,000 CYD vaccinees
Ages: 9 months–60 years

- **25 clinical studies supporting the initial dossier** in 15 countries
- More than **41,000 subjects** included in clinical studies
- **29,000 children, adolescents and adults** received the vaccine*
- **31 clinical studies** have now been conducted, with more than **41,000 subjects** receiving the vaccine†

PHASE I | Non endemic **PHASE II** Endemic | **PHASE III**

*As of August 2015. †As of October 2018.
CYD=chimeric yellow fever 17D-tetravalent dengue vaccine.

1. Guy B, *et al. Expert Rev Vaccines* 2017;16:1–13; 2. Sanofi Pasteur. Internal data. 2020; 3. EMA. First vaccine for prevention of dengue, October 2018. Available at: https://www.ema.europa.eu/en/news/first-vaccine-prevention-dengue; 4. Sanofi Pasteur. Dengvaxia VRBPAC meeting briefing document. March 7, 2019.

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Global view of clinical profile of Sanofi Pasteur vaccine candidate based on efficacy and LTFU interim analyses data

CYD14 efficacy study in Asia[1]
2–14 years (N=10,275)


THE LANCET

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

CYD15 efficacy study in Latin America and the Caribbean[2]
9–16 years (N=20,869)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease[3]

The NEW ENGLAND JOURNAL of MEDICINE

LTFU=long-term follow-up.

1. Capeding MR, *et al. Lancet* 2014;383:1358–65; 2. Villar L, *et al. N Engl J Med* 2015;372:113–23; 3. Hadinegoro SR, *et al. N Engl J Med* 2015;373:1195–1206.

Two Phase III efficacy trials demonstrated a consistent efficacy profile in individuals of any serostatus during the 25-month efficacy phase

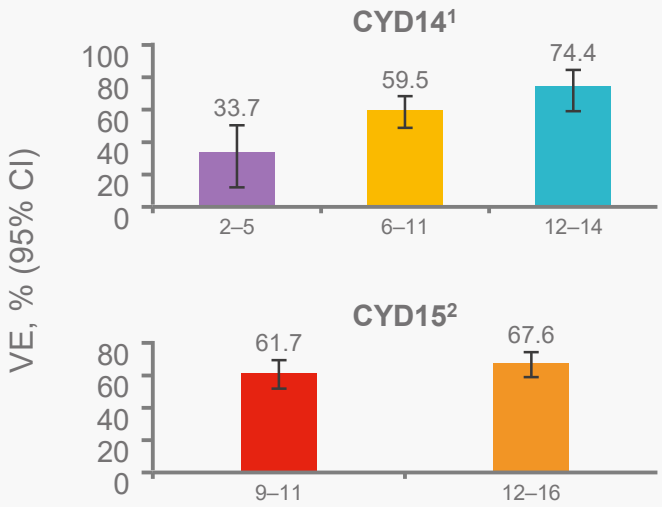
	ASIA (CYD14)[1] 2- to 14-year-olds	LATIN AMERICA (CYD15)[2] 9- to 16-year-olds	Pooled results in the targeted age indication (9- to 16-year-olds)[3]
Efficacy against symptomatic dengue*†	**56.5%** (95% CI: 43.8–66.4)	**60.8%** (95% CI: 52.0–68.0)	**65.6%** (95% CI: 60.7–69.9)
Reduction in hospitalized dengue†	**67.2%** (95% CI: 50.3–78.6)	**80.3%** (95% CI: 64.7–89.5)	**80.8%** (95% CI: 70.1–87.7)
Efficacy against severe dengue†	**70.0%** (95% CI: 35.7–86.6)	**95.5%** (95% CI: 68.8–99.9)	**93.2%** (95% CI: 77.3–98.0)

*Per protocol, 12 months post-dose 3 for CYD14 and CYD15 individual studies; †Intent to treat, 25 months post-dose 1 for hospitalized dengue, severe dengue and all pooled results for CYD14 and CYD15; World Health Organization (WHO) 1997 criteria, intent to treat.
CI=confidence interval.

1. Capeding MR, *et al. Lancet* 2014;383:1358–65; 2. Villar L, *et al. N Engl J Med* 2015;372:113–23; 3. Hadinegoro SR, *et al. N Engl J Med* 2015;373:1195–206.

