Training workshop on emerging infectious diseases – 2026 - Istanbul

Dengue State-of-the-Art Management: Current Strategies and Future Directions

Francesca F. Norman

25th March 2026

National Referral Centre for Tropical Diseases. Infectious Diseases Department. Ramón y Cajal University Hospital, IRYCIS, CIBERINFEC. Madrid.

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- Disclosures:
  - Speaker fees/served as a consultant for Takeda, Bavarian Nordic, MSD

Agenda

01	Introduction
02	Dengue therapeutics
03	Prevention
04	Research Gaps and Future directions
05	Conclusions

Introduction

Dengue in figures: a global emergency

Most common arthropod-borne infection worldwide

Estimated **110 million** symptomatic infections globally/year

Simultaneous **rise** in burden of **non-comunicable diseases** →increased risk of severe and complicated dengue

Economic burden (healthcare costs, productivity loss, vector control expense) projected to reach hundreds of **billions of dollars** by 2050

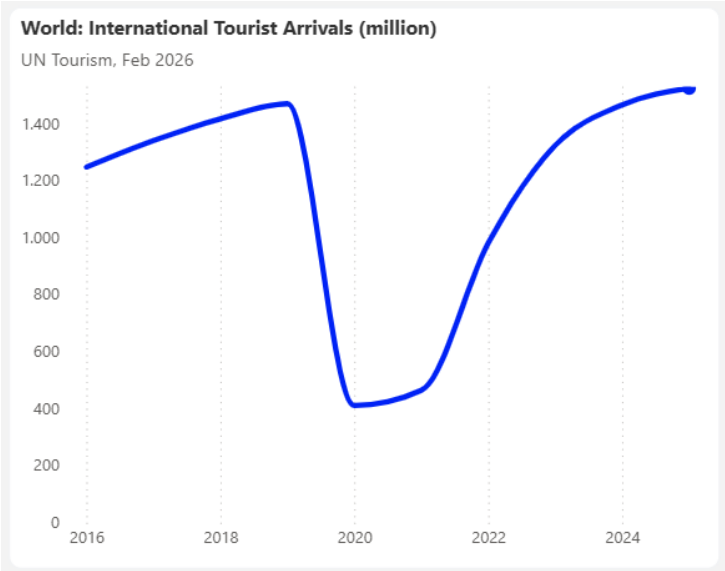
June 2024: WHO identified dengue as **priority pathogen** for all six WHO regions

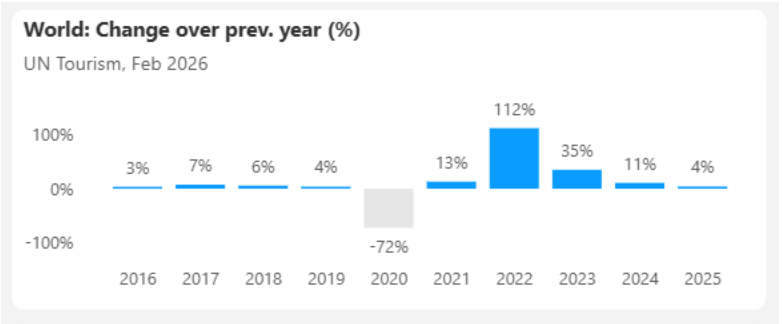
"EXTRAS":

- Climate change
- Geographical expansion mosquito vector
- Urbanisation
- Population movements

McBride et al, BMJ Public Health 2026; Asish et al, Int J Infect Dis 2023; Nkaase et al, Commun Earth Environ 2024; Chen et al, SSRN 2024; WHO PATHOGENS prioritization a scientific framework for epidemic and pandemic research preparedness. 2024. Available: https://www.who.int/publications/m/item/ pathogens-prioritization-a-scientific-framework-for-epidemic-andpandemic-research-preparedness (accessed March 2026)

