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What is the current state of Dengue vaccine development and new technologies?

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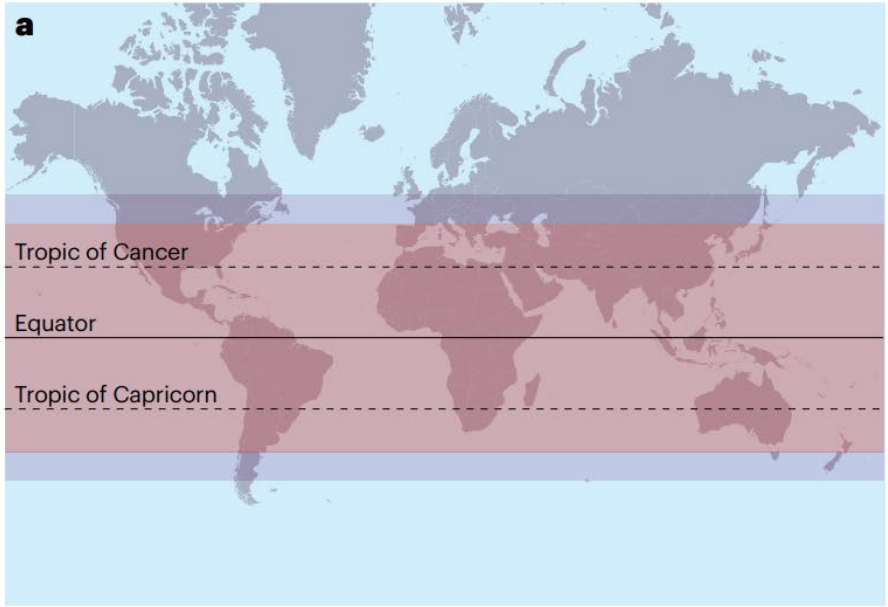
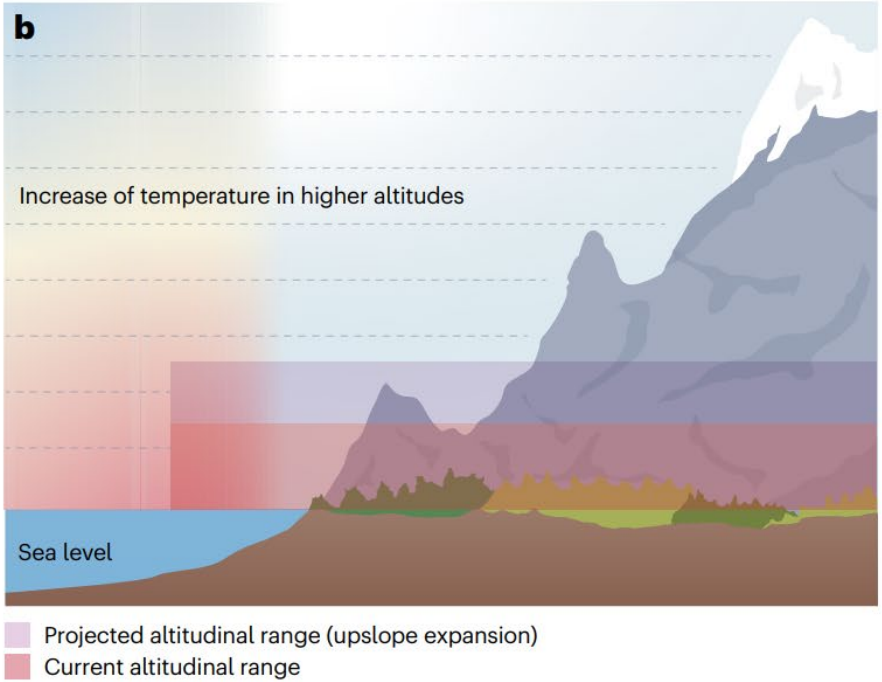
SÃO PAULO SÃO TODOS

