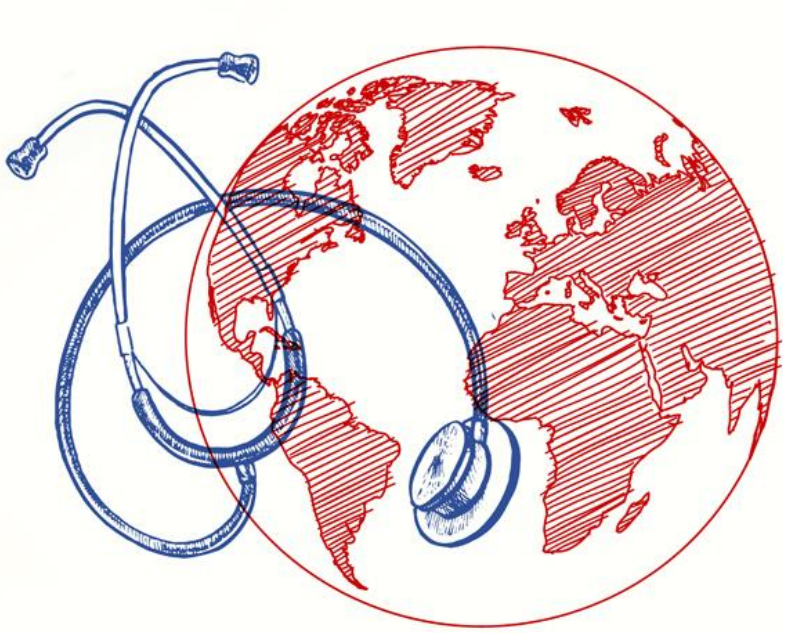
Global Health Cast 58

February 05, 2024



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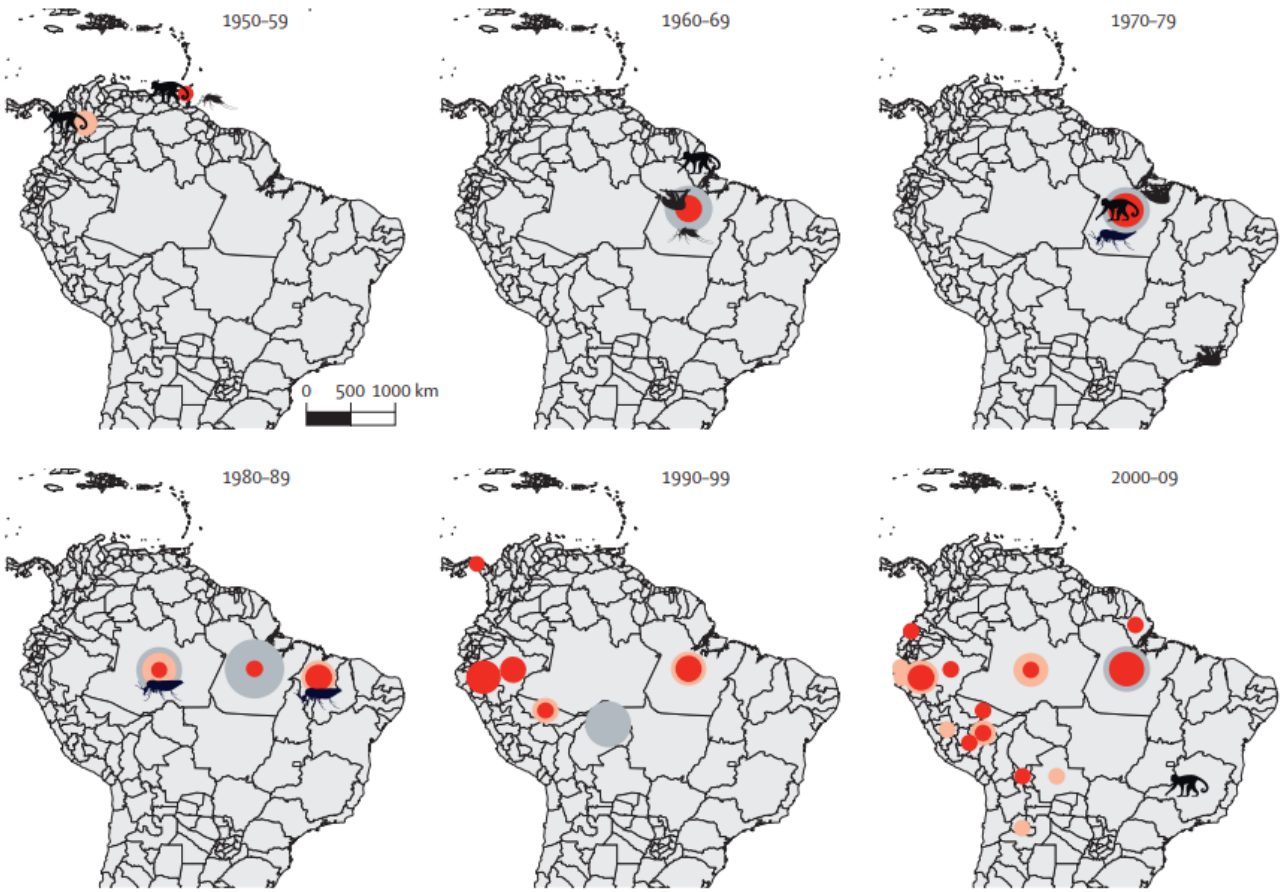
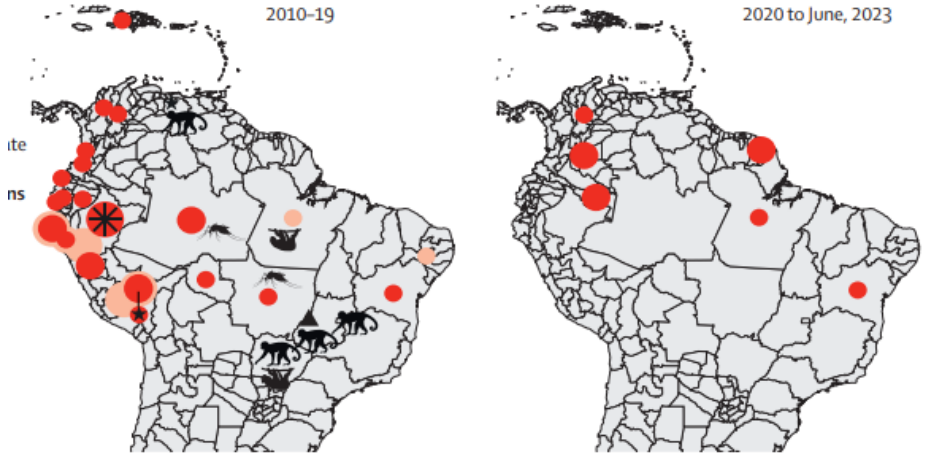
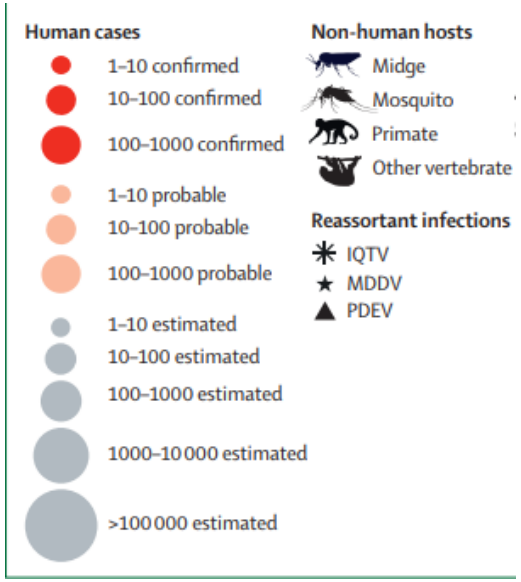
What we talk about today

- Oropouche virus in Latin America
- First documented transmission of Alzheimer's Disease
- FDA accepts first AI algorithm to drug development tool pilot
- Multi-country dengue outbreaks in Africa
- Butantan dengue vaccine phase 3 results out

Oropouche virus detections: humans, vertebrate hosts, midges, mosquitoes







Wesselmann KM, et al, Lancet Infect Dis. 2024 doi: 10.1016/S1473-3099(23)00740-5

Oropouche Virus (OROV) in Latin America

- OROV causes unspecific **febrile symptoms** BUT occasionally can result in **meningoencephalitis**.
- In past 70 years, a **notable increase** in incidence geographical spread of OROV infections has been observed, highlighting a growing public health concern.
- The OROV genome is **tri-segmented**, which allows for reassortment.
- 3 reassortants are known, ***2* (Madre de Dios; Iquitos viruses)** associated with human diseases.
- Human **transmission by bites of midges**, but OROV presence in **various mosquito** species and a **wide range of vertebrate hosts -** potential for widespread emergence.
- However, the virus' transmission cycle is poorly understood.
- Laboratory diagnostics are crucial, but **robust commercial tests are scarcely available**.
- **Pathogenesis and possibility / extent of repeated infection** by different OROV reassortants are unknown.
- **Risk assessments and effective public health strategies to combat Oropouche fever are needed**

