

# *Dengue fever: A growing global threat - epidemiology and modern strategies for control*

[www.butantan.gov.br](http://www.butantan.gov.br)

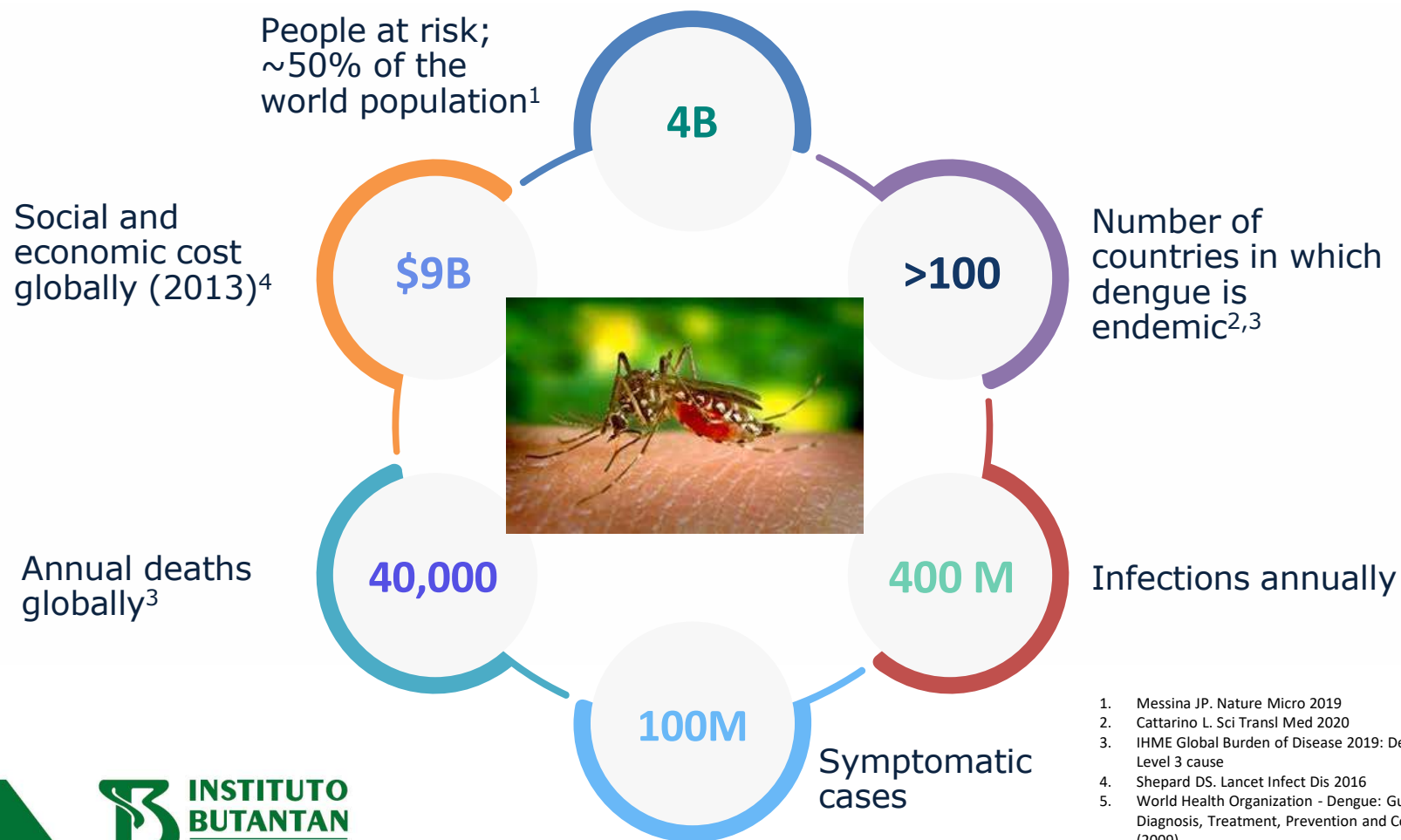


Fernanda Boulos

Chief Medical Officer  
Instituto Butantan

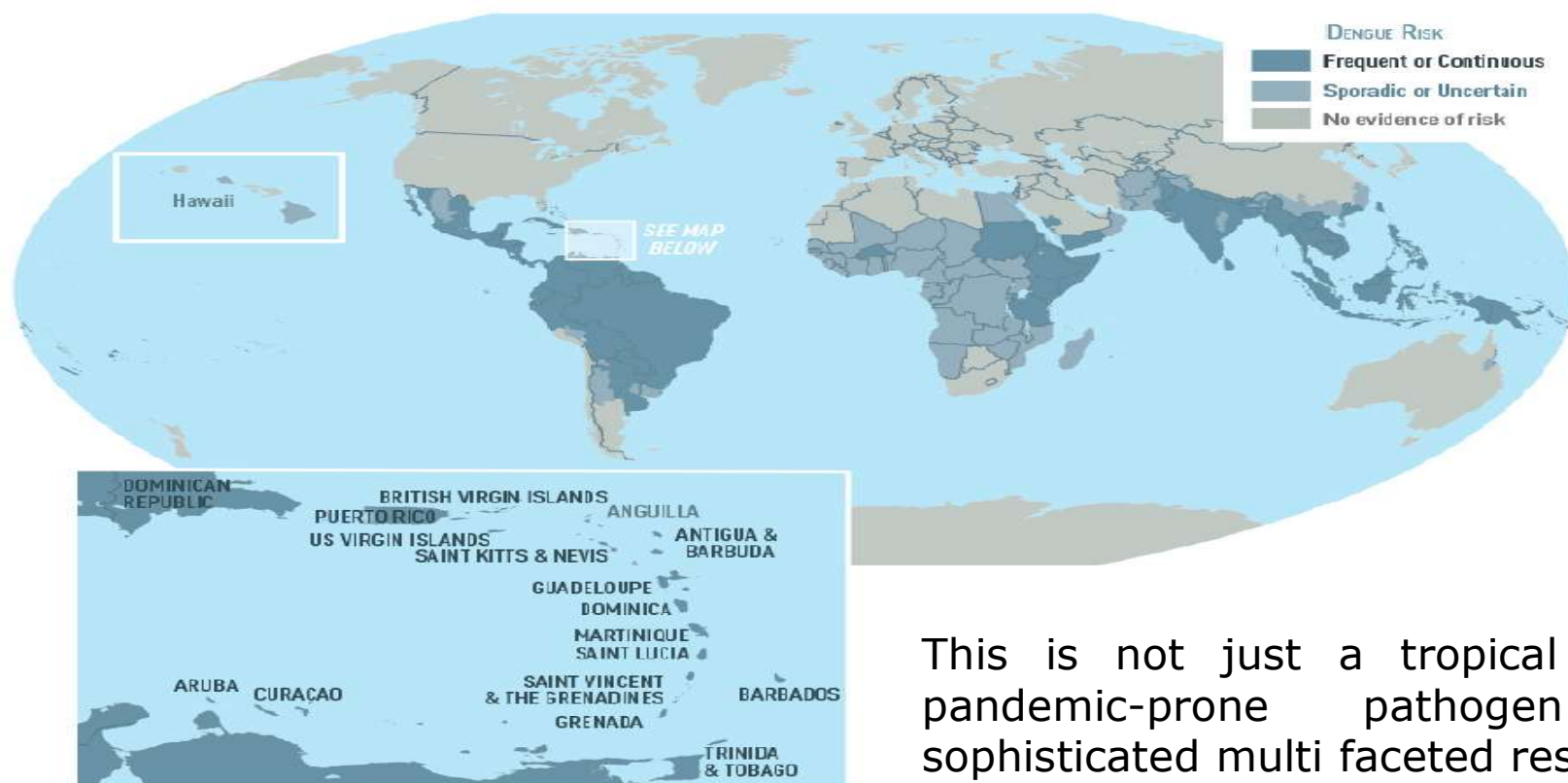
November, 2025

# Dengue is the fastest-growing mosquito-borne viral disease globally



1. Messina JP. Nature Micro 2019
2. Cattarino L. Sci Transl Med 2020
3. IHME Global Burden of Disease 2019: Dengue — Level 3 cause
4. Shepard DS. Lancet Infect Dis 2016
5. World Health Organization - Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control (2009)

# Global Dengue Epidemiology: gradually increasing



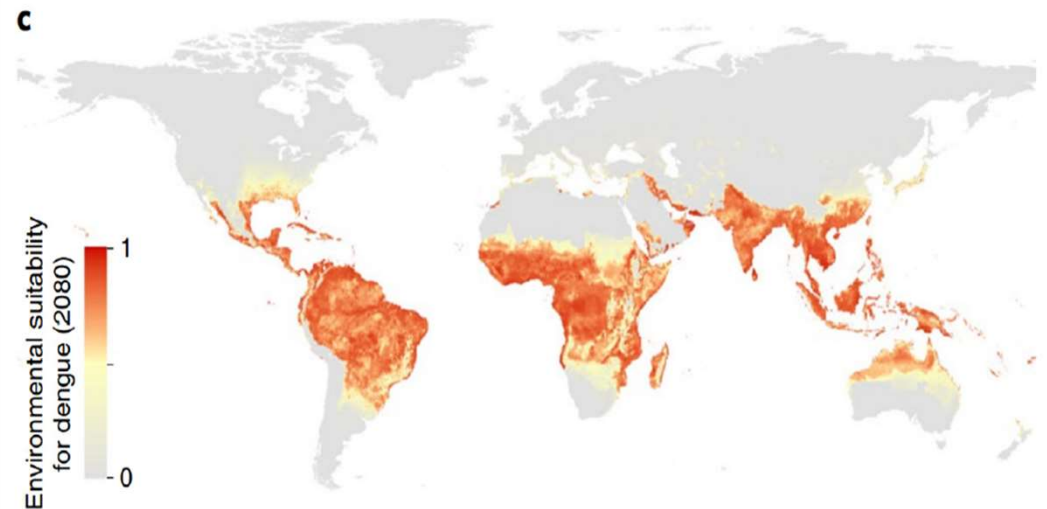
This is not just a tropical disease; it is a pandemic-prone pathogen requiring a sophisticated multi faceted response