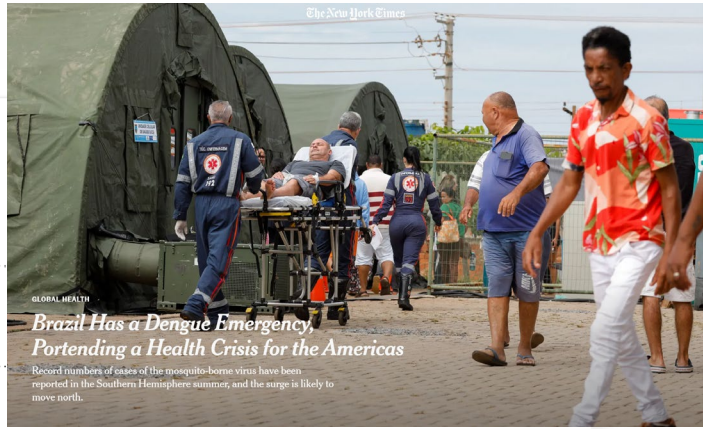
Dengue and global warming





Souza WM & Weaver SC, *Nature Rev Microbiol* 2024;March 14

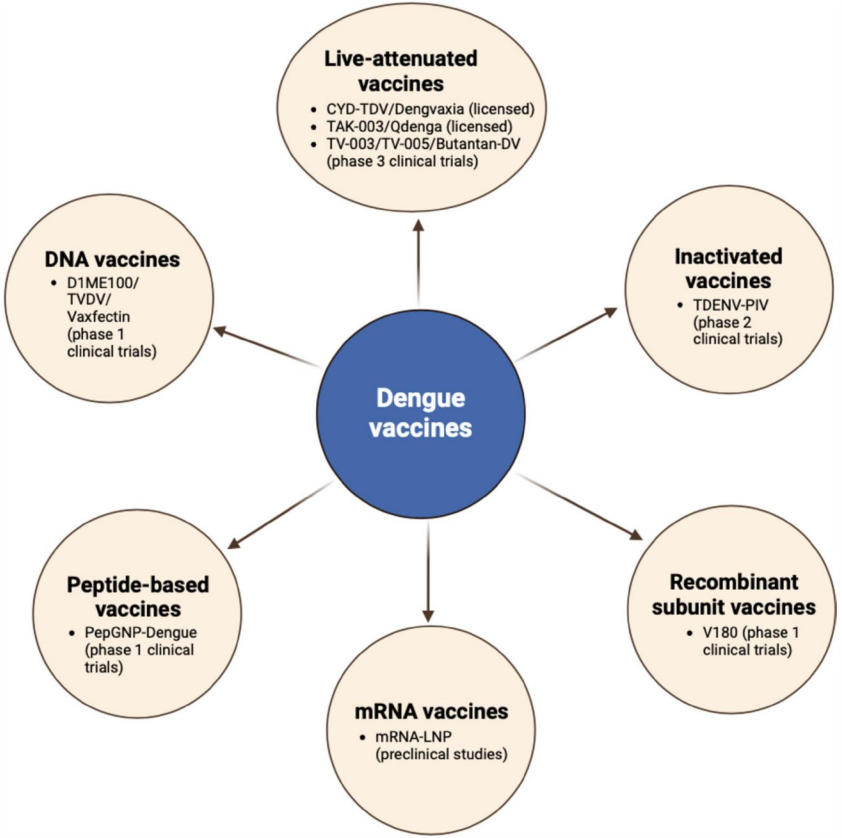
Large epidemic in 2024



https://www.nytimes.com/2024/02/10/health/dengue-brazil-americas.html
https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/a/aedes-aegypti/monitoramento-das-arboviroses

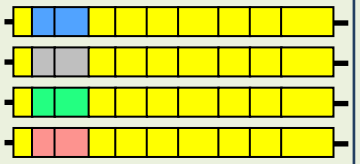
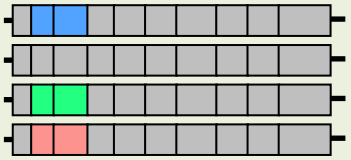
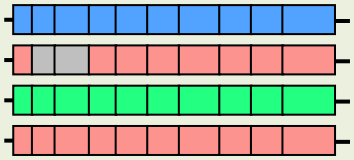
Vaccine technologies

- Live-attenuated
- Inactivated
- DNA
- mRNA
- Peptide-based
- Recombinant subunit
- VLPs



Lee *et al. Vaccine X* 2024

Live-attenuated dengue vaccines

	Dengvaxia (Sanofi Pasteur)	QDENGA (Takeda)	TV003/Butantan-DV (NIH / Butantan)
Status	Licensed	Licensed	Phase 3 completed
Doses	3 doses (0, 6, 12 mos.)	2 doses (0, 3 months)	1 dose
Indicated age	9 - 45	Phase 3 age range 2 - 16	Phase 3 age range 2 - 59
WHO	Pre-vax screening, > 9 yrs	↑ transmission, 6 – 16 yrs	?
Constructs			

Live-attenuated dengue vaccines

For live vaccines – infection is required for immune stimulation

The percentage of subjects with detectable viremia by PCR after a single dose in flavivirus-naïve subjects				
	DENV-1	**DENV-2**	**DENV-3**	**DENV-4**
Sanofi CYD (n=95)[1]	7	0	13	**44**
Takeda TAK (n=74)[2]	0	**69**	0	0
TV003 (n=19)[3]	**58**	**63**	**79**	**79**
TV003 (n=36)[4]	**64**	**97**	**69**	**53**

1. Torresi, et al 2017; CYD lot-to-lot consistency trial. Viremia measured on days 6, 8, 10, 14, & 20
2. Rupp et al 2015; Viremia measured on days 7, 9, 11, 14, &17
3. CIR323, unpublished
4. Russell et al, 2022, *Human Vaccines and Immunotherapeutics*, **Merck V181**. Viremia collected on days 7 & 12 only

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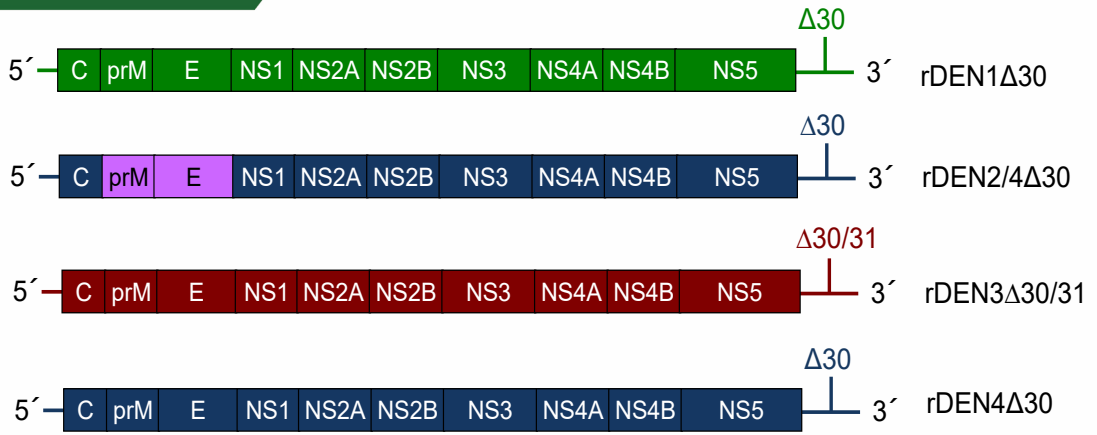
Butantan-DV Live-Attenuated Tetravalent Dengue Vaccine: a Phase 3 Clinical Trial in Children, Adolescents, and Adults