Increased global mobility: international travel and migration

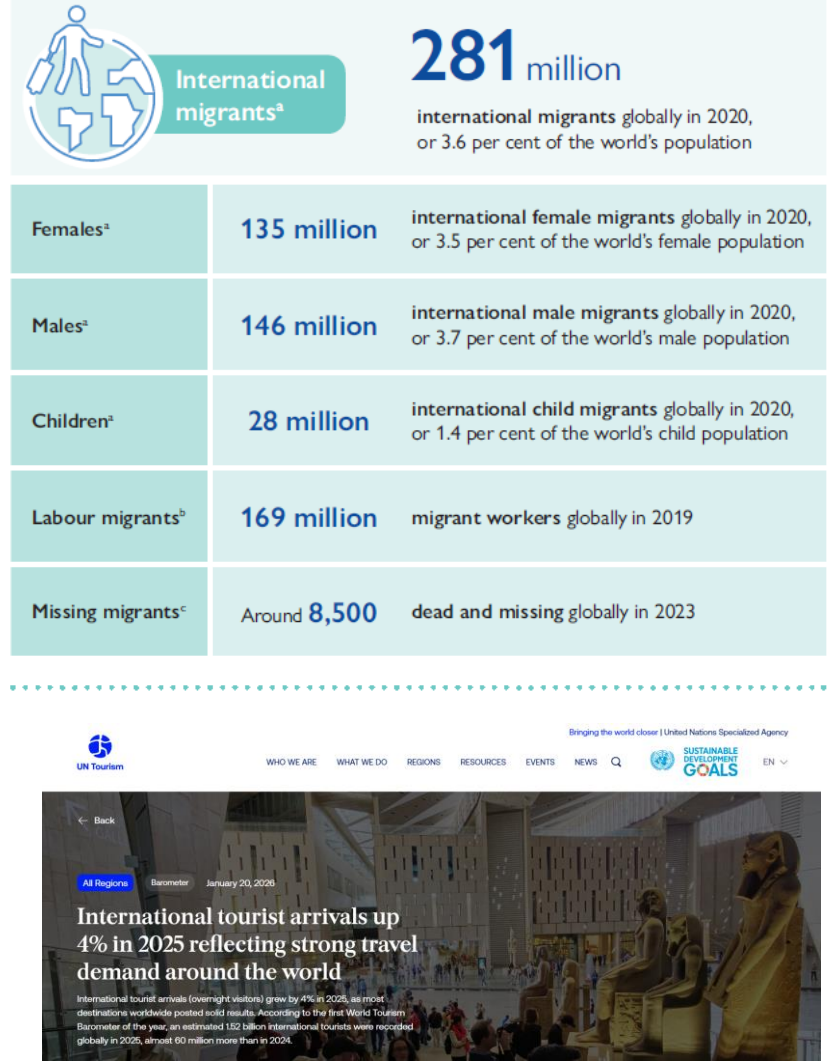




Africa sees strongest results in 2025; Asia and the Pacific rebounds

The World Tourism Barometer by UN Tourism provides comprehensive data for the sector by region, sub-region and destination. Key takeaways from this edition show:

- **Europe**, the world's largest destination region, recorded 793 million international tourists in 2025, a 4% increase from 2024 and 6% more than in 2019. Western Europe (+5%) and Southern Mediterranean Europe (+3%) saw robust performance. Central and Eastern Europe rebounded strongly (+6%) though arrivals remained 9% below 2019 levels.
- The **Americas** (218 million) recorded 1% growth last year, with mixed results across subregions. After a strong first half of 2025, the region saw small declines in Q3 and Q4, partly due to weak results in the United States. South America (+7%) and Central America (+5%) led results by subregion. Some destinations in the Caribbean (+0%) were affected by Hurricane Melissa in the last quarter of the year.
- **Africa** (81 million) saw an 8% increase in arrivals in 2025, with particularly strong results in North Africa (+11%).
- The **Middle East** recorded 3% growth in 2025, equivalent to 39% above pre-pandemic levels, the strongest results relative to 2019. The region virtually reached the mark of 100 million international visitors in 2025.
- Arrivals in **Asia and the Pacific** (331 million) grew 6% last year but are still 9% below 2019 levels as the region continued to rebound. North-East Asia led performance with 13% growth over 2024, while South Asia recovered pre-pandemic levels.



Key migration data at a glance

(latest available)

International migrants[a]

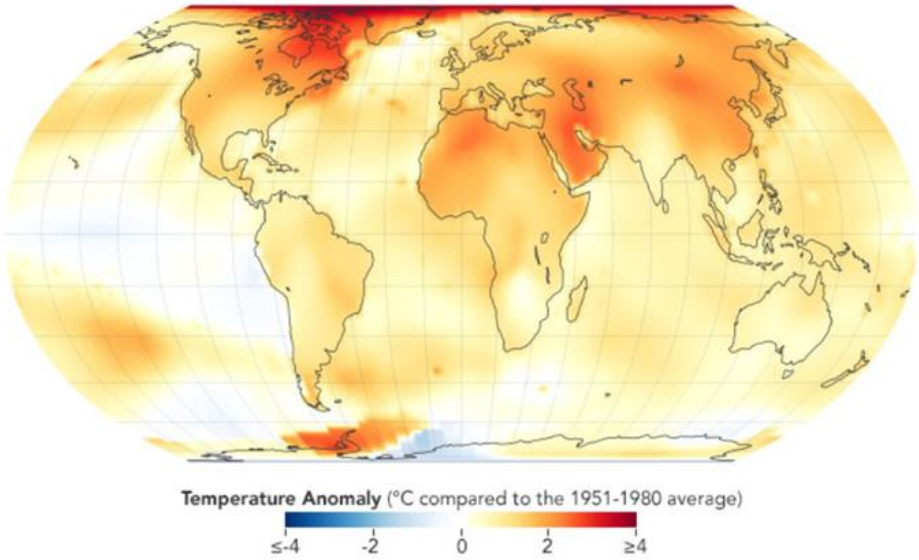
281 million

international migrants globally in 2020, or 3.6 per cent of the world's population

Females[a]	135 million	**international female migrants** globally in 2020, or 3.5 per cent of the world's female population
Males[a]	146 million	**international male migrants** globally in 2020, or 3.7 per cent of the world's male population
Children[a]	28 million	**international child migrants** globally in 2020, or 1.4 per cent of the world's child population
Labour migrants[b]	169 million	**migrant workers** globally in 2019
Missing migrants[c]	Around 8,500	**dead and missing** globally in 2023

Source: UNWTO, access February 2026; McAuliffe, M. and L.A. Oucho (eds.), 2024. World Migration Report 2024. International Organization for Migration (IOM), Geneva

Climate Change



Climate change intensifies interactions between hosts and pathogens→ emergence human diseases

Alterations in precipitation patterns + rising global temperatures

Rainfall or flooding→ stagnant water collections, expanding aquatic habitats for mosquito life cycles

During droughts → breeding sites in artificial or man-made containers

Modest increases in temperature in temperate regions (mainland Europe, US) → vector survival and duration of transmission season

Mora et al, Nat Clim Chang, 2022; Zapletal et al, PLoS One, 2018; Kamiya et al, Epidemics, 2020; Heat map showing temperature anomaly for 2021, vs to 1951-1980 average

Dengue Therapeutics

What do we have now?