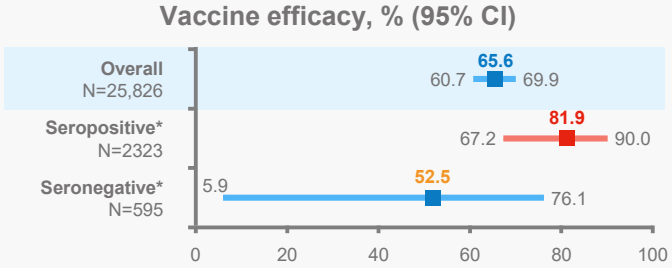
Phase III efficacy results: VE is impacted by age and baseline serostatus

Vaccine efficacy by age (years)



Vaccine efficacy in 9−16-year-olds[3]

Pooled analysis of CYD14 and CYD15



- Vaccine efficacy is impacted by age and baseline serostatus[3]
- An increased risk of hospitalization and severe dengue with vaccination was seen in <9-year-olds, mainly driven by data in 2−5-year-olds in the CYD14 study[3]
- Supplemental analysis was conducted to investigate the effects of age and previous dengue infection on vaccine efficacy[4]

*Serostatus assessed at baseline with the plaque reduction neutralisation test ($PRNT_{50}$) in immunogenicity subset.
CI=confidence interval; N=number of subjects included in the analysis; VE=vaccine efficacy.

1. Capeding MR, *et al. Lancet* 2014;383:1358–65; 2. Villar L, *et al. N Engl J Med* 2015;372:113–23; 3. Hadinegoro SR, *et al. N Engl J Med* 2015;373:1195–206;
4. Sridhar S, *et al. N Engl J Med* 2018;379:327–40.

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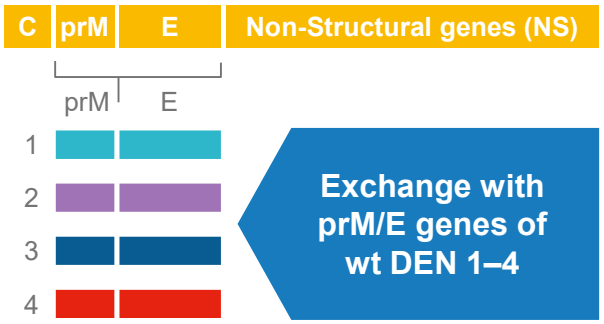
Supplemental analyses
Dengue anti-NS1 IgG ELISA

RATIONALE:
NS1 protein in dengue Virus is different than NS1 protein in Yellow Fever Virus

Yellow Fever Virus 17D cDNA



Exchange with prM/E genes of wt DEN 1–4

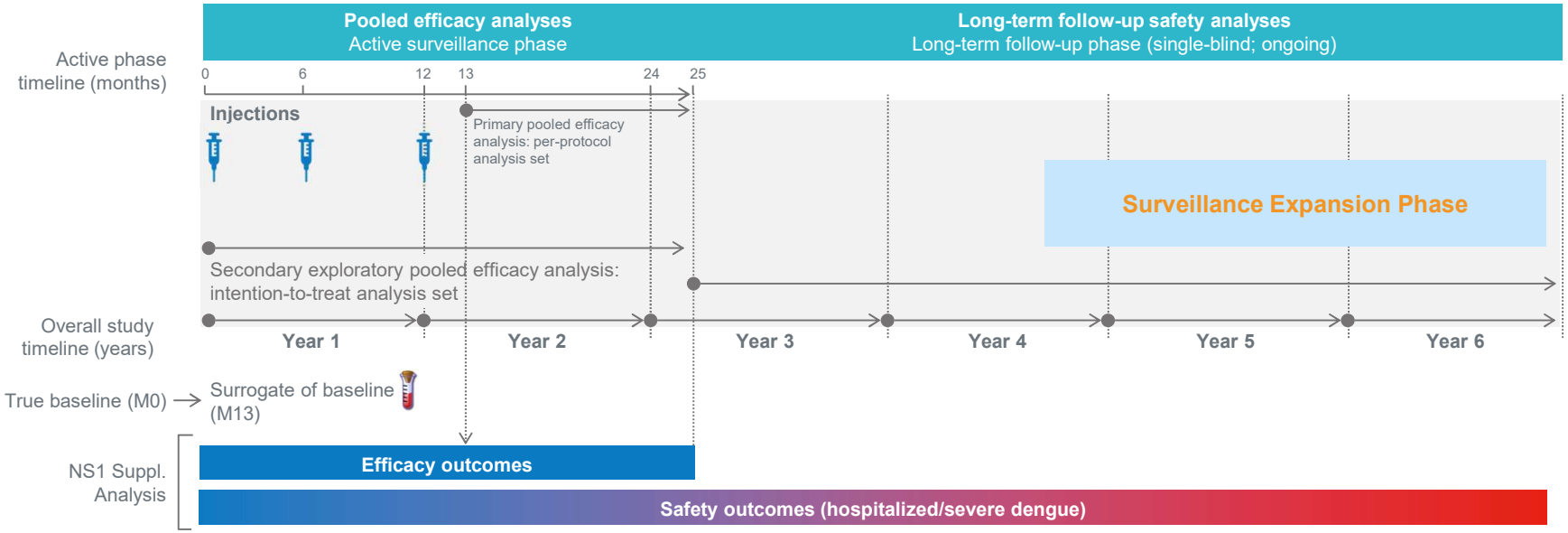
Sanofi Pasteur dengue Vaccine has gene encoding NS1 from Yellow Fever