Butantan-DV Vaccine Candidate

- Lyophilized, live-attenuated, tetravalent dengue vaccine analogous to TV003 developed by the U.S. National Institutes of Health[1,2]
- 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
- Generally well tolerated and immunogenic in a phase 2 study in Brazil[2]
- Primary efficacy results published in February 1st, 2024[3]



Steve Whitehead

[1]Blaney, JE et al and SS Whitehead, *Viral Immunol* 2006;19(1):10-32
[2]Kallas, EG et al, *Lancet Infect Dis*. 2020;20(7):839-850

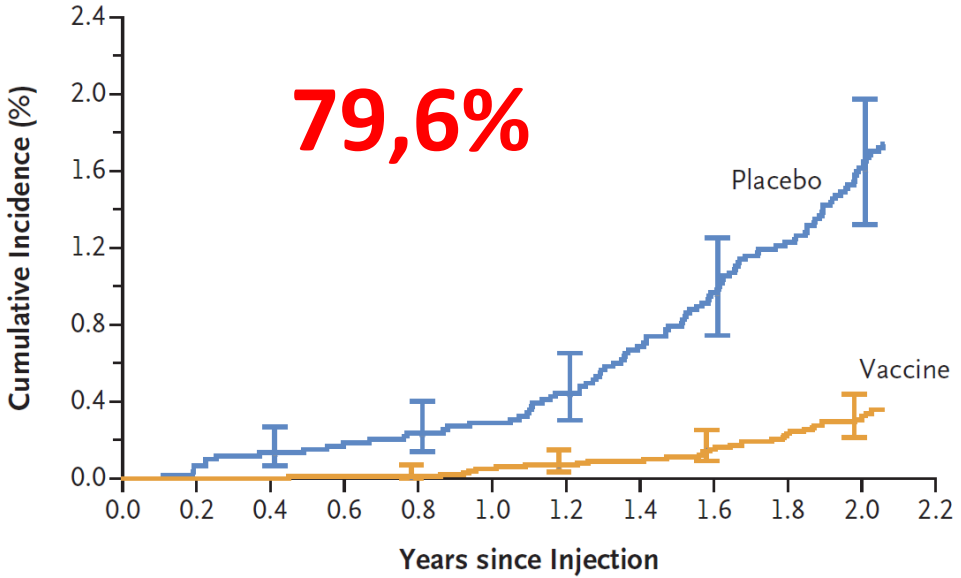
Phase 3, primary results

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. Coller, 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

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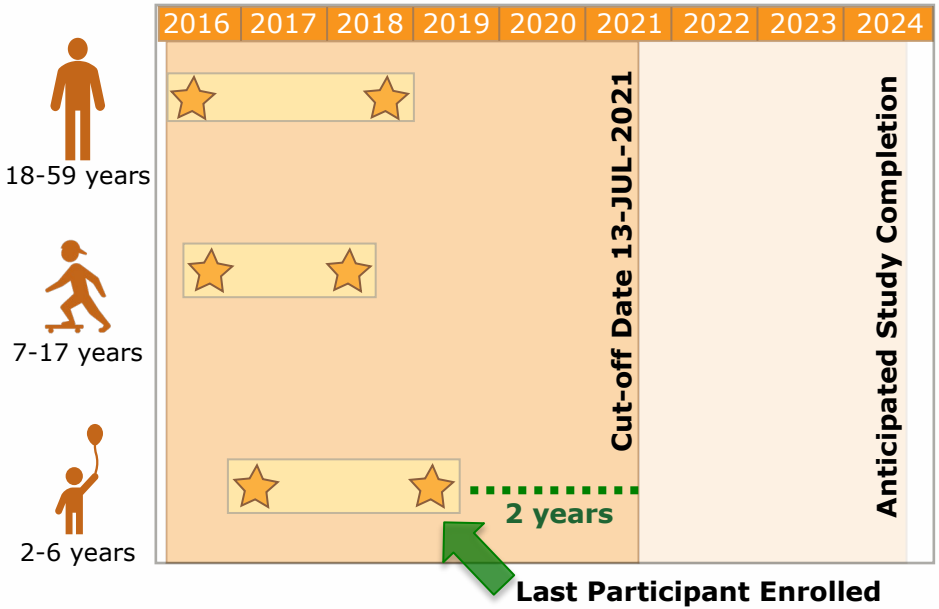
Primary analysis contains dengue cases accrual until cut-off date