Wesselmann KM, et al, Lancet Infect Dis. 2024 doi: 10.1016/S1473-3099(23)00740-5

Article

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Iatrogenic Alzheimer's disease in recipients of cadaveric pituitary-derived growth hormone

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Check for updates

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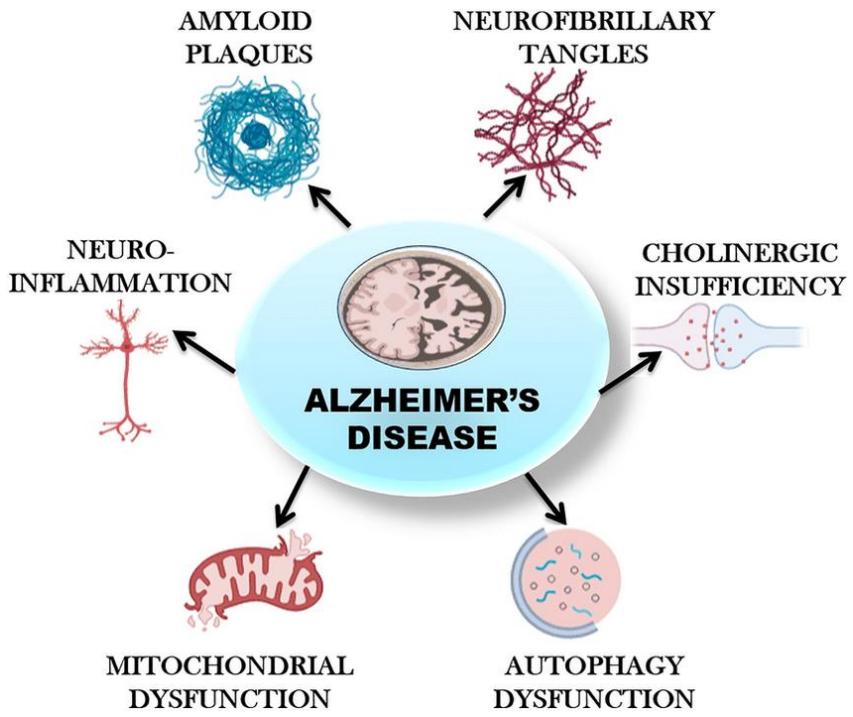
Alzheimer's disease (AD) is characterized pathologically by amyloid-beta (Aβ) deposition in brain parenchyma and blood vessels (as cerebral amyloid angiopathy (CAA)) and by neurofibrillary tangles of hyperphosphorylated tau. Compelling genetic and biomarker evidence supports Aβ as the root cause of AD. We previously reported human transmission of Aβ pathology and CAA in relatively young adults who had died of iatrogenic Creutzfeldt–Jakob disease (iCJD) after childhood treatment with cadaver-derived pituitary growth hormone (c-hGH) contaminated with both CJD prions and Aβ seeds. This raised the possibility that c-hGH recipients who did not die from iCJD may eventually develop AD. Here we describe recipients who developed dementia and biomarker changes within the phenotypic spectrum of AD, suggesting that AD, like CJD, has environmentally acquired (iatrogenic) forms as well as late-onset sporadic and early-onset inherited forms. Although iatrogenic AD may be rare, and there is no suggestion that Aβ can be transmitted between individuals in activities of daily life, its recognition emphasizes the need to review measures to prevent accidental transmissions via other medical and surgical procedures. As propagating Aβ assemblies may exhibit structural diversity akin to conventional prions, it is possible that therapeutic strategies targeting disease-related assemblies may lead to selection of minor components and development of resistance.

"The clinical syndrome developed by these individuals can, therefore, be termed iatrogenic Alzheimer's disease, and Alzheimer's disease should now be recognized as a potentially transmissible disorder."