Sanofi Pasteur dengue Vaccine is not expected to induce meaningful antibodies against the Dengue NS1 protein

Presence of dengue NS1 antibodies may differentiate previous exposure to natural dengue infection from previous exposure to Sanofi Pasteur dengue vaccine

Nascimento EJM, et al. J Virol Methods 2018;257:48–57.

Case cohort supplemental analysis design (NS1 study)
All subjects provided M13 samples as a surrogate of baseline serostatus

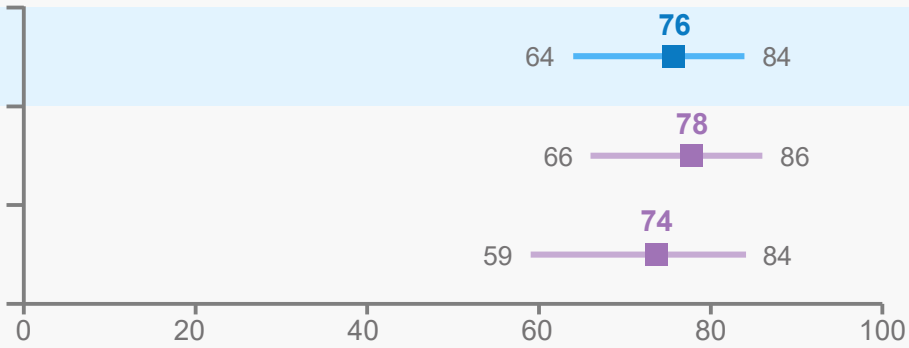


1. Capeding MR, *et al. Lancet* 2014;383:1358–65; 2. Villar L, *et al. N Engl J Med* 2015;372:113–23; 3. Nascimento EJM, *et al. J Virol Methods* 2018;257:48–57;
4. Arredondo-García JL, *et al. Clin Microbiol Infect* 2018;24:755e763.

Supplemental analysis results
High vaccine efficacy in dengue seropositive individuals

Vaccine efficacy against symptomatic dengue for seropositive individuals during 25-month Active Phase

Age (years)	Vaccine n (M)	Control n (M)	Vaccine efficacy, % (95% CI)
9−16	192.7 (1441.4)	372.1 (697.3)	76 (64, 84)
12−16	85 (802.9)	181 (386.1)	78 (66, 86)
9−11	107.7 (638.5)	191.1 (311.2)	74 (59, 84)



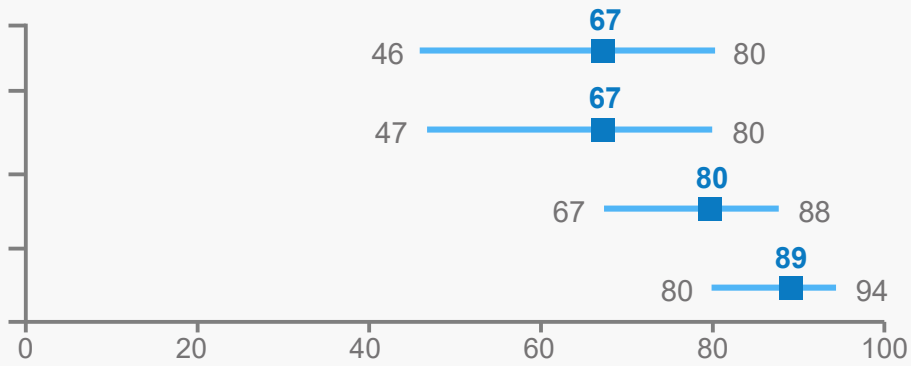
Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) up to Month 25 for seropositive participants according to age strata. Pooled analysis of CYD14 (9−14-year-olds), CYD15 (9−16-year-olds) studies. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort; estimates are from M0–M25. CI, confidence interval; MI-M0, Multiple Imputation, Month 0.