- 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

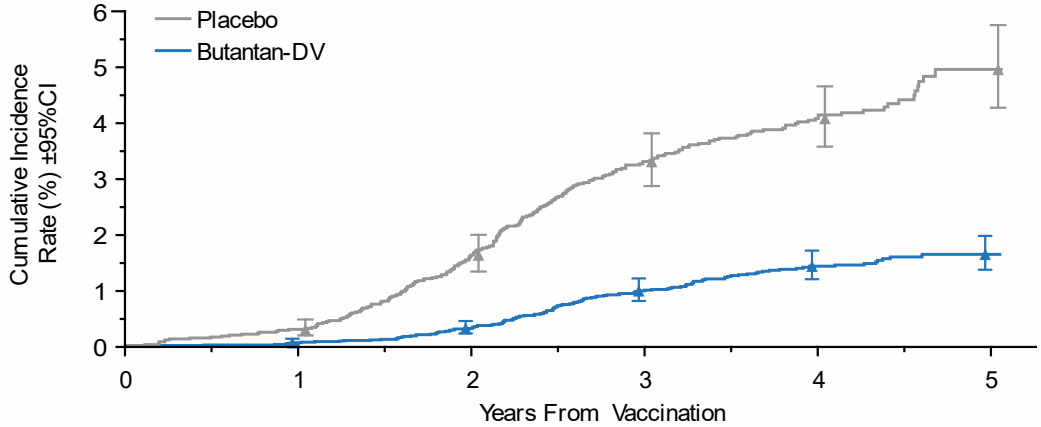
Efficacy and safety of Butantan-DV in participants aged 2–59 years through an extended follow-up: results from a double-blind, randomised, placebo-controlled, phase 3, multicentre trial in Brazil

Mauricio L Nogueira, Monica A T Cintra, José A Moreira, Elizabeth G Patiño, Patricia Emília Braga, Juliana C V Tenório, Lucas Bassolli de Oliveira Alves, Vanessa Infante, Daniela Haydee Ramos Silveira, Marcus Vinicius Guimarães de Lacerda, Dhelio Batista Pereira, Allex 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-Jaramillo, Tulin Shekar, Jung-Jin Lee, Julieta Macey, Sabrina Gozlan Kelner, Beth-Ann G Coller, Fernanda Castro Boulos, Esper G Kallás, on behalf of the Phase 3 Butantan-DV Working Group*



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

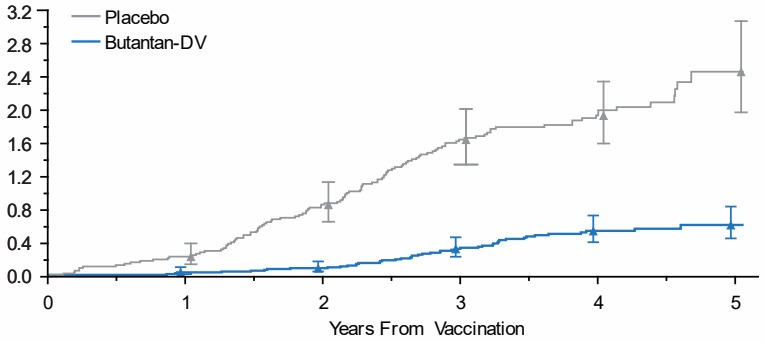
Any DENV Serotype



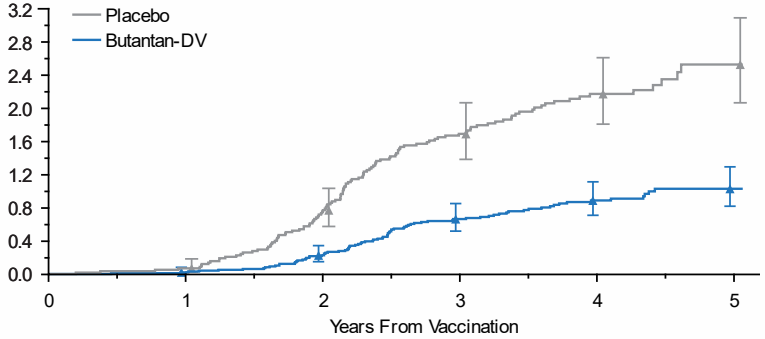
Number of participants at risk

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

DENV-1



DENV-2

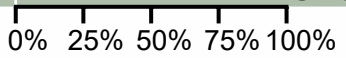


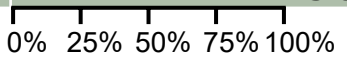
‡Data cut-off: 13-JUL-2021 (Based on the timing when the last participant enrolled and completed 2 years of follow-up). Per-protocol population.

Vaccine Efficacy against VCD 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)**			
	Vaccine Incidence	Placebo Incidence	Vaccine Efficacy[b]	(95% CI)	Vaccine Incidence	Placebo Incidence	Vaccine Efficacy[b]	(95% CI)
Any Serotype[a]								
Regardless of Serostatus	0.17	0.84	1º **79.6%**	(70.0, 86.3)	0.34	1.04	**67.3%**	(59.4, 73.9)
With Prior Exposure	0.08	0.74	**89.2%**	(77.6, 95.6)	0.22	0.95	**76.7%**	(66.9, 83.9)
Without Prior Exposure	0.27	1.03	**73.6%**	(57.6, 83.7)	0.49	1.22	**60.2%**	(46.8, 70.3)
DENV-1[c]								
Regardless of Serostatus	0.04	0.42	2º **89.5%**	(78.7, 95.0)	0.12	0.50	**75.8%**	(65.8, 83.1)
With Prior Exposure	0.01	0.31	**96.8%**	(81.0, 99.8)	0.07	0.37	**80.8%**	(64.8, 90.1)
Without Prior Exposure	0.08	0.58	**85.6%**	(69.1, 94.0)	0.19	0.71	**73.2%**	(59.0, 83.1)
DENV-2[c]								
Regardless of Serostatus	0.13	0.42	2º **69.6%**	(50.8, 81.5)	0.22	0.54	**59.7%**	(46.5, 69.8)
With Prior Exposure	0.07	0.43	**83.7%**	(63.1, 93.5)	0.15	0.58	**73.9%**	(59.4, 83.3)
Without Prior Exposure	0.19	0.45	**57.9%**	(20.8, 78.1)	0.29	0.52	**43.6%**	(15.5, 62.4)





- **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.