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FDA accepts first AI algorithm to drug development tool pilot, with Deliberate AI's anxiety and depression assessment

Deliberate AI's technology takes in a range of patient data—including facial expressions, speech behaviors and acoustics, physical movements, pupil changes and vital signs—to build a quantitative assessment of each patient's mental health.

World Health Organization
REGIONAL OFFICE FOR Africa

WHO African Region Health Emergency Situation Report

Multi-country Outbreak of Dengue

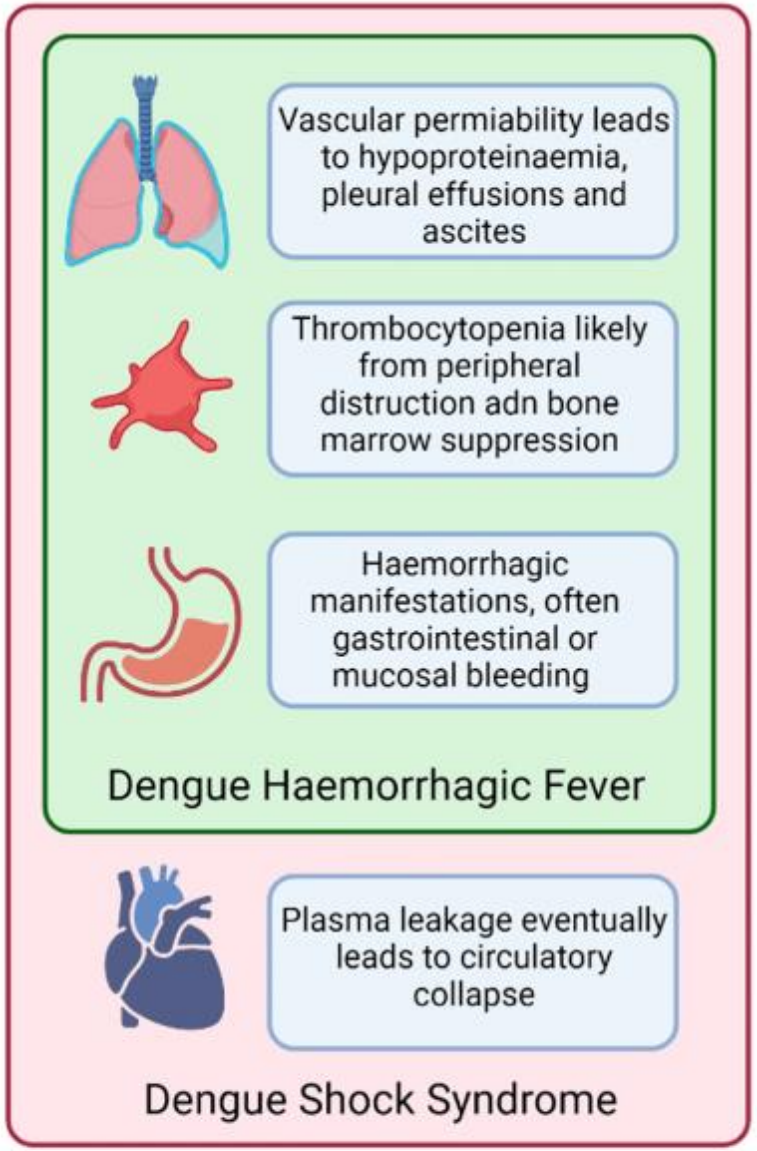
Benin, Burkina Faso, Cabo Verde, Chad, Côte d'Ivoire, Ethiopia, Ghana, Guinea, Mali, Mauritius, Niger, Nigeria, São Tomé and Príncipe, Senegal, and Togo

Consolidated Regional Situation Report # 002 – As of 14 January, 2024

208 289	95 922	782	15
Cumulative suspected cases	Cumulative confirmed cases	Deaths	Countries

HIGHLIGHTS

- **Since the start of 2023, over 5 million cases and 5000 deaths have been reported worldwide from over 80 countries in all six WHO regions**. The global risk level was determined to be high due to the high number of people at risk (40% of the worldwide population), the number and magnitude of outbreaks, climate change consequences, including the ongoing El Niño phenomenon and complex humanitarian crises, the escalation in dengue-related deaths, and the lack of an integrated approach to prevent and control dengue outbreaks.
- **In the WHO African region, as of 14 January 2024, a total of 208 289 suspected cases of dengue, including 95 922 confirmed and probable cases and 782 deaths have been reported from 15 countries** (Benin, Burkina Faso, Cabo Verde, Chad, Côte d'Ivoire, Ethiopia, Ghana, Guinea, Mali, Mauritius, Niger, Nigeria, São Tomé and Príncipe, Senegal, and Togo).
- **Burkina Faso continues to be the country that has been most impacted, accounting for 75% of reported cases and 91% of recorded fatalities**.
- Senegal and Mali have experienced simultaneous outbreaks of dengue, Zika, and chikungunya, highlighting **the issue of under-reporting of cases** due to limited capacity for early detection, and confirmatory diagnostics in most countries and the **need for an integrated arboviral response**.