# Global epidemiologic trends (why now?)

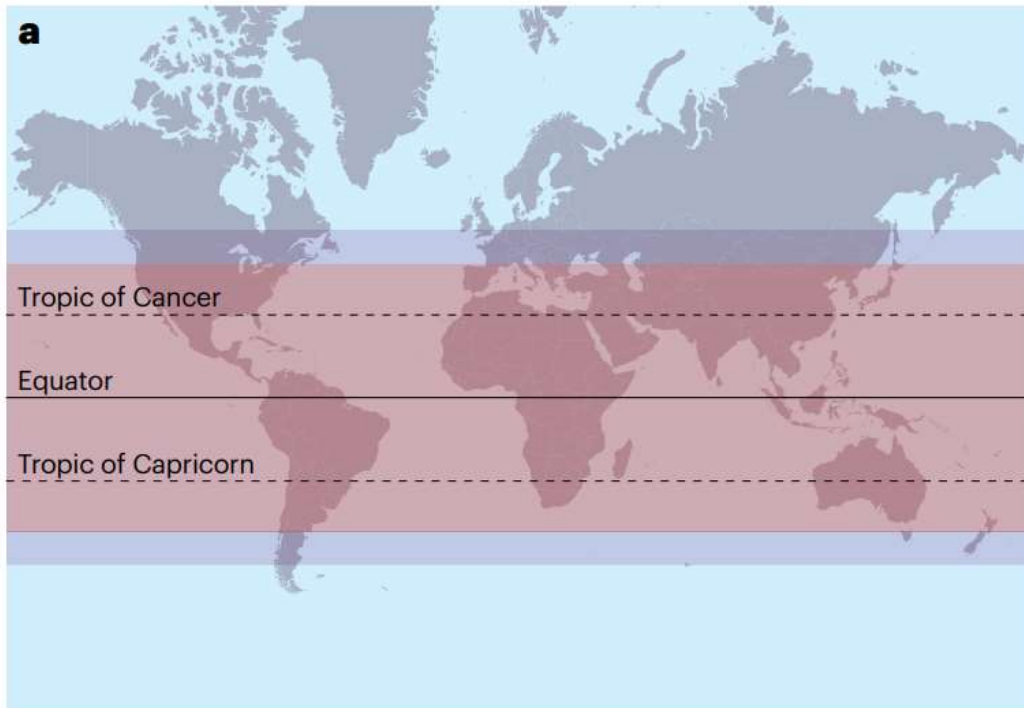
- *Rapid urbanization*: Unplanned urban growth creates ideal breeding grounds (Stagnant water in containers, tires, plastic waste)
- *Globalization & Travel*: Infected Travellers introduce new serotypes to susceptible populations
- *Climate Changes*: Expanding geographic range of vectors. Warmer temperatures accelerates mosquito development and viral replication, while extended rainy seasons create more breeding sites.
- *Inadequate vector control*: Challenges with insecticide resistance, funding and sustainable Community programs

## Probability of occurrence of Dengue in 2080

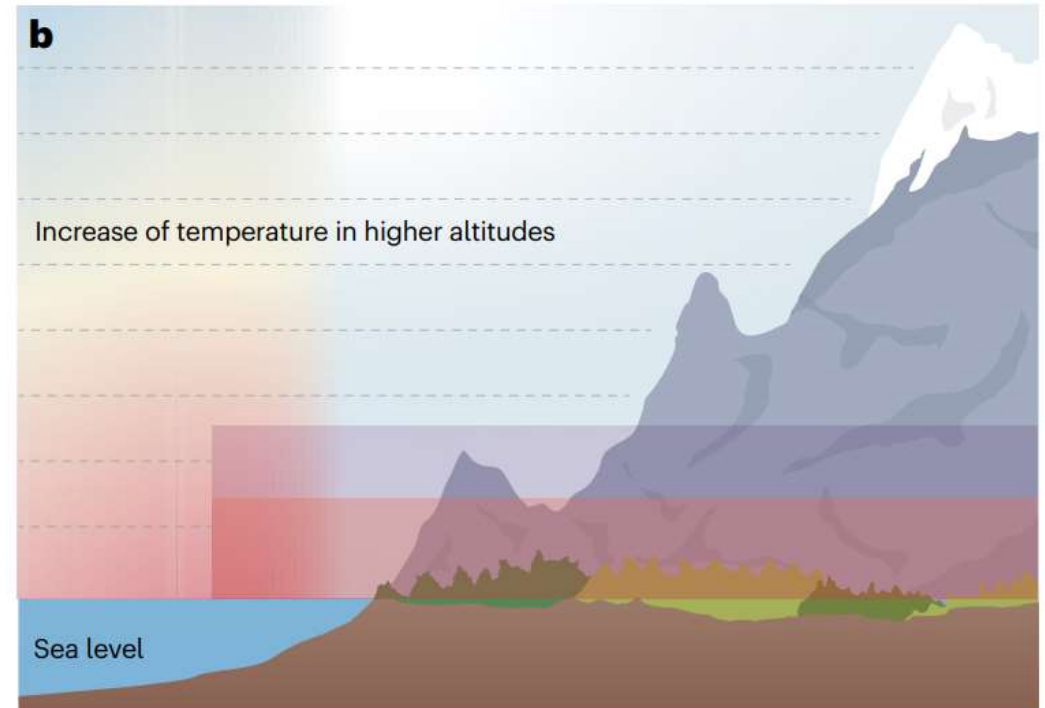
6.1 billion people will be at risk



# Dengue and global warming



- Current vector suitability
- Projected expansion of vector suitability (towards poles)



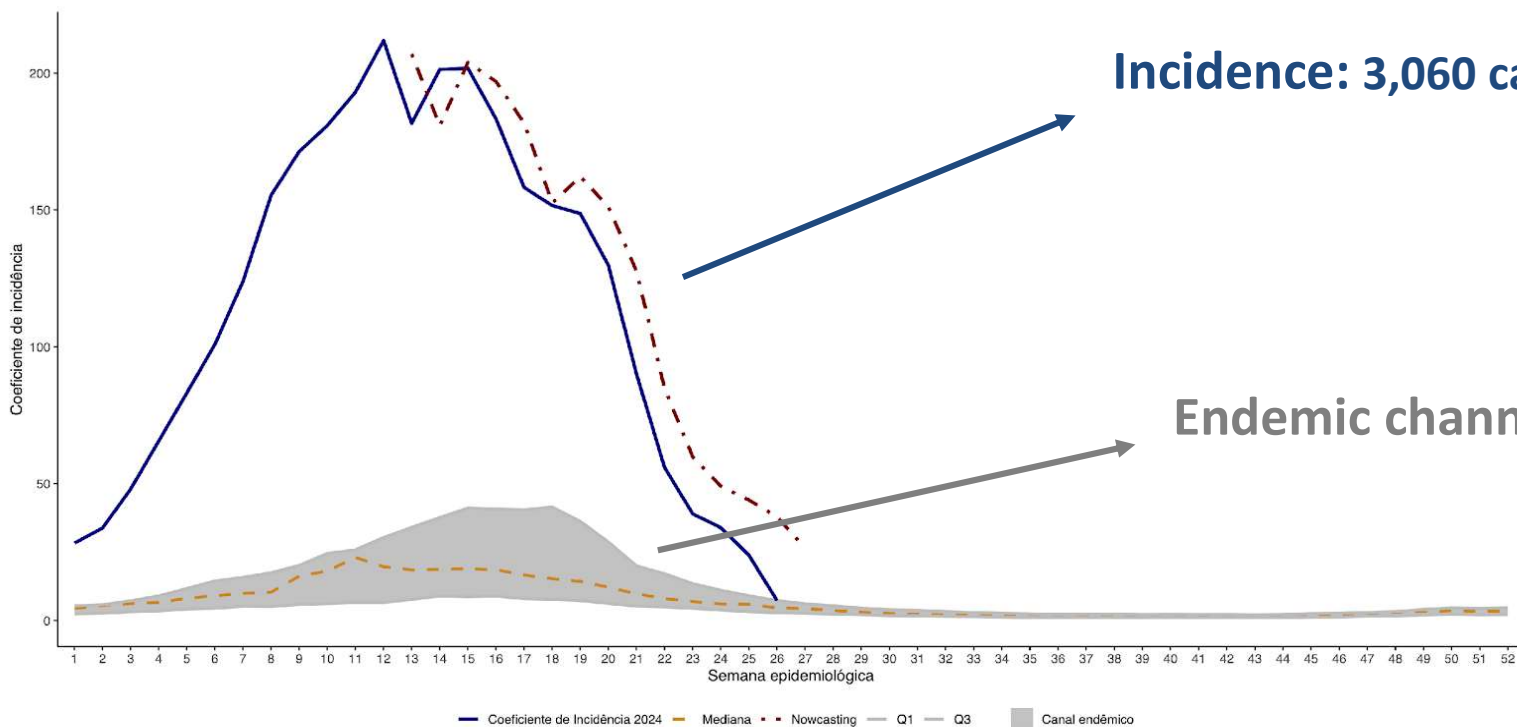
- Projected altitudinal range (upslope expansion)
- Current altitudinal range