[a] Participants with multiple dengue episodes were counted as single case. [b] 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. [c] 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.

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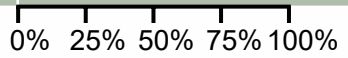
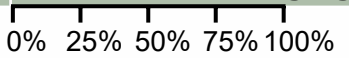
Vaccine Efficacy against VCD of any DENV serotype by age subgroup

	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 Incidence	Placebo Incidence	Vaccine Efficacy[b] (95% CI)	Vaccine Incidence	Placebo Incidence	Vaccine Efficacy[b] (95% CI)
18-59 years old						
Regardless of Serostatus	0.04	0.44	**90.0%** (68.2, 97.5)	0.19	0.69	**72.8%** (57.5, 82.8)
With Prior Exposure	0.02	0.41	**94.8%** (68.5, 99.8)	0.18	0.65	**72.6%** (52.4, 84.5)
Without Prior Exposure	0.12	0.61	**81.1%** (5.73, 97.1)	0.22	0.93	**76.4%** (46.1, 90.2)
7-17 years old						
Regardless of Serostatus	0.18	0.79	**77.8%** (55.6, 89.6)	0.38	1.28	**70.6%** (57.8, 79.8)
With Prior Exposure	0.14	0.80	**82.1%** (53.7, 93.1)	0.27	1.25	**78.7%** (64.0, 87.6)
Without Prior Exposure	0.21	0.84	**75.4%** (29.6, 91.8)	0.56	1.36	**58.6%** (29.4, 75.9)
2-6 years old						
Regardless of Serostatus	0.30	1.50	**80.1%** (66.0, 88.4)	0.51	1.44	**64.6%** (49.4, 75.5)
With Prior Exposure	0.09	2.52	**96.6%** (79.6, 99.8)	0.27	2.03	**86.8%** (63.9, 95.3)
Without Prior Exposure	0.35	1.32	**73.4%** (53.1, 85.6)	0.56	1.34	**57.9%** (36.9, 71.7)





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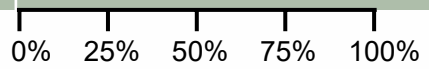
Per-protocol population: *2-Year Follow-up postvaccination for each participant; **Data cut-off: 13-JUL-2021 (Based on the timing when the last participant enrolled and completed 2 years of follow-up).
[a] Participants with multiple dengue episodes were counted as single case. [b] Vaccine efficacy was estimated based on the exact binomial method proposed by Chan and Bohidar, and the 95% CI was estimated using Blaker's exact CI. Incidence rate=cases per 100 person-years at risk.

Vaccine Efficacy against Dengue with Warning Signs or Severe Dengue

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

	Butantan-DV	Placebo		
Dengue with warning signs/Severe dengue	**Cases/ Total no.**	**Cases/ Total no.**	**Vaccine Efficacy[b]**	**(95% CI)**
Regardless of Serostatus	2/10,215	10/5,947	**88.2%**	**(50.8, 98.2)**



- **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**

Per-protocol population: **Data cut-off: 13-JUL-2021 (Based on the timing when the last participant enrolled and completed 2 years of follow-up).
[b] 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.
Brazilian Ministry of Health. (2013). Dengue: diagnosis and clinical handling: adults and children.
World Health Organization. (2009). Dengue guidelines for diagnosis, treatment, prevention and control : new edition

Overall Safety Summary

Adverse Event occurring within 21 days	Butantan-DV (N=10,259) no. (%)	Placebo (N=5,976) no. (%)
With ≥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 ≥1 vaccine-related[a] adverse events	6,527 (63.6)	3,109 (52.0)
administration-site[b]	2,012 (19.6)	879 (14.7)
systemic	5,980 (58.3)	2,725 (45.6)
With ≥1 unsolicited adverse events	3,360 (32.8)	1,917 (32.1)
With ≥1 unsolicited vaccine-related adverse events	1,391 (13.6)	720 (12.0)
With ≥1 serious adverse events	20 (0.2)	8 (0.1)
With ≥1 serious vaccine-related adverse events	3 (0.0)	2 (0.0)