Current management

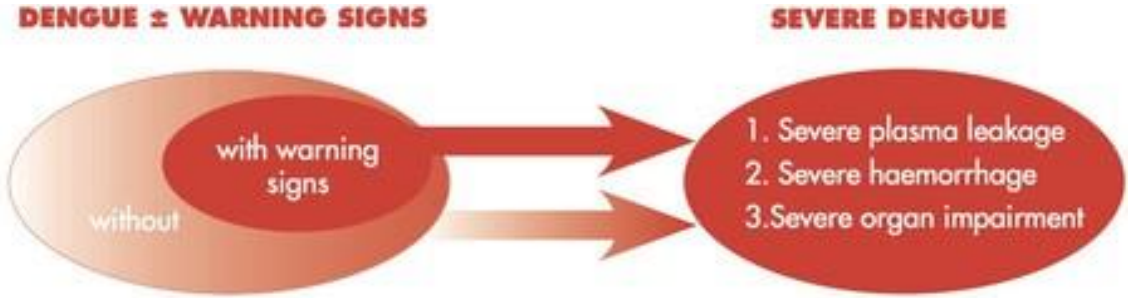
- Relies on fluid resuscitation and pharmacologic interventions.
  - Hydration and monitoring volume status
  - Paracetamol (acetaminophen) and metamizole (dipyrone) if available

- WHO guidelines recommend **against** use of corticosteroids, NSAIDs, Igs, prophylactic platelet transfusions

WHO guidelines for clinical management of arboviral diseases: dengue, chikungunya, Zika and yellow fever. Available at https://www.who.int/publications/i/item/9789240111110. (accessed March 2026); WHO. Target product profiles for treatment for dengue fever. Available at https://www.who.int/news-room/articles-detail/call-for-public-consultation-targetproduct-profiles-for-treatments-for-dengue-fever (accessed March 2026) National Institute of Allergy and Infectious Diseases. Target Product Profile (TPP) for APP Antiviral Therapeutics (accessed March 2026) Available from: https://www.niaid.nih.gov/research/support-antiviral-TPPs.

Patient Triage

Severe disease: those patients who clinicians assess as requiring hospitalization based on a clinical evaluation which includes assessment for the presence of warning signs and existing complications.



CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

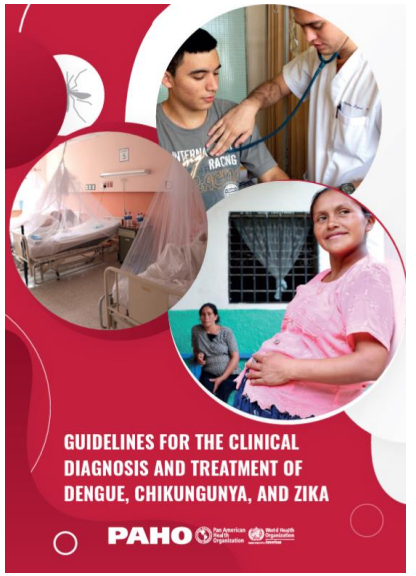
- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

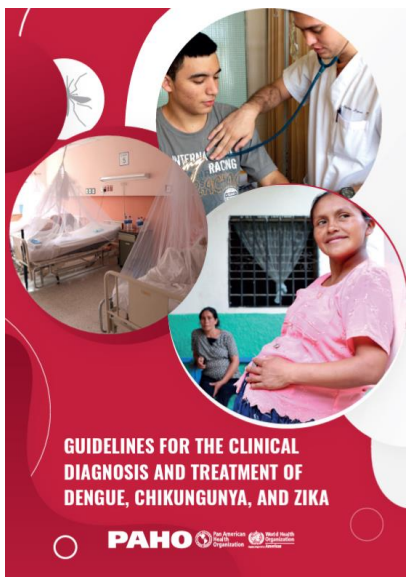
- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs



Non-severe disease: those who do not have features of severe disease and can be managed on an out-patient basis.

Based on the literature review from the 2022 Pan American Health Organization guidelines, the following criteria were identified that might encourage clinicians to hospitalize patients with dengue.

- Dengue with warning signs:
    - abdominal pain: progressive until it is continuous or sustained and intense, and at the end of the febrile stage
    - sensory disorder: irritability, drowsiness, and lethargy
    - mucosal bleeding: bleeding gums, epistaxis, vaginal bleeding not associated with menstruation or more menstrual bleeding than usual and haematuria
    - hepatomegaly: more than 2 cm below the costal margin and abrupt onset
    - vomiting: persistent (three or more episodes in one hour or four episodes in six hours)
    - progressive increase in haematocrit: on at least two consecutive measurements during patient monitoring.
- dengue with criteria of severe disease, according to the WHO 2009 definition
- oral intolerance
- difficulty breathing
- narrowing pulse pressure
- arterial hypotension
- acute renal failure
- prolonged capillary refill time
- pregnancy
- coagulopathy



In addition, clinicians in some settings may elect to admit to hospital those patients with other risk factors, such patients at the extremes of age (elderly, neonates) and those with underlying medical conditions at high risk for adverse disease outcomes.