# Epidemiological situation in Brazil



# 2024 Unprecedented Outbreak

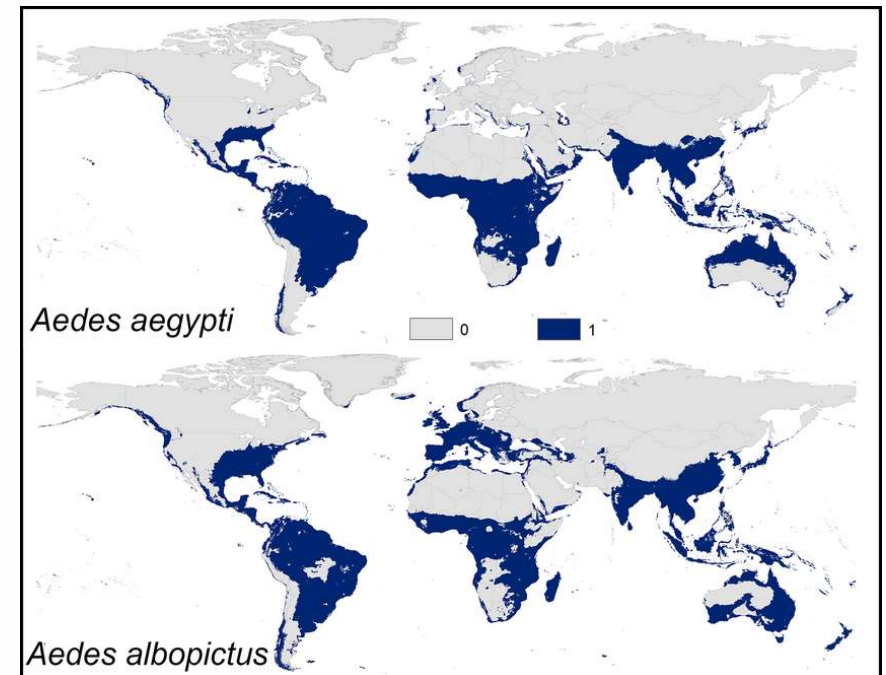


- Incidence curve surpassed endemic channel prior to EW1
- Peak at EW12
- Decrease started on EW 16



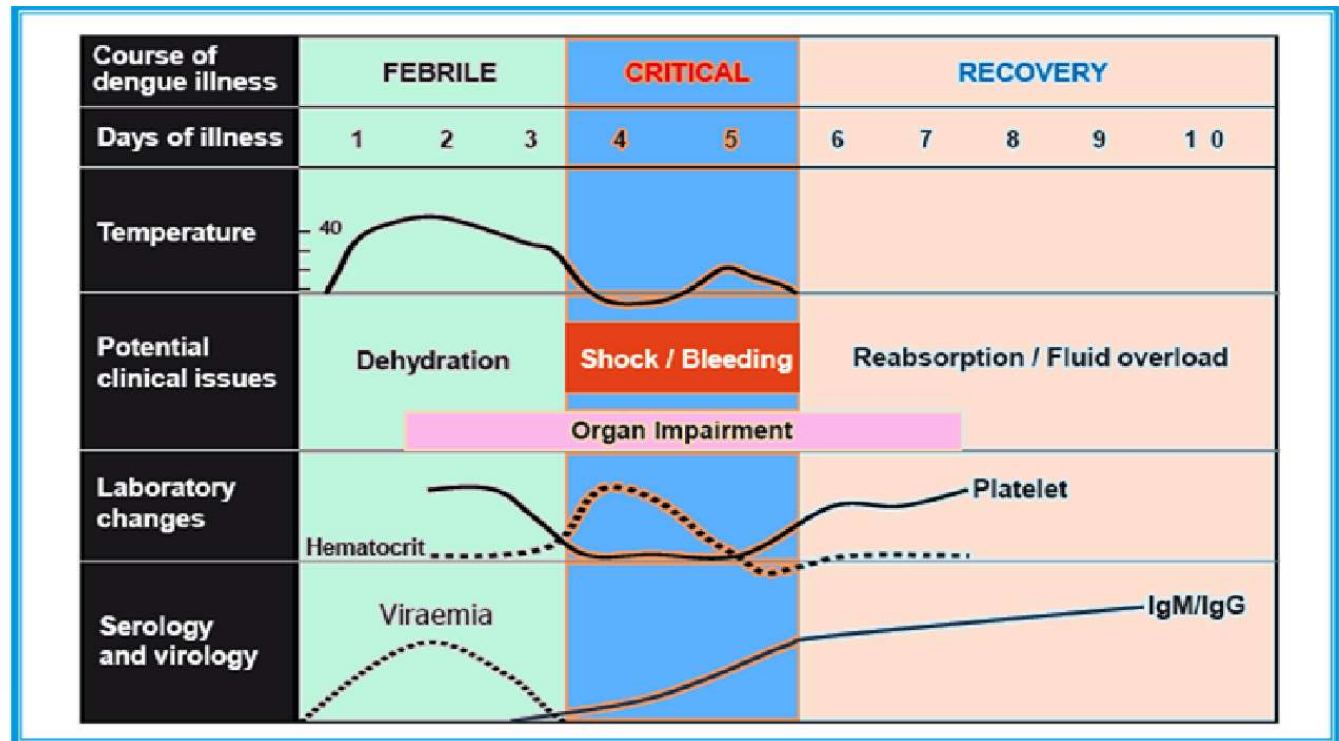
# The pathogen and the vector

- **Family:** *Flaviviridae*
- **Four distinct serotypes:** DENV-1, DENV-2, DENV-3, DENV-4
- **Primary Vector:**
  - *Aedes aegypti*: highly adapted to urban environments, prefers human blood, bites primarily during the day
  - *Aedes albopictus*: secondary vector with a broader geographic range, including temperate regions



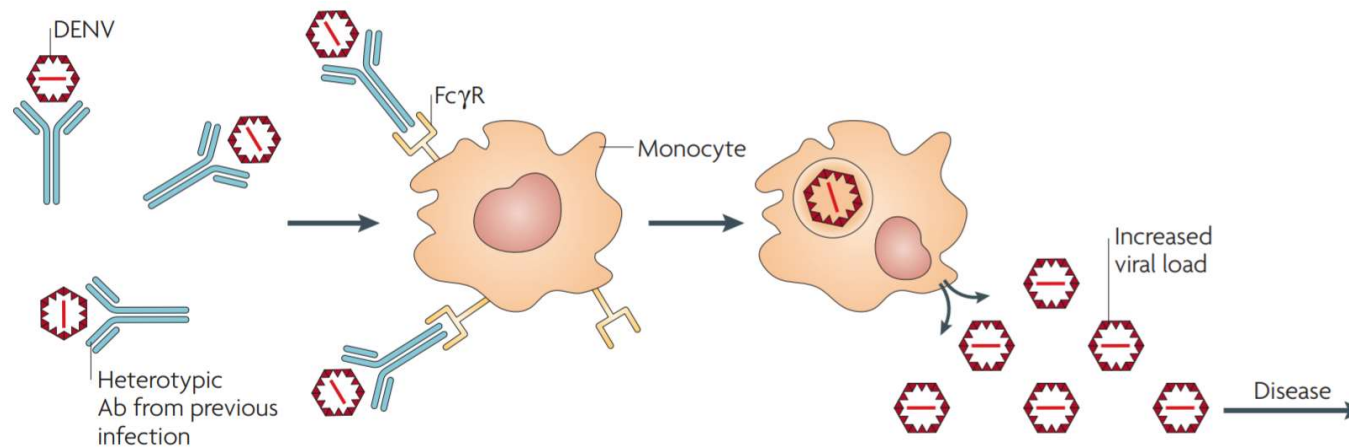
# The Clinical Spectrum and Burden

- ~75% Asymptomatic
- **Symptomatic Disease:**
  - Dengue Fever: Sudden high fever, headache, pain behind the eyes, muscle/joint pain ("breakbone fever"), rash, nausea
  - Severe Dengue/ Dengue Hemorrhagic Fever: Plasma leakage, fluid accumulation, respiratory distress, severe bleeding, organ impairment. Can be fatal.
- Majority of deaths are due to missed warning signs and late presentation

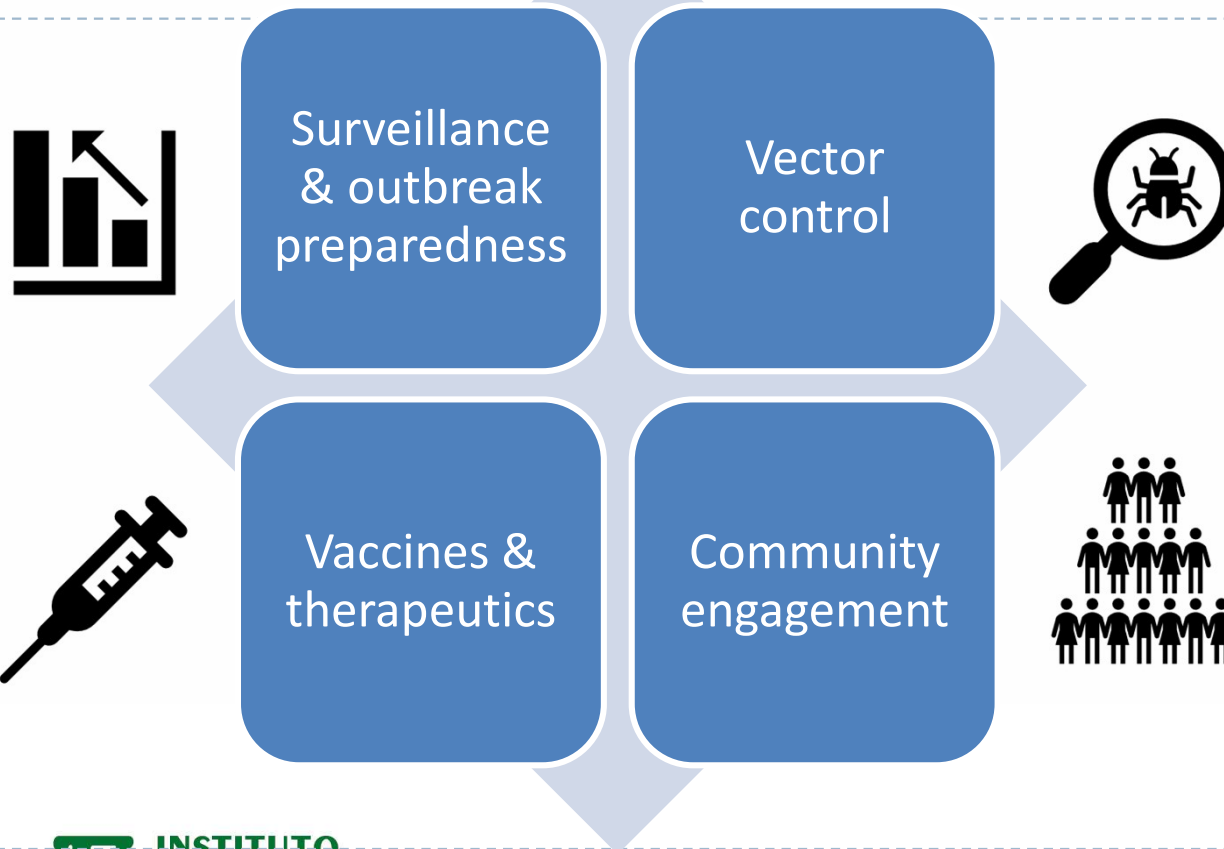


# Antibody-dependent enhancement

Infection with one serotype provides lifelong immunity to that one, but increases the risk of severe disease upon subsequent infection with a different serotype due to antibody dependent enhancement (ADE)