REMINDER

About 1 in 20 people who get sick with dengue will develop severe dengue.

GLOBAL HEALTH PRESS

Phylogenetic Map of Selected Flaviviruses

Dengue-Definition

Dengue is an

- **acute, systemic flavivirus disease;**
- caused by 4 closely related but antigenically distinct Dengue Viruses (DENV), i.e. **serotypes 1, 2, 3, and 4;**
- transmitted to humans primarily by ***Aedes aegypti*** **mosquitoes** (rarely *Ae. albopticus*)**.**
- Clinically
  - ~**75%** of infections are asymptomatic,
  - **~20%** result in mild unspecific flu-like disease (Dengue fever, DF),
  - **~5%** are severe (dengue hemorrhagic fever, **DHF**), usually second infection (**ADE**) (case fatality rate (**CFR): 2.5% globally**).
- Today, half of the world´s population is at risk for infection; there are **100-400 million cases annually with up to 40,000 deaths**
- **No specific therapy** is available, vaccine prevention is of utmost importance

Licenced DENV vaccines

- Efficacy trials with **three dengue vaccines** have been completed.
- **Dengvaxia (Sanofi):** Yellow fever virus–derived vaccine integrated chimerically with the structural regions of the four DENV serotypes. (**three dose-schedule**)
  - **Vaccinated seronegative participants: unexpected breakthrough DENV infections**, including severe disease, in some cases leading to hospitalization for vascular permeability.
  - **Vaccinated seropositive participants were pr**otected against breakthrough DENV illnesses.

- **TAK-003 (Qdenga (Takeda); 2 doses),** contains live, attenuated DENV-2 plus DENV-2 chimeras of the structural regions of DENV-1, DENV-3, DENV-4.
  - **Vaccinated seronegative participants and seropositive participants were highly protected against DENV-2 disease**.
  - Limitation: **absence of DENV-4** infections.
  - **Moderate protection against DENV-1 disease** in both, seronegative / seropositive participants
  - **Possibly: higher hospitalization rate for DENV-3 disease** among vaccinated seronegatives

Halstead BS, N Engl J Med 2024; 390:464-465 DOI: 10.1056/NEJMe2314240

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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