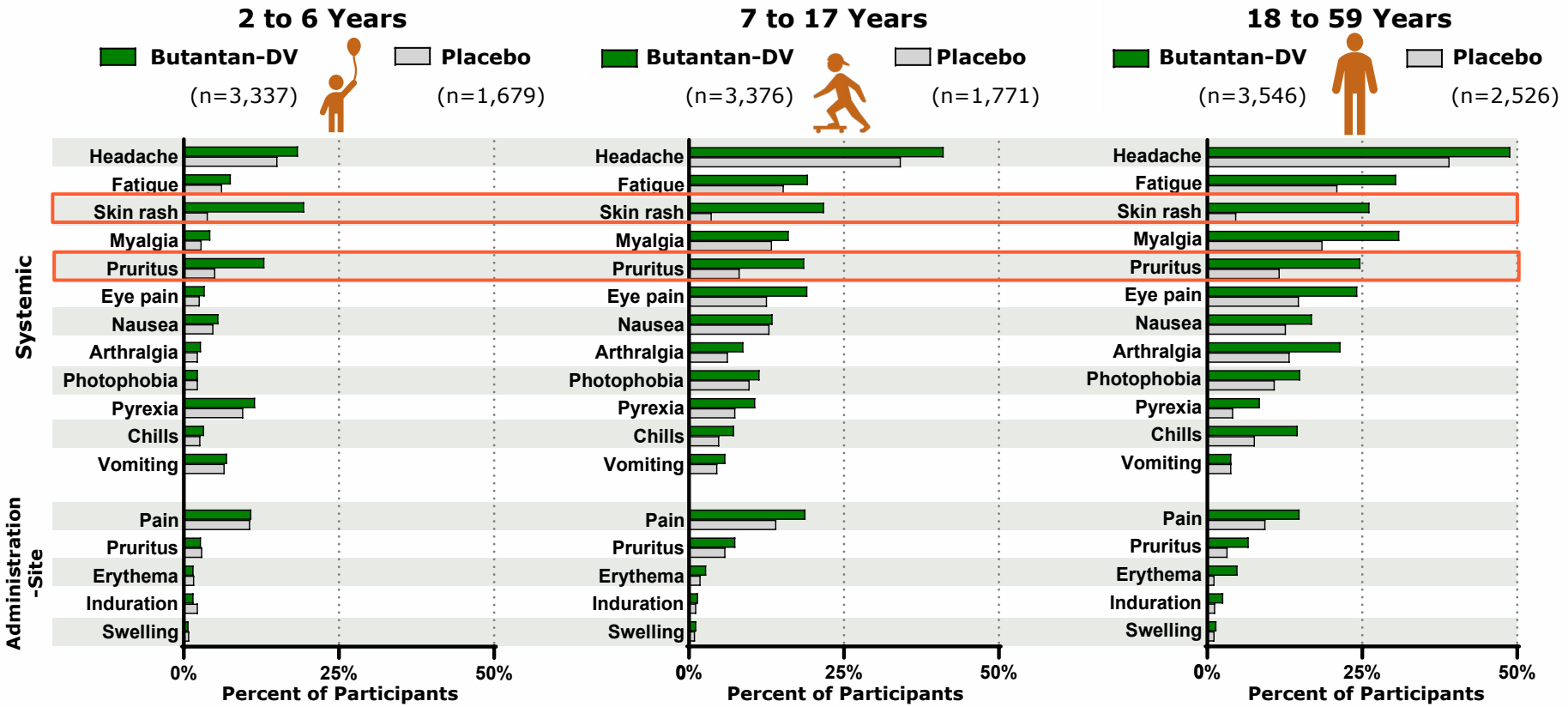
Through the cut-off* there were:

- 67 deaths (37 in the vaccine group, 30 in placebo group), none were deemed related to the study treatment
- 7 serious vaccine-related adverse events total in the vaccine and placebo groups

[a] In this trial, all adverse events that present a reasonable causal relation to the product under investigation will be considered as adverse reactions.
[b] 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).

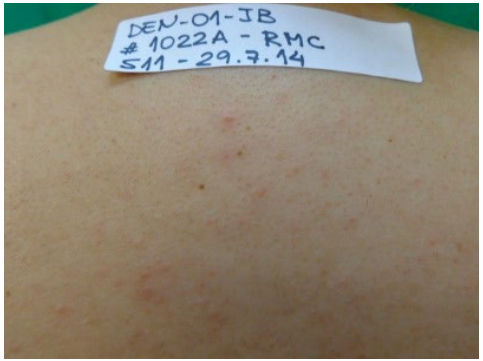
Vaccine-Related AEs Frequency within 21 days postvaccination

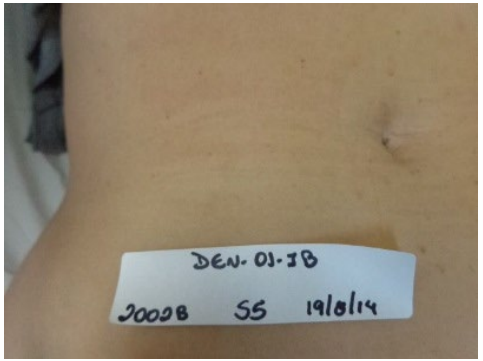
age subgroups

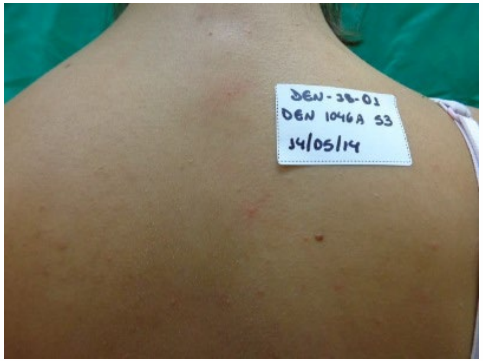


*In this trial, all adverse events that present a reasonable causal relation to the product under investigation will be considered as adverse reactions. All administration-site reactions after administration of the product under investigation were considered as adverse events with sure causal relation 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.