Dengue risk models

PLOS Digital Health

RESEARCH ARTICLE

Early individualized risk prediction using clinical data for children during the febrile phase of dengue in outpatient settings in Vietnam and Thailand

Sorawat Sangkaew[1,2‡], Bethan Cracknell Daniels[3‡], Damien K. Ming[4], Bernard Hernandez[5], Pau Herrero[5,6], Piyarat Suntarattiwong[7], Siripen Kalayanarooj[7], Anon Srikiatkhachorn[8,9], Alan L. Rothman[9], Darunee Buddhari[10], Nguyen Lam Vuong[11,12], Phung Khanh Lam[11,12], Minh Tuan Nguyen[13], Bridget Wills[11,14], Cameron Simmons[15], Christl A. Donnelly[3,16], Sophie Yacoub[11,14‡], Alison Holmes[4,6‡], Ilaria Dorigatti[3‡*]

PLOS Digital Health | https://doi.org/10.1371/journal.pdig.0001171 February 9, 2026

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Demographic characteristics, clinical symptoms, biochemical markers and probability of occurrence of severe dengue: A multicenter hospital-based study in Bangladesh

Jingli Yang[1,2], Abdullah Al Mosabbir[3], Enayetur Raheem[3], Wenbiao Hu[1*], Mohammad Sorowar Hossain[3,4*]

Journal of Medical Virology

WILEY

JOURNAL OF MEDICAL VIROLOGY

RESEARCH ARTICLE OPEN ACCESS

Risk Stratification of Dengue Cases Requiring Hospitalization

Do Duc Anh[1,2] | Mario Recker[1,3] | Nguyen Trong The[2,4] | Sanjeev Krishna[1,5] | Peter G. Kremsner[1,6] | Le Huu Song[2,4] | Thirumalaisamy P. Velavan[1,2,7]

Abdul Rahman *et al. BMC Public Health* (2024) 24:3055
https://doi.org/10.1186/s12889-024-20545-2

BMC Public Health

RESEARCH Open Access

E-dengue System Insights: Exploring the Factors Influencing Dengue-related Deaths in an Urbanized State in a Low-Middle Income Country (LMIC)

Farah Khalida Abdul Rahman[1*], Sharifa Ezat binti Wan Puteh[1] and Mohamad Azfar bin Zainuddin[2]

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Development of a machine learning model for early prediction of plasma leakage in suspected dengue patients

Ramtin Zargari Marandi[1©*], Preston Leung[1©*], Chathurani Sigera[2©], Daniel Dawson Murray[1], Praveen Weeratunga[2], Deepika Fernando[2], Chaturaka Rodrigo[3], Senaka Rajapakse[2‡], Cameron Ross MacPherson[1‡]

What do we want?

WHO Target Product Profile (TPP) development

- WHO product profiles to accelerate development of **neglected health products** for greatest and most urgent unmet public health needs
- Developed as product pipeline matures and before phase 3 trials finalized
- Strategic reference document for product developers, regulatory agencies, procurement bodies, and funders to facilitate alignment between public health and R&D priorities
- TPPs provide guidance on minimally acceptable (essential) and preferred (optimal) criteria for product to be implemented and accessible

WHO guidelines for clinical management of arboviral diseases: dengue, chikungunya, Zika and yellow fever. Available at https://www.who.int/publications/i/item/9789240111110. (accessed March 2026); WHO. Target product profiles for treatment for dengue fever. Available at https://www.who.int/news-room/articles-detail/call-for-public-consultation-targetproduct-profiles-for-treatments-for-dengue-fever (accessed March 2026); National Institute of Allergy and Infectious Diseases. Target Product Profile (TPP) for APP Antiviral Therapeutics (accessed March 2026) Available from: https://www.niaid.nih.gov/research/support-antiviral-TPPs.

Considerations and Rationale for dengue TPP

- **Geographical distribution**:
  - wide and expanding!
  - overlap other mosquito-borne viruses (ZIKV, YFV, CHIKV) and mosquito-borne tropical diseases (malaria)
  - almost half of the world's population live in risk areas
  - leading cause of illness in the endemic areas.
  - common in many popular tourist destinations
- **Clinical presentation**:
  - acute febrile illness to hemorrhagic fever (mild symptoms can be confused with other illnesses causing fever +/- rash)
  - quick progression from febrile phase (peak viremia ~ day 1) to critical phase (within 3-6 days)
  - warning signs of severe disease appear with defervescence as viremia decreases
  - prospective antivirals most effective administered during febrile phase and emphasis should be on PrEP.
  - risk of severe disease increases with secondary DENV infection and decreases with subsequent infections.
- **Diagnosis:**
  - preferred NAAT (PCR) limited by viremia
  - serological tests exhibit cross-reactivity (other flaviviruses, most notably ZIKV)
  - testing widely available in at-risk areas, but may take several days, limiting treatment window.

Adapted from: National Institute of Allergy and Infectious Diseases. Target Product Profile (TPP) for APP Antiviral Therapeutics (accessed March 2026) Available from: https://www.niaid.nih.gov/research/support-antiviral-TPPs.