Sridhar S, *et al. N Engl J Med* 2018;379:327–40 & supplementary appendix.

Vaccination with Sanofi Dengue Vaccine protects against each and any dengue serotype in dengue seropositive subjects 9–16 years of age

Vaccine efficacy against symptomatic dengue for seropositive individuals during 25-month Active Phase

Serotype	Vaccine n (M)	Control n (M)	Vaccine efficacy, % (95% CI)
Serotype 1	71.0 (1441.4)	103.5 (697.3)	67 (46, 80)
Serotype 2	57.1 (1441.4)	83.1 (697.3)	67 (47, 80)
Serotype 3	40.5 (1441.4)	96.0 (697.3)	80 (67, 88)
Serotype 4	20.9 (1441.4)	91.9 (697.3)	89 (80, 94)



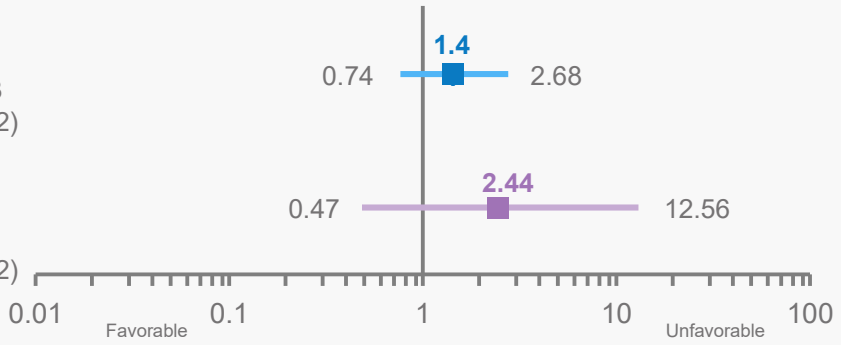
Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) up to Month 25 for seropositive 9−16-year-old participants. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort; estimates are from M0–M25.
CI=confidence interval; MI-M0=Multiple Imputation, Month 0.

Sridhar S, *et al. N Engl J Med* 2018;379:327–40 & supplementary appendix.

Vaccination is not recommended in dengue seronegative individuals due to an increase risk of hospitalized and severe dengue

Hazard ratio/Relative risk of hospitalized and severe dengue

Dengue type	Vaccine n (M)	Control n (M)	Hazard ratio/ Relative risk
Hospitalized	64.2 (375.1)	25.3 (207.2)	1.4 (0.74 – 2.68)
Severe*	14.8 (375.1)	3.6 (207.2)	2.44 (0.47 – 12.56)



- In light of a safety signal of an increased risk of hospitalized and severe dengue in vaccinated seronegative vs unvaccinated individuals identified in the supplementary analysis, the product label for the vaccine was updated to exclude seronegative individuals from vaccination

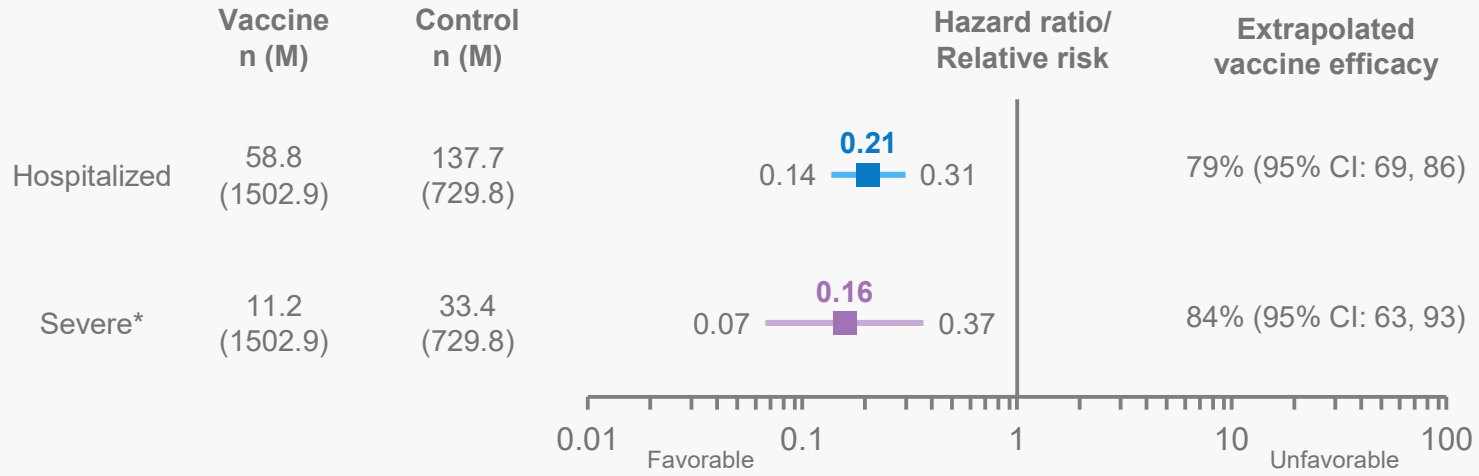
*As per IDMC assessment. Hazard ratio/Relative risk of hospitalized and severe virologically confirmed dengue (VCD) in seronegative participants aged 9–16 years old. Pooled analysis of CYD14 (9−14-year-olds), CYD15 (9−16-year-olds) and CYD23/57 (9−11-year-olds) studies. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort. Error bars: 95% confidence intervals. IDMC=Independent Data Monitoring Committee; MI-M0=Multiple Imputation, Month 0.