# Pillars of dengue prevention and control



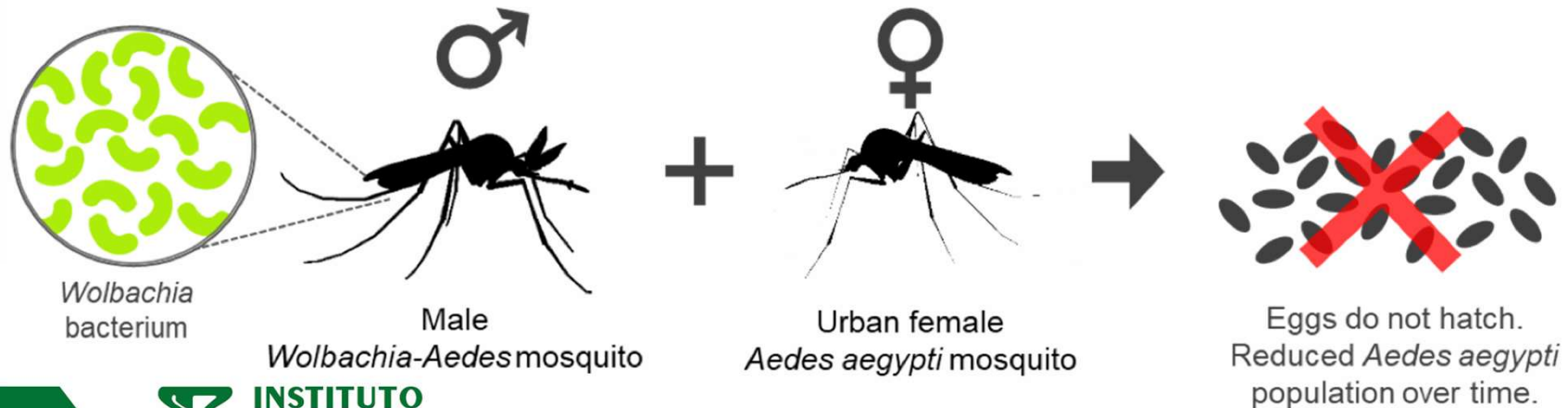
# Enhanced Surveillance & Diagnostics

- Move from passive to active surveillance
- Integrated Data: Combine epidemiological data (case numbers, serotypes) with entomological data (mosquito indices) and environmental data (temperature, rainfall) for predictive modelling.
- Early Warning Systems: Use data to predict outbreaks and trigger pre-emptive interventions
- Diagnostics: Rapid Diagnostic tests for screening, PCR for serotype and confirmation. Critical for tracking circulating strains.
- **You cannot control what you do not measure. Data driven decision making is non negotiable.**



# Next-generation Vector Control

- Environmental management: Source reduction- the most sustainable method. Removing, covering or treating water holding containers.
- Novel Biological tools
  - **Wolbachia**: Releasing mosquitoes infected with Wolbachia bacteria, which inhibits viral replication. No safety risks. No environmental impact.



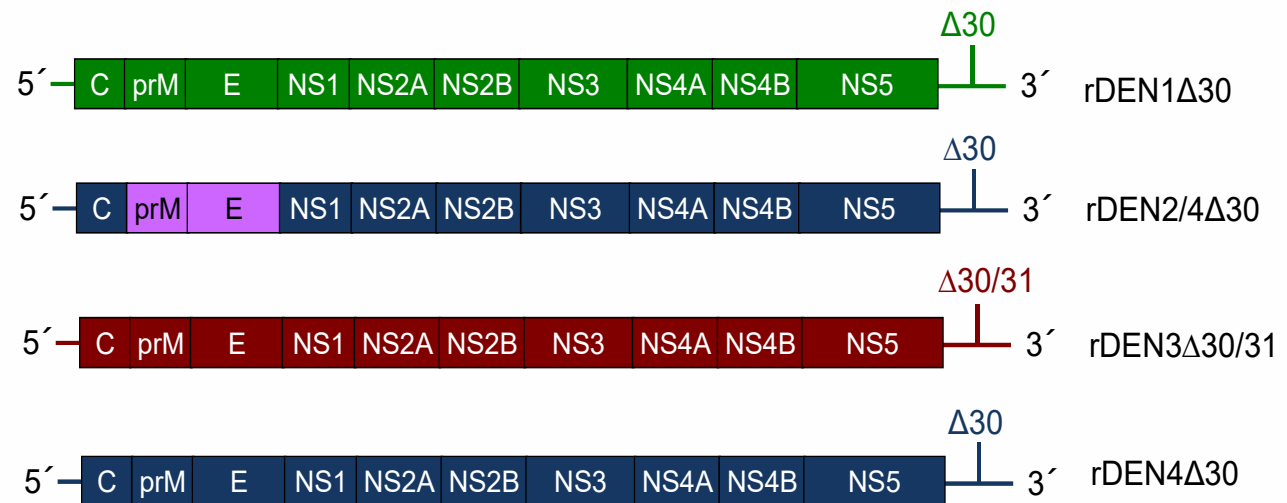
# Butantan-DV: Advancing a technology from NIH

- Dengue 1, 2, 3, 4, (attenuated) vaccine formulation originated at the Laboratory for Infectious Diseases at U.S. National Institutes of Health (NIH)
- NIH licensed the technology to partners interested in advancing development towards licensure



# Butantan-DV Vaccine Candidate

- Lyophilized, live-attenuated, tetravalent dengue vaccine analogous to TV003 developed by the U.S. National Institutes of Health<sup>1,2</sup>
- Attenuation is based on deletion of stem loop structure(s) in the 3 prime untranslated region
- Targets delivery of  $10^3$  plaque forming units of each vaccine virus strain representing all four serotypes
- The DENV-2 vaccine virus strain is a chimeric virus which is based on the DENV-4 background but encodes the DENV-2 structural proteins.

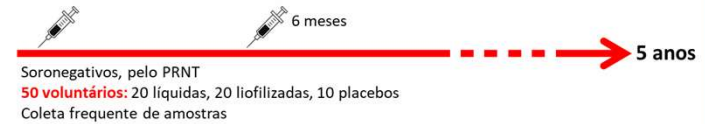


# Butantan-DV: Phase 2

Articles

## Etapa A

50 voluntários,



## Etapa B

250 voluntários,  
primeiros 40 completos



## Safety and immunogenicity of the tetravalent, live-attenuated dengue vaccine Butantan-DV in adults in Brazil: a two-step, double-blind, randomised placebo-controlled phase 2 trial

Esper G Kallas, Alexander Roberto Precioso, Ricardo Palacios, Beatriz Thomé, Patricia Emilia Braga, Tazio Vanni, Lúcia M A Campos, Lilian Ferrari, Gabriella Mondini, Maria da Graça Salomão, Anderson da Silva, Heloisa M Espinola, Joane do Prado Santos, Cecília L S Santos, Maria do Carmo S T Timenetsky, João Luiz Miraglia, Neuza M F Gallina, Daniela Weiskopf, Alessandro Sette, Raphaela Goulart, Rafael Tavares Salles, Alvinio Maestri, Adriana Maluf Elias Sallum, Sylvia Costa Lima Farhat, Neusa K Sakita, Juliana C O A Ferreira, Cassia G T Silveira, Priscilla R Costa, Isaias Raw, Stephen S Whitehead, Anna P Durbin, Jorge Kalil

**In addition to numerous Phase I studies of TV003, Butantan-DV was found to be well tolerated and immunogenic in a phase 2 study in Brazil.**

	Step A				Previous exposure analysis			
	Butantan-DV	TV003	Placebo	p value*	DENV-naive	DENV-exposed	Placebo	p value*
Per protocol†	16	17	9	..	85	101	62	..
DENV-1	15 (94%)	16 (94%)	2 (22%)	<0.0001‡	74 (87%)	82 (81%)	7 (11%)	<0.0001§
DENV-2	15 (94%)	14 (82%)	0	<0.0001¶	78 (92%)	79 (78%)	10 (16%)	<0.0001
DENV-3	13 (81%)	14 (82%)	0	<0.0001**	65 (76%)	83 (82%)	7 (11%)	<0.0001††
DENV-4	14 (88%)	15 (88%)	0	<0.0001‡‡	76 (89%)	78 (77%)	5 (8%)	<0.0001§§
Modified intention to treat	19	17	10	..	97	113	70	..
DENV-1	16 (84%)	16 (94%)	2 (20%)	<0.0001¶¶	81 (84%)	88 (78%)	8 (11%)	<0.0001
DENV-2	16 (84%)	14 (82%)	0	<0.0001***	87 (90%)	86 (76%)	10 (14%)	<0.0001†††
DENV-3	14 (74%)	14 (82%)	0	<0.0001‡‡‡	72 (74%)	87 (77%)	8 (11%)	<0.0001§§§
DENV-4	15 (79%)	15 (88%)	0	<0.0001¶¶¶	83 (86%)	86 (76%)	5 (7%)	<0.0001

Data are n, or n (%). \* $\chi^2$  test. Seroconversion was defined by PRNT<sub>50</sub> cutoff ( $\geq 1/10$ ) for DENV-naive participants or a four-fold or higher increase in neutralising antibody titre after immunisation of DENV-exposed participants. †Participants who did not attend all visits for sample collection for seroconversion analysis were excluded from the per-protocol analysis. ‡p>0.999 for Butantan-DV versus TV003. §p=0.278 for DENV-naive versus DENV-exposed. ¶p=0.601 for Butantan-DV versus TV003. ||p=0.011 for DENV-naive versus DENV-exposed. \*\*p>0.999 for Butantan-DV versus TV003. ††p=0.336 for DENV-naive versus DENV-exposed. ‡‡p>0.999 for Butantan-DV versus TV003. §§p=0.028 for DENV-naive versus DENV-exposed. ¶¶p=0.605 for Butantan-DV versus TV003. |||p=0.305 for DENV-naive versus DENV-exposed. \*\*\*p>0.999 for Butantan-DV versus TV003. †††p=0.010 for DENV-naive versus DENV-exposed. ‡‡‡p=0.695 for Butantan-DV versus TV003. §§§p=0.641 for DENV-naive versus DENV-exposed. ¶¶¶p=0.662 for Butantan-DV versus TV003. |||||p=0.085 for DENV-naive versus DENV-exposed.