Immunization-induced rash







Kallas *et al. Lancet Infect Dis*, 2020

Controlled human infection

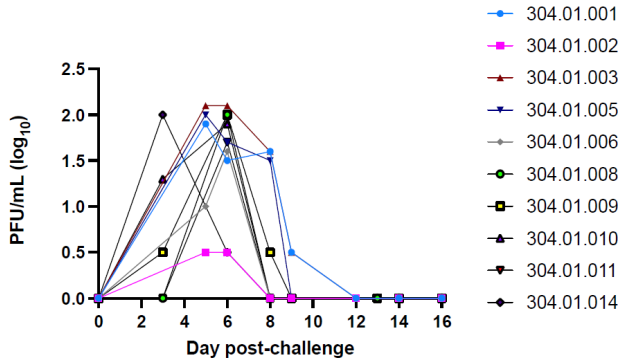
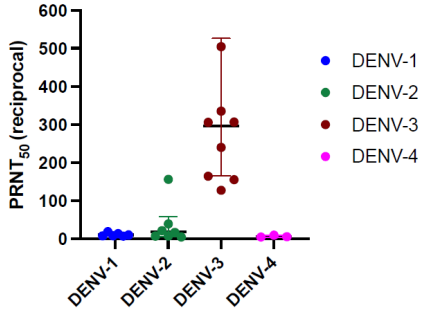


Figure 1B:



The Journal of Clinical Investigation — CLINICAL MEDICINE

TV005 dengue vaccine protects against dengue serotypes 2 and 3 in two controlled human infection studies

Kristen K. Pierce,[1,2] Anna P. Durbin,[3] Mary-Claire R. Walsh,[1,2] Marya Carmolli,[2] Beulah P. Sabundayo,[3] Dorothy M. Dickson,[2] Sean A. Diehl,[2] Stephen S. Whitehead,[4] and Beth D. Kirkpatrick[1,2]

[1]Department of Medicine and [2]Department of Microbiology and Molecular Genetics, The University of Vermont Larner College of Medicine, Vaccine Testing Center, Burlington, Vermont, USA. [3]The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. [4]National Institute of Allergy and Infectious Diseases (NIAID), Laboratory of Viral Diseases, Bethesda, Maryland, USA.

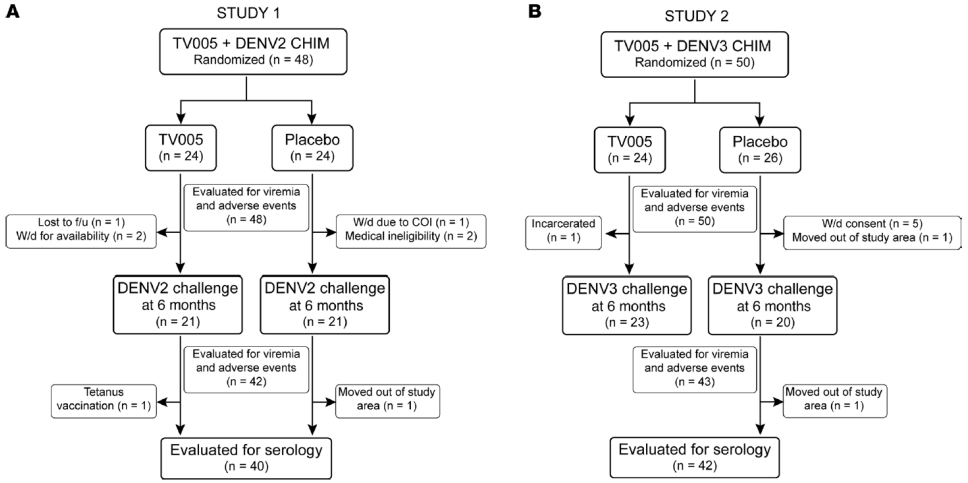


Figure 1. CONSORT diagrams of enrollment, retention, and interventions. (**A**) Study 1 (CIR299) is a placebo-controlled trial of the efficacy of TV005 against rDEN2Δ30 challenge. (**B**) Study 2 (CIR309) is a placebo-controlled trial of the efficacy of TV005 against rDEN3Δ30 challenge. COI, conflict of interest; f/u, follow-up; W/d, withdrew.

rDEN2Δ30 (Tonga/74) and rDEN3Δ30 (Sleman/78)

Pierce et al. *medxRiv,* 2023. Pierce et al. *J Clin Invest,* 2024.

Controlled human infection

Table 1. Demographics of study participants vaccinated with the TV005 tetravalent dengue vaccine or placebo, followed by challenge with DENV2 or DENV3

	Study 1: TV005 vaccination followed by DENV2 challenge		Study 2: TV005 vaccination followed by DENV3 challenge	
	TV005 (*n* = 24)	Placebo (*n* = 24)	TV005 (*n* = 24)	Placebo (*n* = 26)
Age (yr)				
Mean (SD)	30.2 (9.9)	30.5 (7.5)	31.3 (9.5)	32.1 (8.9)
Range	18–48	21–48	20–49	18–49
Sex				
Male	15 (62%)	9 (38%)	16 (67%)	13 (50%)
Female	9 (38%)	15 (62%)	8 (33%)	13 (50%)
Race				
White	10 (42%)	11 (46%)	12 (50%)	16 (62%)
African American	10 (42%)	10 (42%)	10 (42%)	10 (38%)
Asian	2 (8%)	0	0	0
Indian/Alaska Native	0	0	1 (4%)	0
Hawaiian/Pacific Islander	1 (4%)	0	0	0
Multiracial	0	3 (12%)	0	0
Unknown	1 (4%)	0	1 (4%)	0