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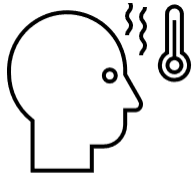

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What do we want?

- WHO (TPP) proposed treatment:
- **non-severe dengue:** “a dispersible tablet with excellent bioavailability given in a short course of ≤7 days or single-dose injectable with high safety requiring no routine monitoring and pan-serotype efficacy in reducing symptom severity and duration, and ideally also reducing progression to severe dengue”
- **severe dengue:** “an intravenous drug which reduces development of and duration of organ failure requiring invasive organ support with a positive risk-benefit ratio… reproductive toxicity studies for any dengue drug…conducted ahead of phase 3 trials to enable inclusion of pregnant and lactating women… in pivotal studies”
- research efforts should go hand-in-hand with development of accessible rapid diagnostic tests (to facilitate test-and-treat approach)

WHO guidelines for clinical management of arboviral diseases: dengue, chikungunya, Zika and yellow fever. Available at https://www.who.int/publications/i/item/9789240111110. (accessed March 2026); WHO. Target product profiles for treatment for dengue fever. Available at https://www.who.int/news-room/articles-detail/call-for-public-consultation-targetproduct-profiles-for-treatments-for-dengue-fever (accessed March 2026); National Institute of Allergy and Infectious Diseases. Target Product Profile (TPP) for APP Antiviral Therapeutics (accessed March 2026) Available from: https://www.niaid.nih.gov/research/support-antiviral-TPPs.

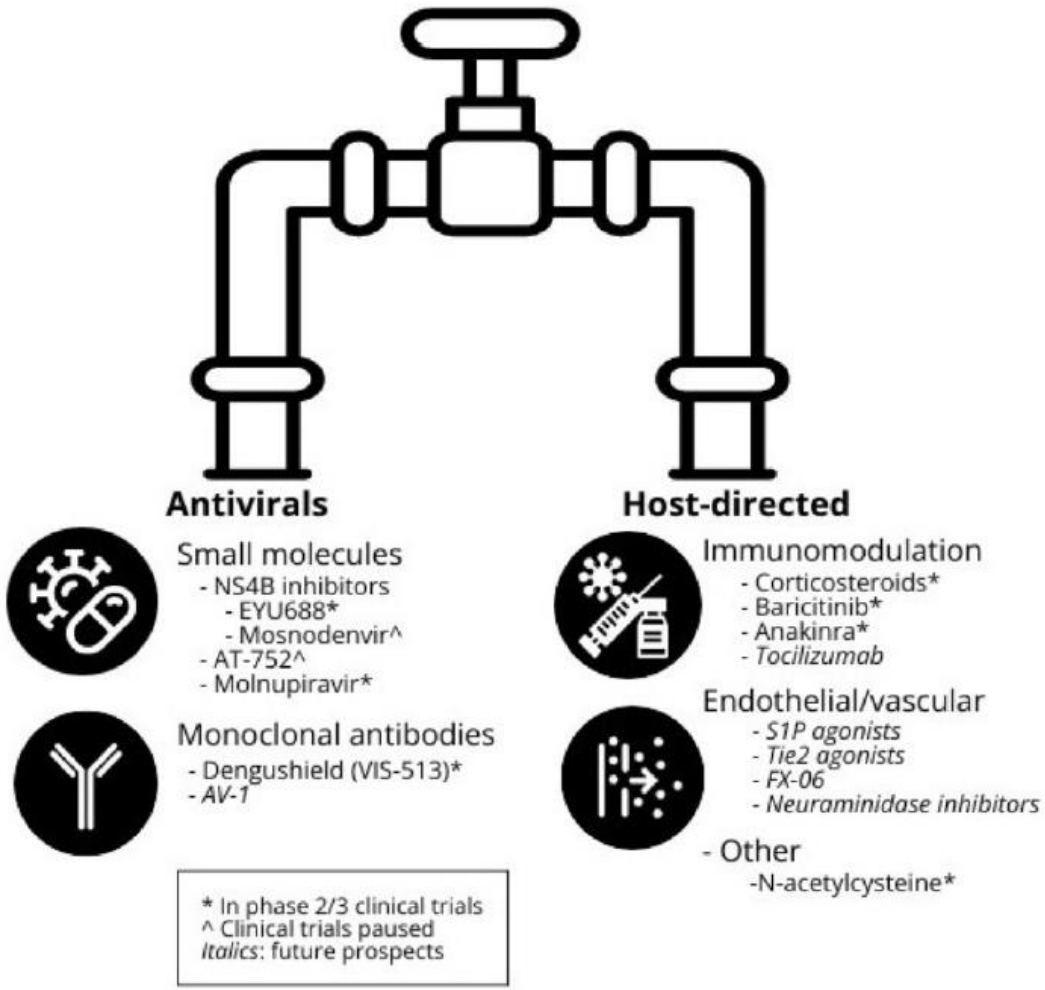

Figure 1 The dengue therapeutics pipeline—candidates in phase 2/3 clinical trials and future prospects.