Table 4: Frequency of seroconversion after the first dose of immunisation in step A and in all Butantan-DV recipients stratified by previous exposure

Kallas, EG et al, *Lancet Infect Dis.* 2020;20(7):839-850



# Phase 3 Trial Design

**Single dose** of Butantan-DV or Placebo (2:1 randomization)

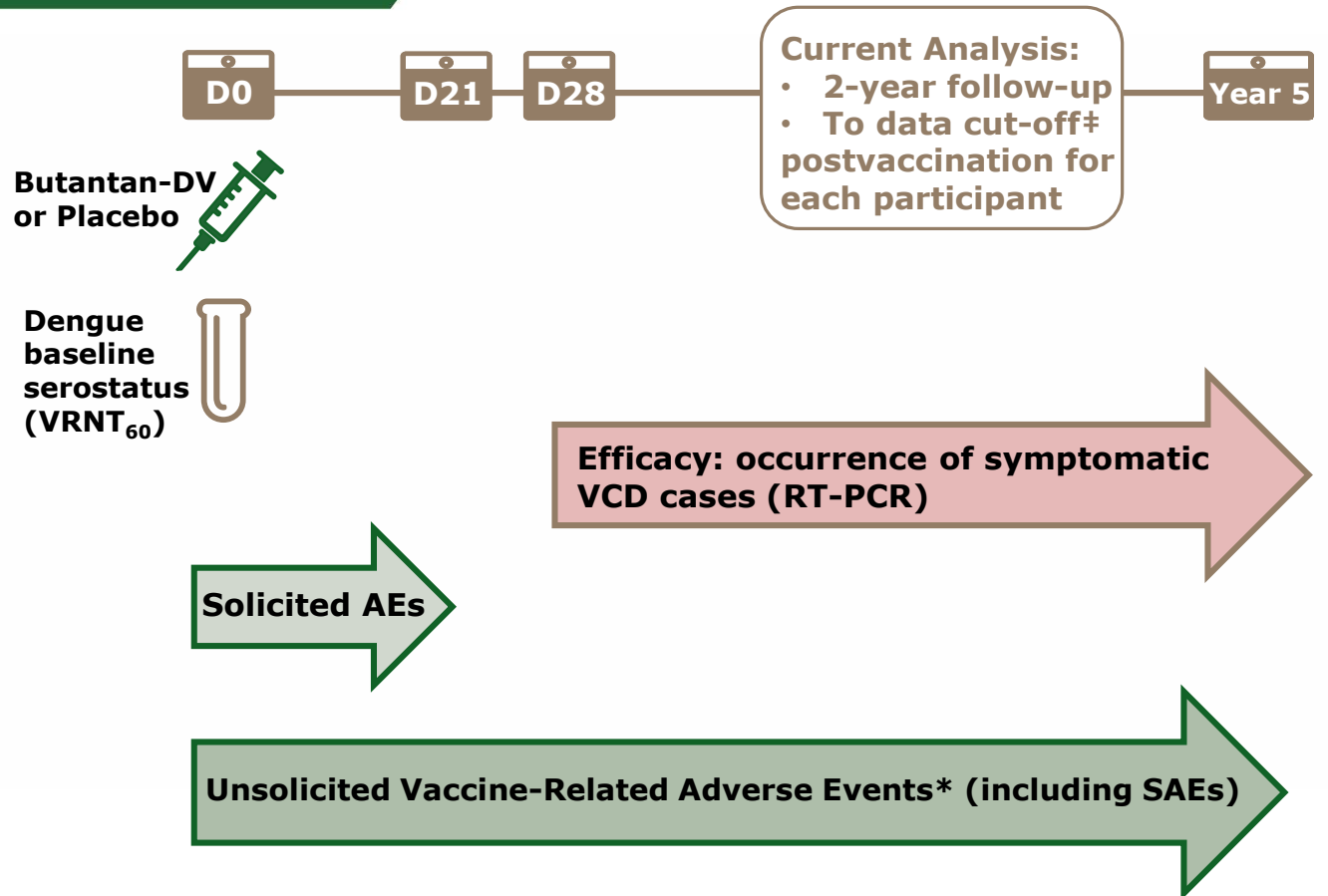
Target enrollment: >16,000

Stratified by age:

- 2-6 years old
- 7-17 years old
- 18-59 years old

Projected 5 years follow-up

ClinicalTrials.gov: NCT02406729  
WHO International Clinical Trials  
Registry Platform (ICTRP) identifier:  
U1111-1168-8679





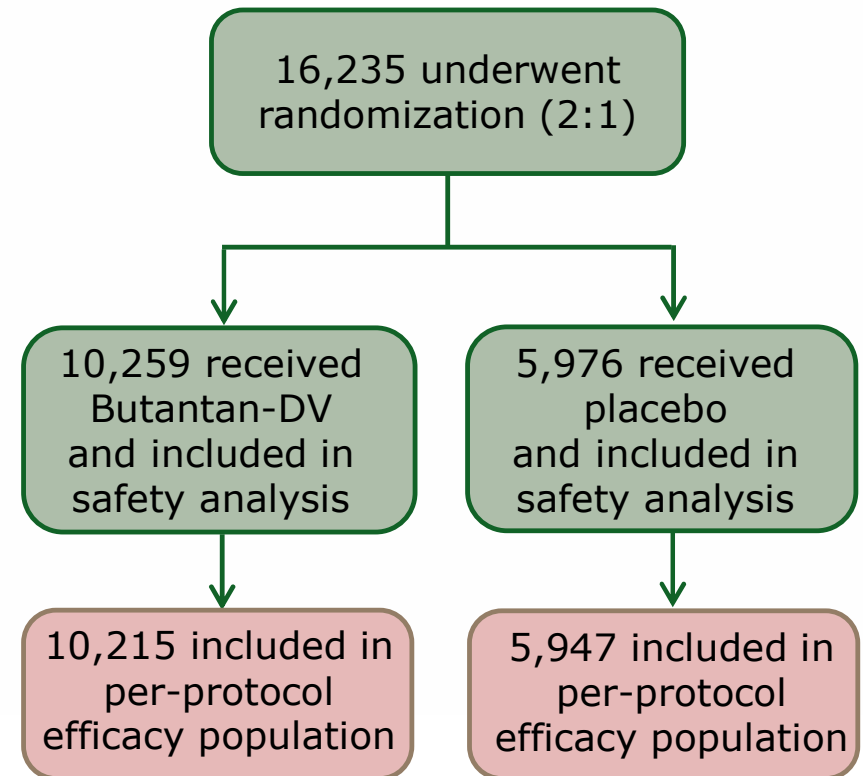
# Participant Disposition

16 clinical sites across Brazil



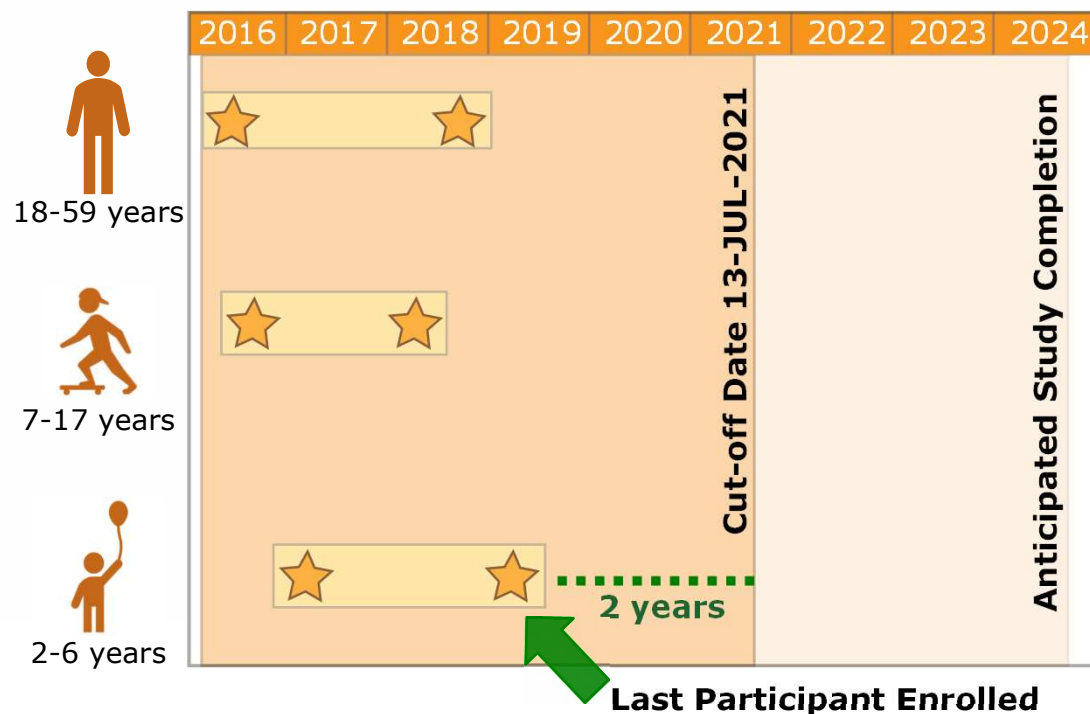
Enrollment of 2-6 year olds was initiated after an interim safety analysis of 450 participants from each of the older old age groups (900 participants total)