Sridhar S, et al. N Engl J Med 2018;379:327–40 & supplementary appendix.

SANOFI PASTEUR

Consistent reduction in the risk of hospitalized and severe dengue in seropositive 9−16-year-olds up to 5 years after first injection

Hazard ratio/Relative risk of hospitalized and severe dengue

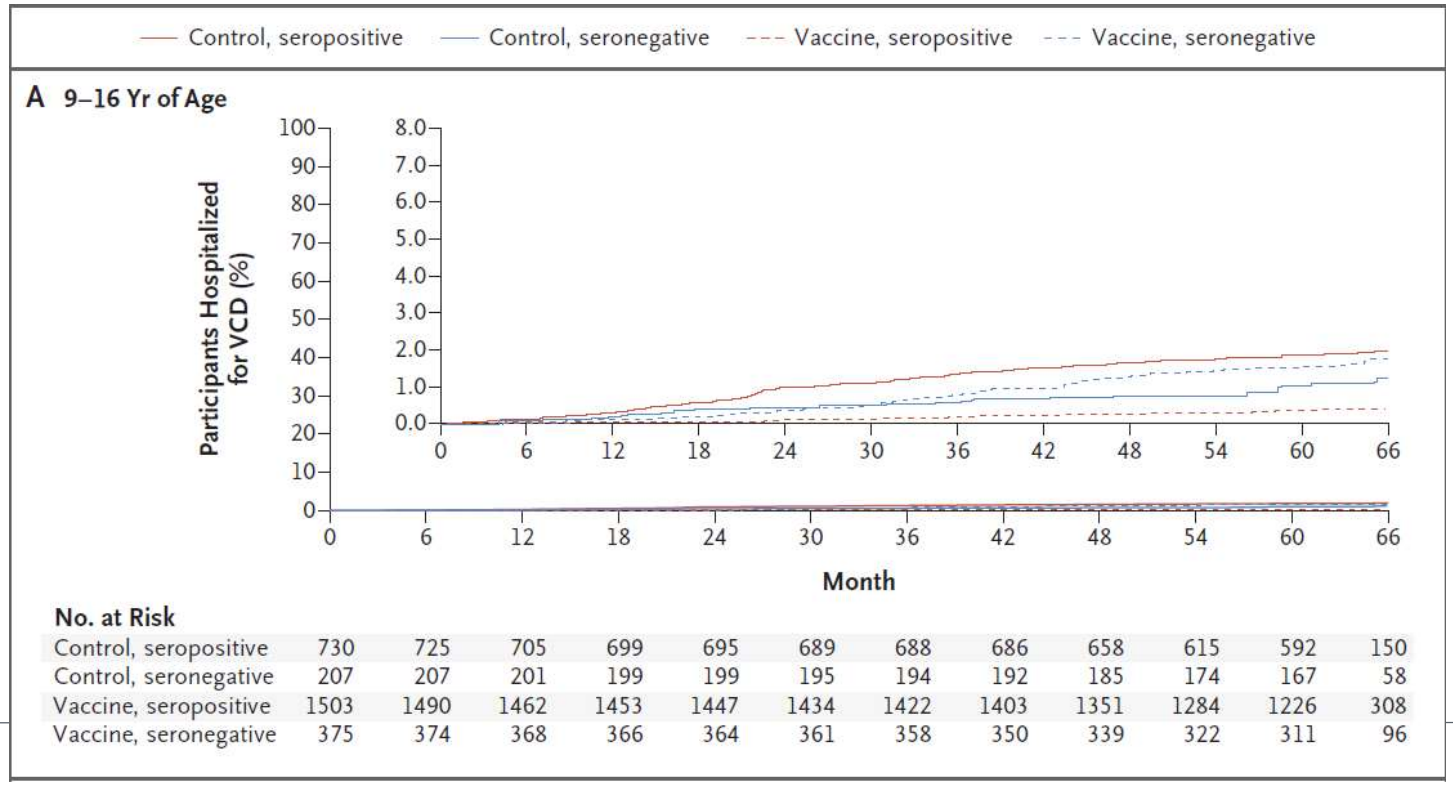


*As per IDMC assessment. Hazard ratio/Relative risk of hospitalized and severe virologically confirmed dengue in seropositive participants aged 9–16 years old. Pooled analysis of CYD14 (9−14-year-olds), CYD15 (9−16-year-olds) and CYD23/57 (9−11-year-olds) studies. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort. Error bars: 95% CIs.
CI=confidence interval; IDMC=Independent Data Monitoring Committee; MI-M0=Multiple Imputation, Month 0.

Sridhar S, *et al. N Engl J Med* 2018;379:327–40.

Cumulative Incidence Curves of Hospitalization for VCD from Month 0 According to Baseline Serostatus as Classified by PRNT50 at Baseline in Different Age Groups (Multiple-Imputation Approach)

Data are from a pooled analysis of the CYD14, CYD15, and CYD23 (and CYD57) trials. The cumulative incidence curves are curtailed at month 66 to ensure that at least 20% of the participants remained at risk in each subcohort.



No. at Risk

Control, seropositive	730	725	705	699	695	689	688	686	658	615	592	150
Control, seronegative	207	207	201	199	199	195	194	192	185	174	167	58
Vaccine, seropositive	1503	1490	1462	1453	1447	1434	1422	1403	1351	1284	1226	308
Vaccine, seronegative	375	374	368	366	364	361	358	350	339	322	311	96

Sridhar S et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018 Jul 26;379(4):327-340. doi: 10.1056/NEJMoa1800820. Epub 2018 Jun 13. PMID: 29897841.

Vaccination increases the risk of severe dengue by 0.2% over 5 years in seronegative individuals aged 9–16 years

- Severe dengue is defined as temperature ≥38 °C on ≥2 consecutive days and virological confirmation, as well as ≥1 of the following criteria:[1]
  - Platelet count ≤100x10^9/L, bleeding, and plasma leakage; shock; bleeding requiring blood transfusion; encephalopathy; liver impairment; impaired kidney function; and myocarditis, pericarditis, or heart failure