Table 2. Primary efficacy endpoint and frequency of viremia in vaccine or placebo recipients following DENV2 or DENV3 challenge

	No. with viremia (%)	No. with rash (%)	No. with neutropenia (%)[A]
After DENV2 challenge			
TV005 vaccinees + DENV2 challenge (*n* = 21)	0	0	0
Placebo + DENV2 challenge (*n* = 21)	21 (100%)	21 (100%)	1 (4.8%)
P value[B]	<0.0001	<0.0001	0.50
After DENV3 challenge			
TV005 vaccinees + DENV3 challenge (*n* = 23)	0	0	2 (8.7%)
Placebo + DENV3 challenge (*n* = 20)	17 (85%)	20 (100%)	5 (25%)
P value[B]	<0.0001	<0.0001	0.15

[A]Neutropenia is defined as an ANC of 1,000/mm^3 or less. [B]One-sided Fisher's exact test was used to determine endpoints of higher proportion among placebo recipients versus TV005 vaccinees.

Pierce et al. *J Clin Invest,* 2024.

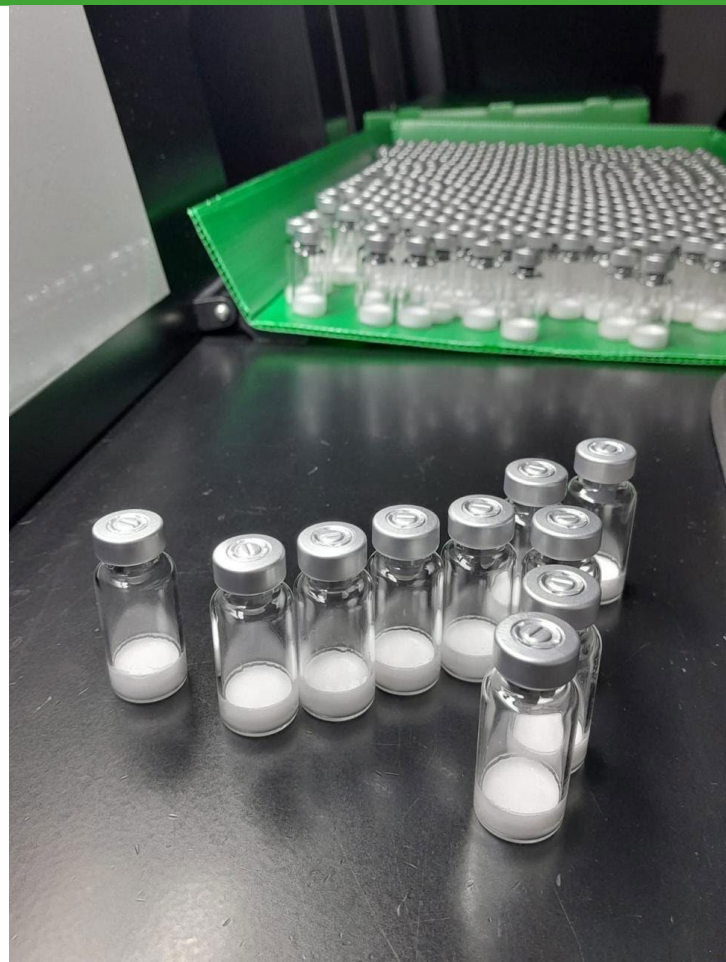
Three vaccines

Sponsor & product	Sanofi Dengvaxia	Takeda Qdenga	Butantan Butantan-DV
Reference	Capeding, 2014	Lopez-Medina, 2020	Kallas, 2024
N (Phase 3)	18,835	19,021	16,162
Doses, interval	3 doses, 6/6 months	2 doses, 3 months	Single dose
Efficacy by serotype (2 years of F-U)	D1: **50%** (29 – 65%) D2: **42%** (14 – 61%) D3: **74%** (62 – 82%) D4: **78%** (60 – 88%)	D1: **69%** (57 – 78%) D2: **91%** (86 – 94%) D3: **51%** (34 – 64%) D4: **50%** (-19 – 79%)	D1: **90%** (79 - 95%) D2: **70%** (51 - 82%) ? ?
Efficacy by age (2 years of F-U)	2-5 a: **34%*** 6-11 a: **60%*** 12-14 a: **74%***	4-5 a: **56%** 6-11 a: **75%** 12-16 a: **77%**	2-6 a: **80%** 7-17 a: **78%** 18-60 a: **90%**

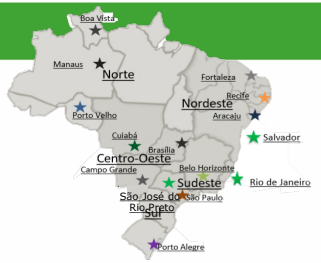
* Sanofi: efficacy only in the first year

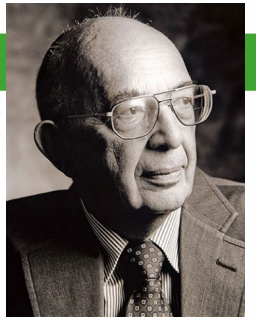
Butantan-DV updates

- Single dose, lyophilized vials
- Production in progress
- ANVISA: rolling submission is underway
- Local Development and Innovation Program project approved by the Brazilian MoH, March 2025
- Planned clinical studies:
  - Population ≥60 y.o.
  - Immunosupressed population
  - Coadministration with chikungunya vaccine



Acknowledgements





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