Review

BMJ Public Health

Dengue therapeutics consortium 2025: a global collaboration in action

Angela McBride [1] Ho Quang Chanh,[2] Huynh Trung Trieu,[3] Huyen Bang Tran,[2] Kathryn B Anderson,[4] Rosemary A Aogo,[5] Panisadee Avirutnan,[6]

BMJ Group

McBride A, *et al. BMJ Public Health* 2026;**4**:e004043. doi:10.1136/bmjph-2025-004043

> 300 trials listed on clinicaltrials.gov:
36 non-vaccine products

Two approaches:
1) inhibition DENV replication using direct-acting antivirals or inhibitors of host factors essential for viral replication; mAbs
2) inhibition of host responses to infection that contribute to plasma leakage

https://clinicaltrials.gov/search?cond=dengue&viewType=Table (accessed March 2026); McBride etal, BMJ Public Health, 2026

New Microbes and New Infections 66 (2025) 101614

Contents lists available at ScienceDirect

New Microbes and New Infections

journal homepage: www.journals.elsevier.com/new-microbes-and-new-infections

Systematic Review

Novel and repurposed antiviral molecules for arbovirus infections with epidemic Potential: A systematic review

Jacopo Logiudice [a,b], Giorgio Tiecco [a,b], Alessandro Pavesi [a,b], Francesca Bertoni [a,b], Roberta Gerami [a,b], Isabella Zanella [c,d], Anna Artese [e], SPARROW group [1], Eugenia Quiros-Roldan [a,b,*]

- Candidate molecules with potential effect against dengue
- No significant effect for most candidate anti-dengue antivirals
- Potential anti-dengue molecules, tested in vitro or combination in vitro/in vivo (mainly with AG129 mouse models)
- Tested drugs mostly experimental, some repurposed antivirals, antibiotics, or chemotherapies
  - In vitro studies tested ribavirin (+/- in combination), mycophenolic acid, bortezomib, micafungin, montelukast, atorvastatin and ezetimibe, and doxorubicin derivatives
  - In vivo results supported antiviral effects of ezetimibe and atorvastatin, combination of CM10-18 and ribavirin, favipiravir, sofosbuvir, montelukast, bortezomib, and micafungin.
- Further research needed…

Logiudice J, et al, New Microbes New Infect. 2025

Table 1
Number and typology of articles about dengue virus (DENV), with cell culture or animal models utilized. Molecules tested were collected by typology, repurposed or experimental.

Articles, n (%) [a]	99 (100)
In vitro, n (%)	60 (60.6)
In vivo, n (%)	1 (1)
In vitro and in silico, n (%)	11 (11.1)
In silico, n (%)	4 (4)
In vitro and *in vivo*, n (%)	15 (15.1)
Cell cultures, n (%)	95 (100)
Vero cells, n (%)	21 (22.1)
Huh7, n (%)	21 (22.1)
BHK-21, n (%)	10 (10.5)
Combination of more than 1 cell culture, n (%)	34 (35.7)
Others, n (%)	9 (9.4)
Animal models, n (%)	16 (100)
Mice	14 (100)
AG129, n (%)	12 (75)
C57BL/6J, n (%)	1 (6.3)
BALB, n (%)	1 (6.3)
ICR, n (%)	2 (12.5)
Tissue, n (%)	**16 (100)**
Blood, n (%)	5 (31.3)
Blood and other tissues, n (%)	5 (31.3)
Brain, n (%)	2 (12.5)
Spleen, n (%)	1 (6.3)
Others, n (%)	3 (18.8)
Molecules tested, n (%)	120 (100)
Viral replication inhibitors, n (%)	50 (41.6)
Viral entry inhibitors, n (%)	25 (20.8)
Viral protease inhibitors, n (%)	14 (11.6)
Viral capside inhibitors, n (%)	6 (4.9)
Immunomodulant, n (%)	15 (12.5)
Others, n (%)	7 (5.8)
Unknown, n (%)	3 (2.5)
Repurposed, n (%)	27 (22.4)
Experimental, n (%)	93 (77.6)
Known antivirals, n (%)	5 (18.5)
Known antibiotics, n (%)	4 (14.8)
Known agents used in tropical medicine, n (%)	1 (3.7)
Chemotherapy or antitumoral, n (%)	4 (14.8)
Others, n (%)	13 (48.1)
Serotype, n (%)	
DENV2, n (%)	62 (62.6)
Combination of DENV2 AND another serotype, n (%)	22 (22.2)
Others, n (%)	15 (15.2)

[a] a single study can test more than one model.

Article

Blocking NS3–NS4B interaction inhibits dengue virus in non-human primates

- JNJ-1802—a highly potent DENV inhibitor that blocks the NS3–NS4B interaction within the viral replication complex
- small-molecule inhibitor JNJ-1802 is highly effective against viral infection with DENV-1 or DENV-2 in non-human primates