Age (years)	n
2-6 	5,016
7-17 	5,147
18-59 	6,072
<b>TOTAL</b>	<b>16,235</b>



# Primary analysis contains dengue cases accrual until cut-off date

- The cut-off date is based upon guidance received from ANVISA which stated that the primary efficacy analysis should include a minimum of 2 years of follow-up for all participants
- All participants contributed with a 2-year follow-up time, but given the enrollment was achieved in a 3-year period, this analysis will include additional follow-up time (up to 5 years) for some participants



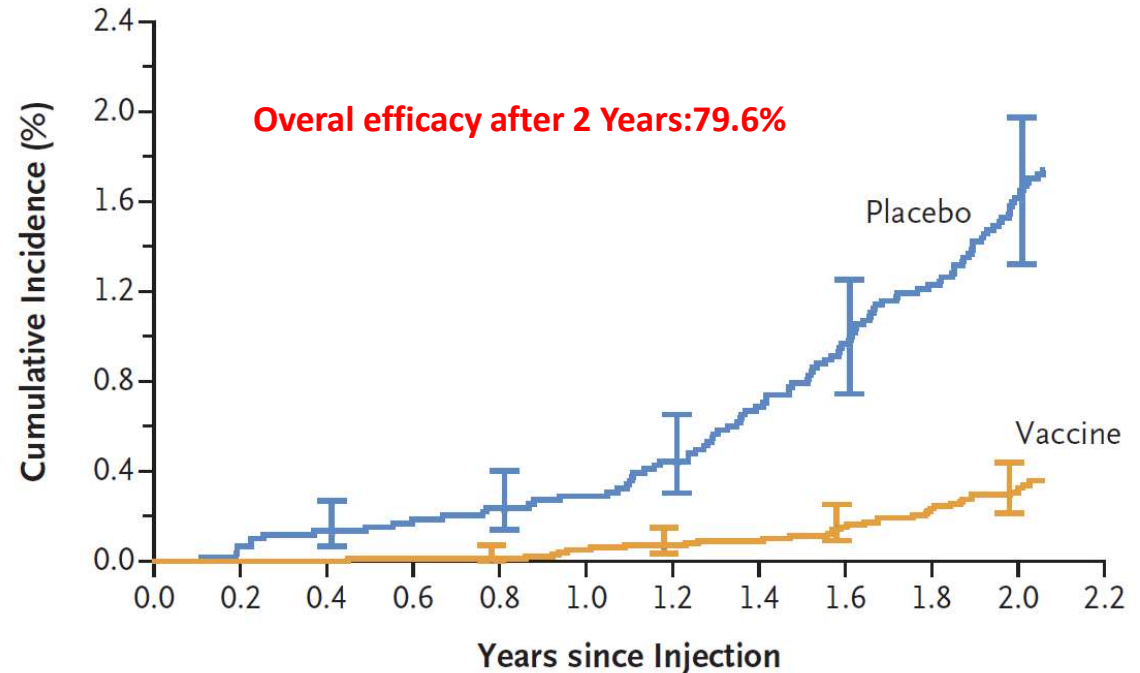
# Phase 3, primary results

## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2024 VOL. 390 NO. 5

### Live, Attenuated, Tetravalent Butantan–Dengue Vaccine in Children and Adults

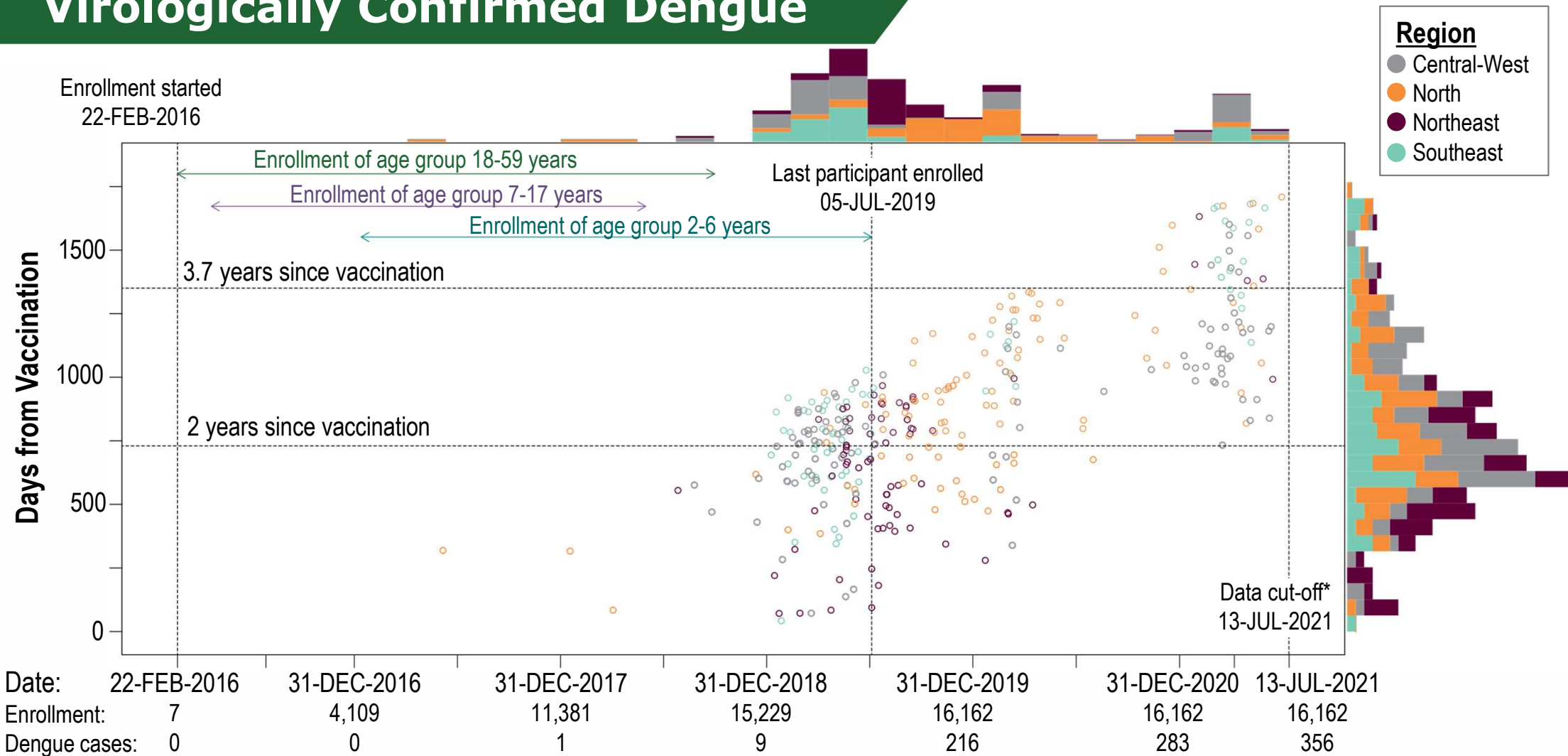
E.G. Kallás, M.A.T. Cintra, J.A. Moreira, E.G. Patiño, P.E. Braga, J.C.V. Tenório, V. Infante, R. Palacios, M.V.G. de Lacerda, D.B. Pereira, A.J. da Fonseca, R.Q. Gurgel, I.C.-B. Coelho, C.J.F. Fontes, E.T.A. Marques, G.A.S. Romero, M.M. Teixeira, A.M. Siqueira, A.M.P. Barral, V.S. Boaventura, F. Ramos, E. Elias Júnior, J. Cassio de Moraes, D.T. Covas, J. Kalil, A.R. Precioso, S.S. Whitehead, A. Esteves-Jaramillo, T. Shekar, J.-J. Lee, J. Macey, S.G. Kelner, B.-A.G. Collier, F.C. Boulos, and M.L. Nogueira



#### No. at Risk

Placebo	5,946	5,865	5,811	5,741	5,668	5,571
Vaccine	10,213	10,014	9,925	9,840	9,750	9,628

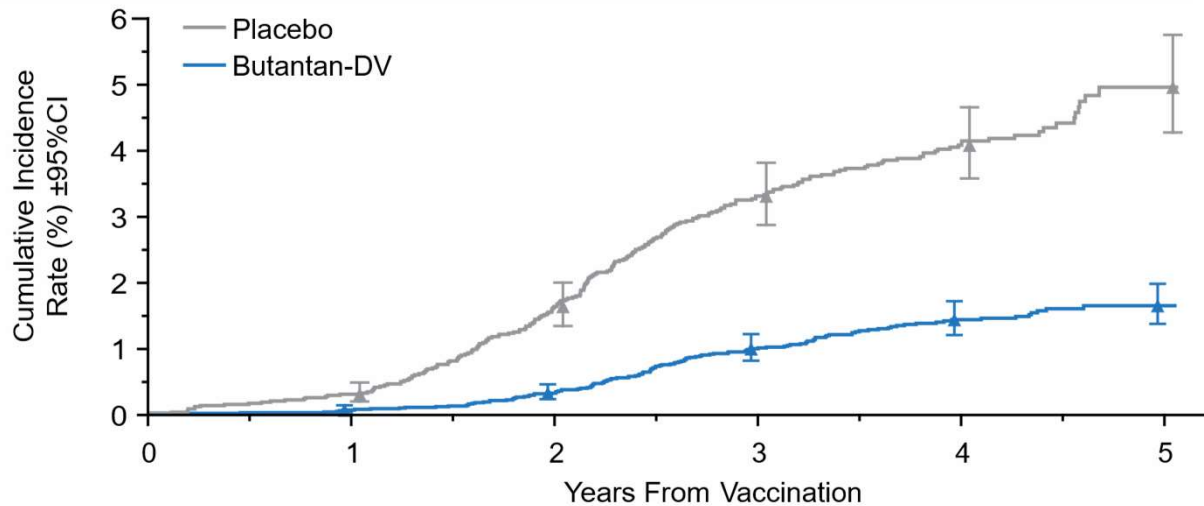
# Temporospatial Distribution of Virologically Confirmed Dengue



\*Data cut-off: 13-JUL-2021 (Based on the timing when the last participant enrolled and completed 2 years of follow-up). Per-protocol population.