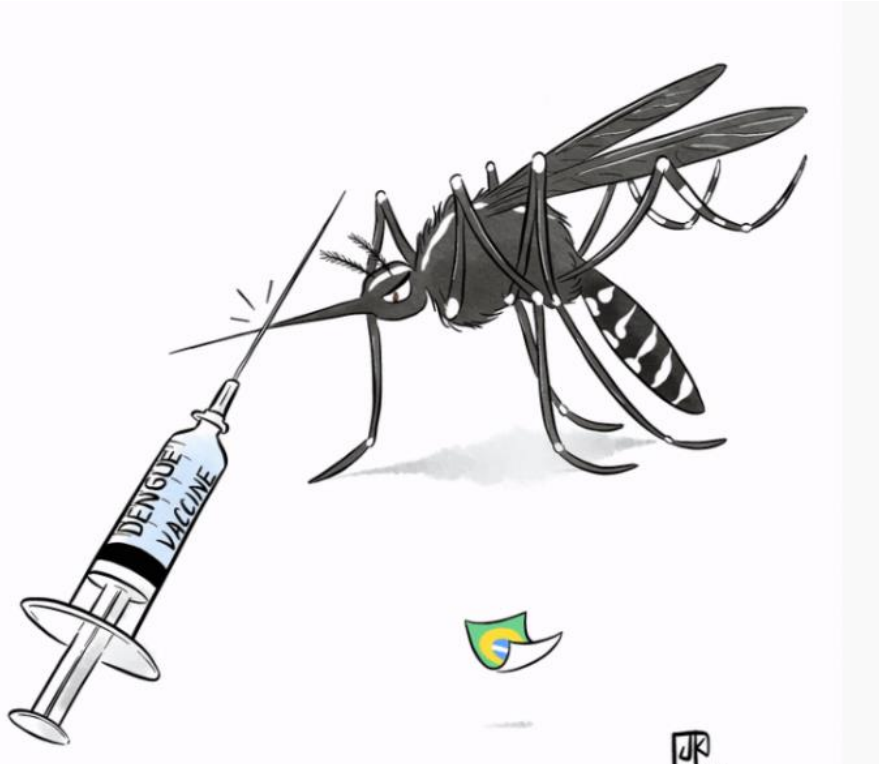
ABSTRACT

BACKGROUND

Butantan–Dengue Vaccine (Butantan-DV) is an investigational, single-dose, live, attenuated, tetravalent vaccine against dengue disease, but data on its overall efficacy are needed.

METHODS

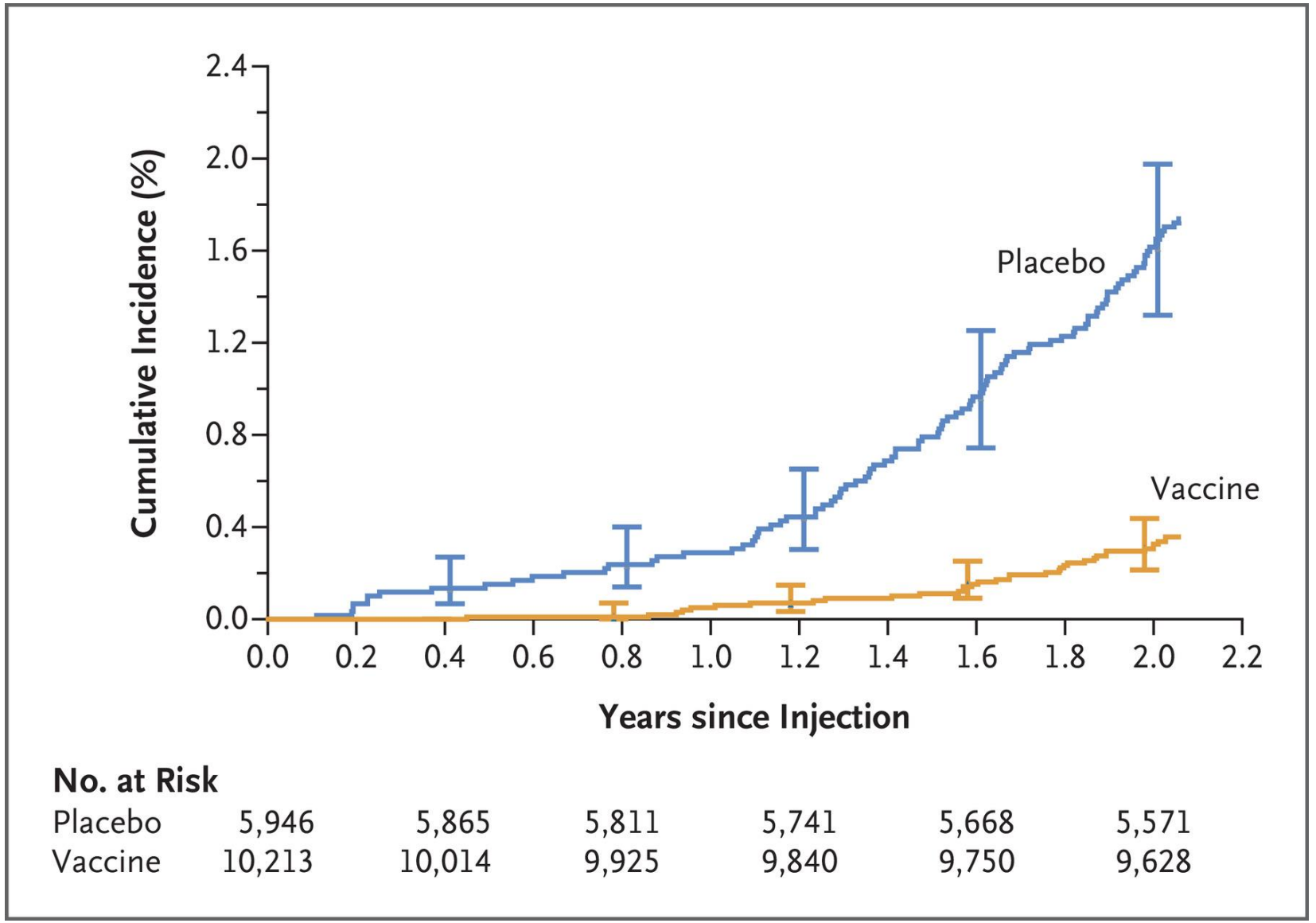
In an ongoing phase 3, double-blind trial in Brazil, we randomly assigned participants to receive Butantan-DV or placebo, with stratification according to age (2 to 6 years, 7 to 17 years, and 18 to 59 years); 5 years of follow-up is planned. The objectives of the trial were to evaluate overall vaccine efficacy against symptomatic, virologically confirmed dengue of any serotype occurring more than 28 days after vaccination (the primary efficacy end point), regardless of serostatus at baseline, and to describe safety up to day 21 (the primary safety end point). Here, vaccine efficacy was assessed on the basis of 2 years of follow-up for each participant, and safety as solicited vaccine-related adverse events reported up to day 21 after injection. Key secondary objectives were to assess vaccine efficacy among participants according to dengue serostatus at baseline and according to the dengue viral serotype; efficacy according to age was also assessed.