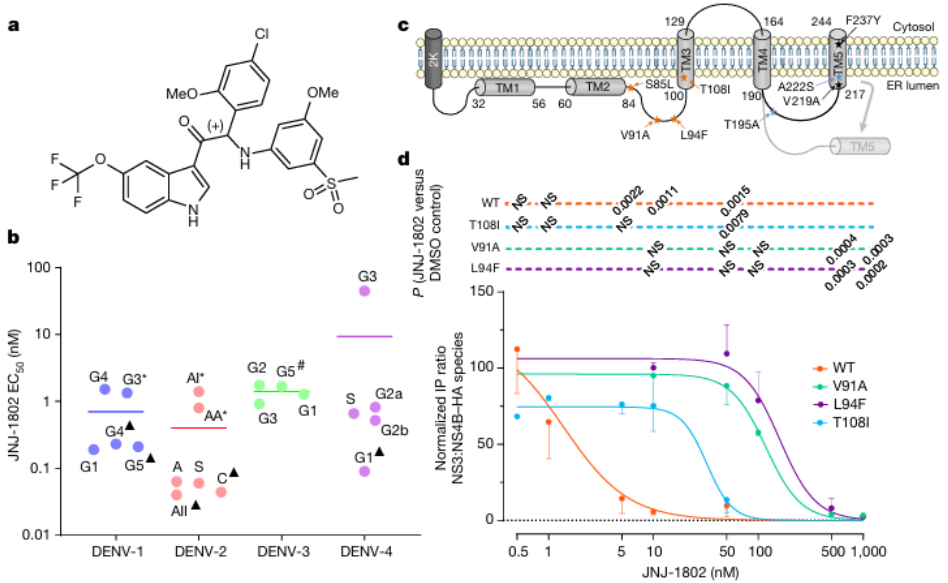

Fig. 1 | The molecular structure, in vitro pan-genotype and -serotype activity, and mechanism of action of JNJ-1802. a, The molecular structure of JNJ-1802. **b**, In vitro antiviral activity in Vero E6 cells against a panel of clinical isolates[23]. Data are mean EC_{50} values. The asterisk and hash symbols indicate diagram was created in part using the Servier Medical Art library (https://smart.servier.com/). **d**, JNJ-1802 prevents DENV NS3–NS4B interaction. Three independent co-immunoprecipitation experiments were performed to establish the JNJ-1802 dose–response curve for the NS3–NS4B interaction.

Goethals et al, Nature, 2023

Mosnodenvir JNJ-1802

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daily Mosnodenvir as Dengue Prophylaxis in a Controlled Human Infection Model

A.P. Durbin,[1] L. Van Wesenbeeck,[2] K.K. Pierce,[3] G. Herrera-Taracena,[4] L. Ebone,[1]

- oral, pan–DENV serotype small-molecule
- blocks viral replication by inhibiting de novo interaction between DENV nonstructural protein 3 (NS3) and NS4B
- Phase 2a, double-blind, RCT, 31 participants in controlled human infection model (CHIM)
- Assessed:
  - safety and efficacy, including DENV-associated adverse events
  - time to detection of viremia, peak viremia
  - DENV IgM and IgG responses
  - pharmacokinetics
- Demonstrated safety of mosnodenvir
- Significantly lower DENV RNA load in participants in high dose mosnodenvir group vs placebo

oral mosnodenvir once daily:

- low dose (40-mg loading, 10-mg maintenance)
- medium dose (200 mg→ 50 mg)
- high dose (600 mg→ 200 mg)
- matched placebo

(Loading doses 5 days; maintenance doses 21 days)

Participants received sc underattenuated DENV-3 strain (rDEN3Δ30) with first maintenance dose (day 1)

Primary efficacy end point: DENV-3 RNA load

Durbin AP, et al, N Engl J Med. 2025; Goethals et al; Nature 2023

Innovative Medicine

Johnson & Johnson to Discontinue Phase 2 Field Study Evaluating Investigational Antiviral for the Prevention of Dengue

No safety issues identified to date

Raritan, N.J. (October 4, 2024) – Johnson & Johnson announced today it is discontinuing the Phase 2 field study (NCT05201794) evaluating the efficacy of investigational antiviral candidate mosnodenvir for the prevention of dengue virus in adults aged 18-65 years. The decision to discontinue this study is part of a strategic reprioritization of the Company's Communicable Diseases research and development (R&D) portfolio. No safety issues were identified.

Alpha. The machine, housed at UB and powered by nearly 200 of some of NVIDIA's most advanced GPUs, is modest by AI standards.

But the second machine, Beta, will be an order of magnitude more powerful, driven by NVIDIA's latest, coveted Blackwell chips—a rare coup for the academic community. Those chips will be linked by a powerful network, allowing them to pass information far faster and with less hardware than even systems like DOE's El Capitan—the most powerful supercomputer in the world—according to Ian Fisk, an Empire AI board member and the Simons Foundation's chief technology officer. "That improvement in efficiency translates into the number of science problems you can look at," Fisk adds.

In its first year, Empire AI has already served more than 350 researchers at the member institutions. One is Columbia University statistician Tian Zheng, who is attempting to combine many scattered clues—weather records, neighborhood flood reports, and city incident logs—to predict where flash floods will strike in urban areas. Such fine-grained forecasts are beyond the reach of conventional climate models. "There are stages of research [that are] high risk and exploratory in nature," she says. Having access to Empire AI's widely available, powerful machines "vastly expands your imagination."

For New York University (NYU) neuroscientist Christine Constantinople, the biggest change has been speed. She trains virtual neural networks to mimic how brains make decisions. Runs that took 1 week on NYU's clusters now finish in 1 day on Empire AI, letting her explore different architectures, scale up model size, and iterate more freely. "It becomes transformative in terms of your ability to explore different possible models," she says.