- **In the supplemental analysis, the risk of developing severe dengue was increased by 0.2% (from 2/1000 to 4/1000) over 5 years in vaccinated seronegative individuals aged 9–16 years (compared with unvaccinated seronegative individuals)[1]**
- This risk of severe dengue is almost the same as the risk in unvaccinated seropositive individuals aged 9–16 years (4.8/1000)[1]
- The severe cases were predominantly grade I or II hemorrhagic fever[1]
- The onset of the increased risk of severe dengue was mainly during the third year after the first dose of the vaccine, and all individuals fully recovered[1]
- In the original Phase III trials, no deaths occurred during the planned follow-up period[2]

Vaccination is not recommended in dengue seronegative individuals due to an increased risk of hospitalized and severe dengue

1. Sridhar S, et al. N Engl J Med 2018;379:327–40 & supplementary appendix; 2. Hadinegoro SR, et al. N Engl J Med 2015;373:1195–206.

Contents

WHO updated recommendations on the use of the first licensed dengue vaccine – September 2018

To countries considering vaccination as part of their dengue control program → **WHO**

- Acknowledges **public health role** and **protective benefit of the vaccine against subsequent dengue infection in seropositive individuals**
- Recommends **serological screening prior to vaccination as preferred approach** (increase public health impact and minimize vaccination risks)[1-2]

As most of dengue infections are asymptomatic →

If **no prior dengue infection documented** in medical record → **Serotesting is to be considered prior to vaccinate**[1]

If pre-vaccination screening is not feasible, vaccination is possible in areas with at least 80% seroprevalence rates (recently documented) by age 9 years old

ELISA=enzyme-linked immunosorbent assay; IgG=immunoglobulin G; SAGE=Strategic Advisory Group of Experts; WHO=World Health Organization

World Health Organization. Weekly Epidemiological Record 2018;93:457–76.