# Incidence Density of Virologically Confirmed Dengue (VCD) through the cut-off

## Any DENV Serotype



Efficacy and safety of Butantan-DV in participants aged 2–59 years through an extended follow-up: results from a double-blind, randomised, placebo-controlled, phase 3, multicentre trial in Brazil



Mauricio L. Nogueira, Monica A T. Cintra, José A. Moreira, Elizabeth G. Patiño, Patricia Emilia Braga, Juliana CV Tenório, Lucas Bassoli de Oliveira Alves, Vanessa Infante, Daniela Haydee Ramos Silveira, Marcus Vinícius Guimarães de Lacerda, Dhelio Batista Pereira, Alex Jardim da Fonseca, Ricardo Queiroz Gurgel, Ivo Castelo-Branco Coelho, Cor Jesus Fernandes Fontes, Ernesto T. A. Marques, Gustavo Adolfo Sierra Romero, Mauro Martins Teixeira, André M. Siqueira, Viviane Sampaio Boaventura, Fabiano Ramos, Erivaldo Elias Júnior, José Cassio de Moraes, Stephen S. Whitehead, Alejandra Esteves-Jaramilla, Tulin Shekar, Jung-jin Lee, Julieta Macey, Sabrina Gozlan Kéner, Beth-Ann G. Collier, Fernanda Castro Boulos, Esper G. Kallós, on behalf of the Phase 3 Butantan-DV Working Group\*

**Overall efficacy after 3,7 Years: 67.3%**

## Number of participants at risk

Butantan-DV	10,213	9,870	9,628	8,119	4,926	28
Placebo	5,946	5,776	5,571	4,729	30,13	15



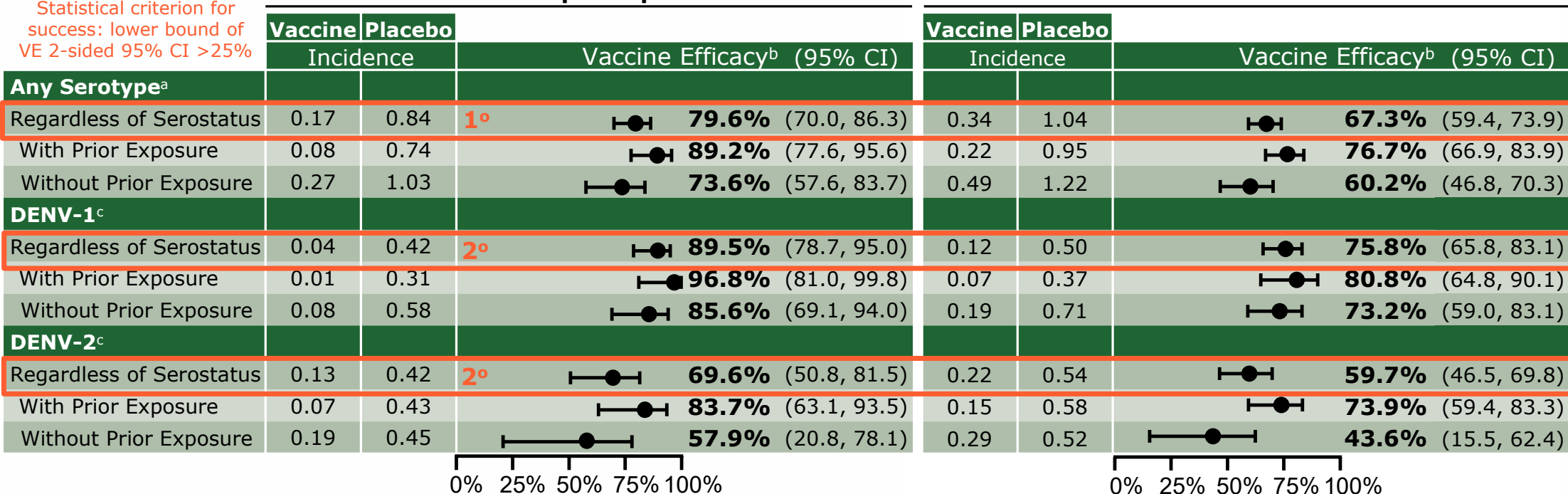
\*Data cut-off: 13-JUL-2021 (Based on the timing when the last participant enrolled and completed 2 years of follow-up). Per-protocol population.

# Vaccine Efficacy against VCD per serotype after Day 28 postvaccination

**#Pre-specified hypothesis testing:**  
Statistical criterion for success: lower bound of VE 2-sided 95% CI >25%

Through 2 years of follow-up for each participant\*

Through the data cut-off (2 or more years of follow up for each participant)\*\*



▪ There were no cases of DENV-3 or DENV-4 during the follow-up of the study

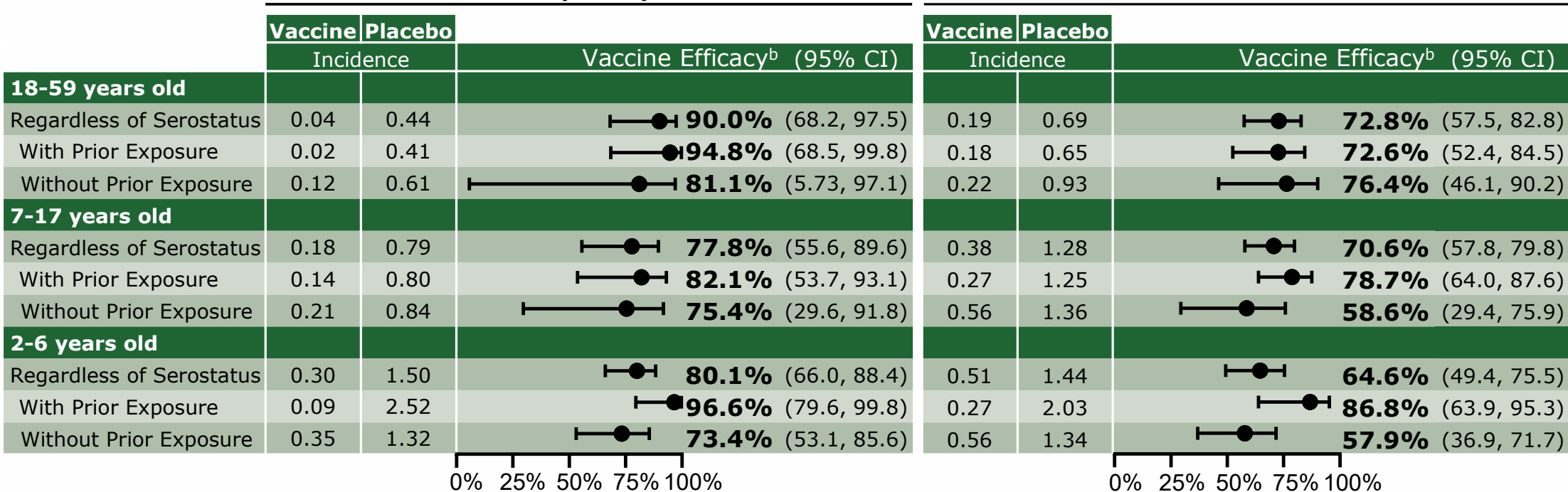
Per-protocol population: \*2-Year Follow-up postvaccination for each participant; \*\*Data cut-off: 13-JUL-2021 (Based on the timing when the last participant enrolled and completed 2 years of follow-up). #The vaccine efficacy objective was considered met if the lower bound of the 2-sided 95% confidence interval (CI) was greater than 25% for DENV disease caused by any serotype (combined) for the primary objective or by each serotype (separately) for the secondary objectives.

<sup>a</sup> Participants with multiple dengue episodes were counted as single case. <sup>b</sup> Vaccine efficacy was estimated based on the exact binomial method proposed by Chan and Bohidar, and the 95% CI was estimated using Blaker's exact CI. <sup>c</sup> Participants with positive dengue-specific serotype result in a single symptomatic virologically confirmed dengue (VCD) episode or multiple symptomatic VCD episodes will be counted in each corresponding row for secondary objective. Incidence rate=cases per 100 person-years at risk.

# Vaccine Efficacy against VCD of any DENV serotype by age subgroup

Through 2 years of follow-up for each participant\*

Through the data cut-off (2 or more years of follow up for each participant)\*\*



# Vaccine Efficacy against VCD after Day 28 postvaccination Through 5 years of follow-up

**\*Pre-specified hypothesis testing:**  
 Statistical criterion for success: lower bound of VE 2-sided 95% CI >25%

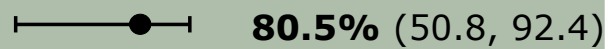
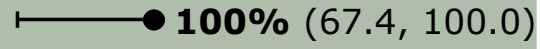
**Through 5 years of follow-up\***

		Butantan-DV		Placebo		Vaccine Efficacy (95% CI)
		Cases/ total no.	Person- years at risk	Cases/ total no.	Person- years at risk	
<b>Any DENV serotype</b>						
<b>*1°</b>	Regardless of Serostatus	177/10,209	47,038	291/5,940	27,087	<b>65.0%</b> (57.8, 71.0)
	With Prior Exposure	46/4,985	23,242	120/3,023	13,910	<b>77.1%</b> (67.6, 83.9)
	Without Prior Exposure	125/4,819	21,905	167/2,678	12,041	<b>58.9%</b> (48.0, 67.6)
<b>DENV-1</b>						
<b>*2°</b>	Regardless of Serostatus	75/10,209	47,250	161/5,940	27,396	<b>73.0%</b> (64.3, 79.7)
	With Prior Exposure	16/4,985	23,305	47/3,023	14,087	<b>79.4%</b> (63.1, 89.0)
	Without Prior Exposure	58/4,819	22,041	112/2,678	12,171	<b>71.4%</b> (60.5, 79.3)
<b>DENV-2</b>						
<b>*2°</b>	Regardless of Serostatus	102/10,209	47,164	134/5,940	27,428	<b>55.7%</b> (42.3, 66.1)
	With Prior Exposure	30/4,985	23,273	73/3,023	14,026	<b>75.2%</b> (61.9, 84.4)
	Without Prior Exposure	67/4,819	21,999	59/2,678	12,264	<b>36.7%</b> (9.1, 55.5)