Overall efficacy: **79.6%** in disease prevention
Efficacy against dengue in seropositive: **89.2%**
Efficacy against dengue in seronegative: **73.6%**

The study also evaluated efficacy against each DENV serotype
Against DENV-1: **89.5%**
Against DENV-2: **69.6%**
DENV-3 and DENV-4 not circulating during the evaluation period

Efficacy of Butantan DENV Vaccine, Brazil



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

Kallas et al., N Engl J Med 2024; 390:397-408 DOI: 10.1056/NEJMoa2301790

Butantan DENV vaccine efficacy

Confirmed Dengue	Cumulative Vaccine Efficacy (95% CI) %	Vaccine Cases no.(total no.)	Vaccine Person-Yrs at Risk	Vaccine Estimated Incidence (95% CI)	Placebo Cases no. (total no.)	Placebo Person-Yrs at Risk	Placebo Estimated Incidence (95% CI)
Any DENV serotype							
Seropositives	**89.2** (77.6 to 95.6)	8/4,994	10,063	0.08 (0.03 to 0.16)	45/3,023	6,092	0.74 (0.54 to 0.99)
Seronegatives	**73.6** (57.6 to 83.7)	26/4,826	9,573	0.27 (0.18 to 0.40)	55/2,690	5,350	1.03 (0.77 to 1.34)
DENV-1							
Seropositives	**96.8** (81.0 to 99.8)	1/4,994	10,065	0.01 (0.00 to 0.06)	19/3,023	6,101	0.31 (0.19 to 0.49)
Seronegatives	**85.6** (69.1 to 94.0)	8/4,826	9,582	0.08 (0.04 to 0.17)	31/2,690	5,365	0.58 (0.39 to 0.82)
DENV-2							
Seropositives	**83.7** (63.1 to 93.5)	7/4,994	10,063	0.07 (0.03 to 0.14)	26/3,023	6,107	0.43 (0.28 to 0.62)
Seronegatives	**57.9** (20.8 to 78.1	18/4,826	9,579	0.19 (0.11 to 0.30)	24/2,690	5,376	0.45 (0.29 to 0.66)

Butantan DENV Vaccine Study in Brazil

- **Absence of cases of DENV-3 and DENV-4**: due introduction of Zika virus (ZIKV) to Brazil in 2015.
  - The number of ZIKV infections exploded to epidemic proportions and was followed in both 2017 and 2018 by an **80% reduction in total dengue cases and** deaths.
  - Among 270 study participants with DENV-disease symptoms, none were severely ill or hospitalized.
  - This is in stark contrast to the frequency of severe dengue or hospitalization of vaccinees and controls in clinical trials of Dengvaxia and TAK-003
  - ZIKV, a flavivirus, behaves antigenically like a fifth DENV. **A person with monotypic DENV immunity who has been infected with ZIKV converts to the immune status of a person who has been infected with two DENV serotypes.**
  - **WHO (SAGE):** Seropositves ≥9 years: to receive three doses Dengvaxia.
    Considering: Persons 6 - 16 years, highly endemic countries: two doses of Qdenga.
    Given PH implications (DENV ante portas!), Butantan trial to be expanded.

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- First documented transmission of Alzheimer's Disease
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- Butantan dengue vaccine phase 3 results out