Dengue status can be established using multiple methods

Medical history[1,2]

- Previous laboratory-confirmed dengue infection can be ascertained based on the individual's medical history*
- However, dengue infections can be asymptomatic

ELISA[3–5]

- ELISA is the most commonly used laboratory assay to establish previous dengue infection (as per dengue IgG)
- However, because the test is laboratory based, it takes at least a day to obtain results, and is costly
- Cross-reactivity with other viruses can also occur

RDT[6]

- Many of the available RDTs were developed to detect acute dengue infection not past infection and may not have optimal sensitivity for that purpose[7]
- A new Dengue IgG RDT optimized for the detection of past infection is soon to be/has recently been licensed[8,9]

*Dengue history must be based on a recorded laboratory confirmation of past acute infection, which could have been tested at the time of infection by a direct diagnostic method such as PCR or NS1 antigen to detect (part of) the virus or using an indirect diagnostic method such as dengue-specific serology to detect anti-dengue antibodies by ELISA or an RDT.2

ELISA=enzyme-linked immunosorbent assay; PCR=polymerase chain reaction; RDT=rapid diagnostic test.

1. WHO. Updated Questions and Answers related to the dengue vaccine Dengvaxia® and its use, 2017. Available at: https://www.who.int/immunization/diseases/dengue/q_and_a_dengue_vaccine_dengvaxia_use/en/; 2. WHO. Dengue Vaccine WHO position paper – September 2018; 3. Luo R, et al. Clin Microbiol Infect 2019;25:659–66; 4. Lin AV. Methods Mol Biol 2015;1318:61–67; 5. Thommes E, et al. Poster presented at the American Society of Tropical Medicine & Hygiene 68th Annual Meeting, November 2019, Washington, DC, USA; 6. Bonaparte M, et al. J Travel Med 2019 (Epub ahead of print); 7. World Health Organization. Weekly Epidemiological Record 2018;93:457–76; 8. Liberal V, et al. Poster presented at ASTMH, November 2020; 9. Sanofi Pasteur Press release [date TBC].

Key characteristics of rapid diagnostic tests to assess past dengue infection

Dengue seronegative

High specificity → **Ability of a test to detect true seronegative result**

A test with high specificity reduces the possibility of vaccinating individuals who have not had a past dengue infection

Dengue seropositive

High sensitivity → **Ability of a test to detect true seropositive individuals**

A test with high sensitivity is effective in detecting those with a past infection and thereby ensuring that they benefit from vaccination

World Health Organization. Weekly Epidemiological Record 2018;93:457–76.

Sanofi Pasteur dengue vaccine approved for individuals 9 to 45 years of age with past dengue virus infection living in endemic areas

9/12–16/45/60 years
[Adjust to local SmPC]

Indicated for the prevention of dengue disease caused by dengue virus **serotypes 1, 2, 3 and 4** in individuals **9/12–16/45/60 years of age with past dengue virus infection** and living in **endemic areas**

[Adjust to local SmPC]

3-dose schedule

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

- Vaccination recommended only in individuals with prior dengue infection
- For individuals not previously infected by dengue virus, vaccination should not be recommended
- Previous infection by dengue virus can be substantiated through serotesting or medical history

[Remove image if vaccine not approved in local market]