# Vaccine Efficacy against Dengue with Warning Signs/Severe Dengue and post-hoc against Hospitalization

Through 5 years of follow-up\*

	Butantan-DV	Placebo	
Pre-specified analysis	Cases/ Total no.	Cases/ Total no.	Vaccine Efficacy (95% CI)
Dengue with warning signs/severe dengue, regardless of hospitalization	6/10,209	18/5,940	 <b>80.5%</b> (50.8, 92.4)
Post-hoc analysis			
Hospitalization due to dengue	0/10,209	8/5,940	 <b>100%</b> (67.4, 100.0)
			0% 25% 50% 75% 100%

- The case definitions correspond to those used by the Brazilian Ministry of Health from 2013 which adopts the definitions proposed by the 2009 World Health Organization classification
- **There was no imbalance in the proportion of participants with dengue with warning signs or severe dengue between intervention groups**

# Overall Safety Summary

	<b>Butantan-DV (N=10,259)</b>	<b>Placebo (N=5,976)</b>
<b>Adverse Event occurring within 21 days</b>	no. (%)	no. (%)
With $\geq 1$ adverse events	7,137 (69.6)	3,595 (60.2)
administration-site	2,012 (19.6)	879 (14.7)
systemic	6,204 (60.5)	2,864 (47.9)
With $\geq 1$ vaccine-related <sup>a</sup> adverse events	6,527 (63.6)	3,109 (52.0)
administration-site <sup>b</sup>	2,012 (19.6)	879 (14.7)
systemic	5,980 (58.3)	2,725 (45.6)
With $\geq 1$ unsolicited adverse events	3,360 (32.8)	1,917 (32.1)
With $\geq 1$ unsolicited vaccine-related adverse events	1,391 (13.6)	720 (12.0)
With $\geq 1$ serious adverse events	20 (0.2)	8 (0.1)
With $\geq 1$ serious vaccine-related adverse events	3 (0.0)	2 (0.0)

Through the cut-off\* there were:

- No deaths related to the study treatment
- 3 serious vaccine-related adverse events total in the vaccine group



<sup>a</sup> In this trial, all adverse events that present a reasonable causal relation to the product under investigation will be considered as adverse reactions.

<sup>b</sup> All administration-site reactions after administration of the product under investigation were considered as adverse events with sure causal relation to the vaccination. Vaccine-related adverse events are equivalent to Adverse Reactions

\*Data cut-off: 13-JUL-2021 (Based on the timing when the last participant enrolled and completed 2 years of follow-up).

# Vaccine-Related AEs Frequency within 21 days postvaccination

## age subgroups

### 2 to 6 Years

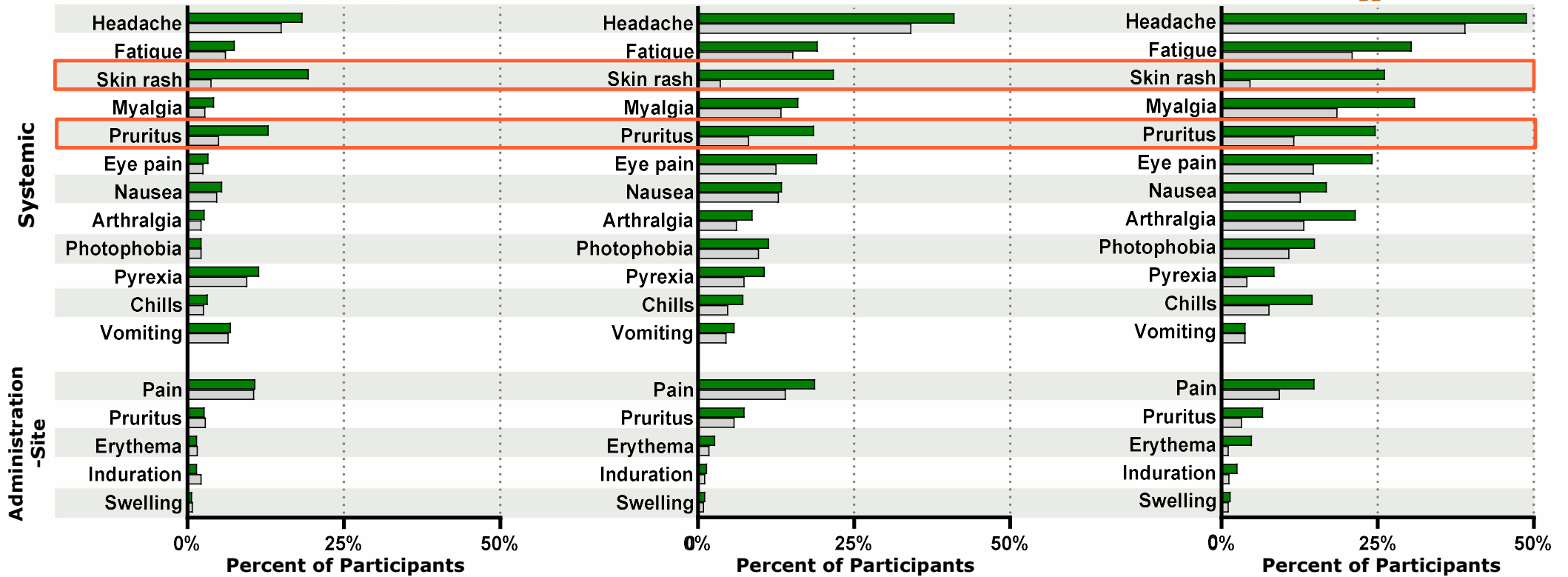
### 7 to 17 Years

### 18 to 59 Years

Butantan-DV (n=3,337) Placebo (n=1,679)

Butantan-DV (n=3,376) Placebo (n=1,771)

Butantan-DV (n=3,546) Placebo (n=2,526)

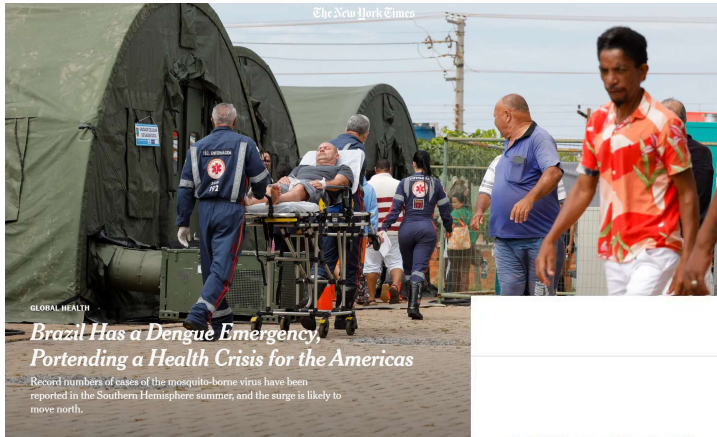


\* In this trial, all adverse events that present a reasonable causal relation to the product under investigation will be considered as adverse reactions. All administration-site reactions after administration of the product under investigation were considered as adverse events with sure causal relation to the vaccination. Vaccine-related adverse events are equivalent to Adverse Reactions. Pyrexia (fever) was solicited on the suspected dengue form from vaccination through Day 21 postvaccination. For specific administration-site and systemic adverse events, every participant is counted a single time for each applicable row and column.

# Summary

- A single dose of Butantan-DV was **efficacious against symptomatic virologically confirmed dengue** due to DENV-1 and DENV-2, regardless of baseline serostatus or age, **through five years** of follow-up
  - No cases of DENV-3 or DENV-4 were observed during the entire study period
- The safety profile of Butantan-DV was consistent with previous studies
- **No safety concerns were observed during the entire five-year follow-up**
  - There was no imbalance in the proportion of participants with dengue with warning signs or severe dengue between intervention groups
- Butantan-DV demonstrated **efficacy against dengue with warning signs/severe dengue**
  - **Efficacy against hospitalization was 100% in a post-hoc analysis**
- The study covered a wide age range (2-59 years of age) and included a substantial proportion of participants (46.4%) without evidence of prior dengue exposure

# Important unmet medical need in public health



The New York Times

GLOBAL HEALTH

## *The Push for a Better Dengue Vaccine Grows More Urgent*





A public research institute in Brazil has proved a new shot protects against the disease, but can't make it fast enough to stop the huge outbreak sweeping Latin America.

“ The only good news about dengue in Brazil at the moment is the publication of clinical trial results for a new vaccine tested by the public health research center **Instituto Butantan** in São Paulo. That vaccine requires just one shot, and the trial found that it protected 80 percent of those vaccinated against developing dengue virus disease. The research center will ask the Brazilian government to approve the vaccine, and it has facilities to produce it, aiming to start delivering shots in 2025. ”

**INSTITUTO BUTANTAN**  
A serviço da vida

<https://www.nytimes.com/2024/02/10/health/dengue-brazil-americas.html>  
<https://www.nytimes.com/2024/04/11/health/dengue-vaccine-brazil.html>

# The way forward

-  • *Integrate:* Move away from siloed approaches. Combine vector control, vaccination, and surveillance into a cohesive national program.
-  • *Innovate:* Scale up and invest in promising new Technologies.
-  • *Invest:* Secure sustainable funding for long term control, not just emergency outbreak response.
-  • *International collaboration:* Share data, best practices, and resources. Dengue does not respect borders.

**Thank you**



**Fernanda Boulos**  
**Chief Medical Officer**

**[fernanda.boulos@fundacaobutantan.org.br](mailto:fernanda.boulos@fundacaobutantan.org.br)**