Monodose vaccine

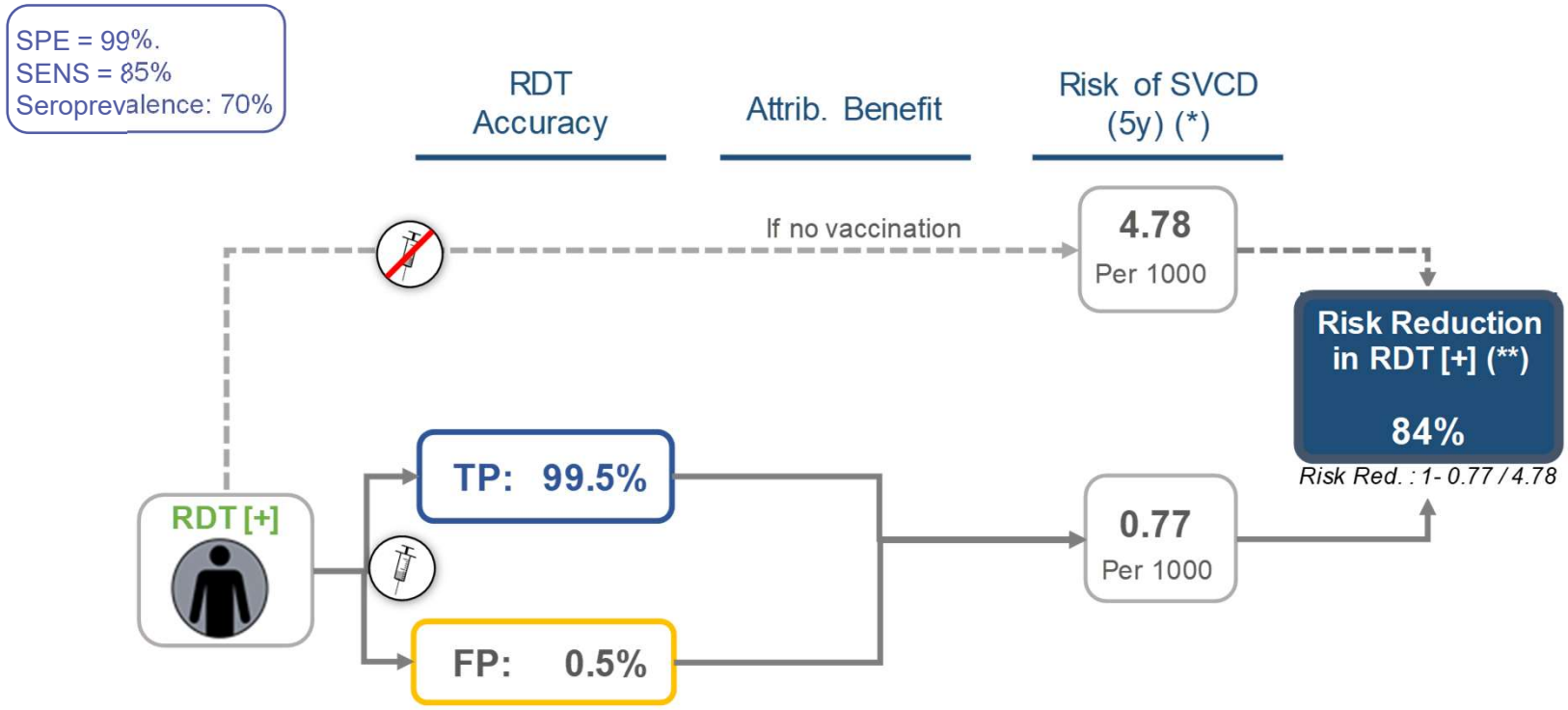
[Remove image if vaccine not approved in local market]

Multidose vaccine

Dengvaxia SmPC, Sanofi Pasteur, 2020 [Adjust to local SmPC and adapt slide accordingly]

Benefits of 'Screen & Vax": Vaccination of RDT [+] is associated with a 84% risk reduction for severe dengue

Pre-read



* Sridhar S, et al. NEJM (2018)

TP = True positives
FP = False positives

Static model
SVCD: Severe Viro. Confirmed Denge

Status of Dengvaxia registration & distribution

As of 6 Jan. 2020

- Argentina
- Brazil
- Costa Rica
- El Salvador
- Guatemala
- Indonesia
- Mexico (2015)
- Paraguay
- Peru
- Singapore
- Thailand
- Australia
- Bangladesh
- Bolivia
- Cambodia
- Honduras
- Venezuela
- Myanmar
- Dominican Republic
- EU (2018)
- US (2019)
- Panama
- Colombia

WHO has awarded prequalification status to Dengvaxia®

- On 25 March 2020, WHO awarded prequalification status to Dengvaxia®, underlying the vaccine's quality, safety and efficacy[1]
- WHO prequalification is a key step that allows for the procurement of vaccines by UNICEF and other United Nations agencies like the PAHO[2]

PAHO=Pan American Health Organization; UNICEF=United Nations Children's Fund; WHO=World Health Organization.

1. WHO. WHO prequalified vaccines, 21 May 2020. Available at: https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=329;
2. WHO. Prequalification of medicines by WHO, 31 January 2013. Available at: https://www.who.int/news-room/fact-sheets/detail/prequalification-of-medicines-by-who.

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