Weill Cornell Medicine computational biomedicine researcher Ekta Khurana hopes to harness AI to diagnose an aggressive, treatment-resistant subtype of prostate cancer her team has identified. They plan to train machine-learning models on pathology images from patient biopsies—work Cornell's own clusters couldn't support. With Alpha, however, they managed to train a model on hundreds of images; with Beta, they hope to reach more than 10,000.

By 2027, Empire AI anticipates completing its third supercomputer, Gamma, which will be another 10 times more capable than Beta. A fourth machine, Delta, would come after that. "The idea is to keep a machine which is state of the art for the length of the program," Fisk says.

By then, California may have advanced its own effort. The state's new AI law, besides addressing the safety and transparency of large commercial AI models, also includes language supporting the creation of CalCompute. The governor's office is tasked with naming a group to design the program's framework by January 2027, which would still require funding through the state budget.

Federal efforts to create AI infrastructure continue. A panel of experts has recommended spending $2.6 billion over 6 years to move NAIRR beyond existing NSF-funded GPU clusters—where unmet demand often results in long queues, says Hanna Hajishirzi of the Allen Institute. Although a 56% cut in NSF's 2026 budget proposed by President Donald Trump would make it difficult for the agency to advance NAIRR past its pilot run, the administration has consistently indicated that AI is one of its few scientific priorities. Last week, for instance, Trump signed an executive order for a new Genesis Mission that directs DOE to integrate troves of federal scientific data sets into a centralized platform for AI-based research.

The directive comes on the heels of an announcement in October that DOE would join with NVIDIA and Advanced Micro Devices to build nine new AI-focused supercomputers (see story, p. 975). With the companies covering part of the cost of the systems, the deals could help DOE labs keep up with the latest hardware. But it's unclear how far that support will go. Tech firms usually "aren't in the business of philanthropy," Norman says.

The challenge ahead is finding the right balance between federal and state support. "During a year where it wasn't so easy to do research, [Empire AI] was such a bright light for our institutions to have something that didn't depend on federal funding," says Stacie Bloom, NYU's chief research officer and Empire AI board member.

But state-level initiatives alone can't ensure equitable access. "What about a researcher in Arkansas? I don't think Arkansas is going to come up with an AI computing initiative," Norman says. □

INFECTIOUS DISEASES

Abandoned antiviral shows promise against dengue

Big Pharma maker won't bring drug to market for crippling disease **GRETCHEN VOGEL**

Two years ago, the pharmaceutical firm Johnson & Johnson (J&J) announced some rare good news about dengue, a crippling viral infection that threatens half of the world's population. A clinical trial had shown an antiviral compound could prevent the disease in people deliberately exposed to the virus. "The development of a dengue antiviral is critically important to global health," the company said in a press release at the time.

Last week, the full data from that trial were published in *The New England Journal of Medicine*, and encouraging data from two other trials are under review at journals. And yet the drug, called mosnodenvir, is in limbo. Last year, J&J abruptly stopped all its work on infectious diseases, including dengue. "Having watched the development for the last 10 years, I think we were all very disappointed," says Sophie Yacoub, a dengue researcher at the University of Oxford who has advised J&J but was not involved in the studies of the antiviral.

Negotiations are underway to find another company to adopt mosnodenvir and try to bring it to market, Yacoub notes. Given the positive results, she says, "It's not the end. We will see it again."

Eng Eong Ooi, who studies emerging infectious diseases at the Duke–National University of Singapore Medical School, agrees. The newly published study is "a major milestone in dengue," says Ooi, who has also consulted for J&J but was not involved in the mosnodenvir trials.

An estimated 400 million people in tropical and subtropical countries contract dengue annually. The disease causes fever, severe joint pain, rashes, and, in some cases, a potentially fatal hemorrhage that kills tens of thousands every year. There are no approved treatments.

A dengue vaccine made by Takeda, a Japanese company, has been approved in 41 countries, but the company has been unable to keep up with global demand. Sanofi has ended production of another vaccine, citing low demand, and it's unclear when a third vaccine, made by the Butantan Institute and approved in Brazil on 26 November, might become widely available. Because the

https://www.jnj.com/media-center/press-releases/johnson-johnson-to-discontinue-phase-2-field-study-evaluating-investigational-antiviral-for-the-prevention-of-dengue (accessed March 2026); https://www.science.org/doi/epdf/10.1126/science.aee4261 (accessed March 2026)

Safety, Pharmacokinetics, and Activity of AT-752, a Novel Nucleotide Prodrug with Pan-Serotype Activity against Dengue Virus: A Phase 2, Randomized, Double-Blind Study

Arantxa Horga ✉, Mauro M. Teixeira, Swapnav Borthakur, Shannan Lynch, Janice Chin, Laura Ishak, Xiao-Jian Zhou, Keith Pietropaolo, Bruce Belanger, Yang Lei, Qi Huang, and Janet Hammond

AJTMH ASTMH
THE AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE
Official Journal of the American Society of Tropical Medicine and Hygiene

- AT-752, guanosine nucleotide prodrug inhibitor, pan-serotype antiviral activity against DENV
- Phase 2, randomized, double-blind, placebo-controlled study
  - activity, safety, pharmacokinetics
- oral AT-752 (750 mg thrice daily for 5 days) vs placebo
- 21 adults with confirmed DENV
- primary endpoint: change from baseline in viral load (RT-PCR) Days 1–8, 14, and 28
  - Non-evaluable, late presentation, with low baseline viremia levels (no accurate quantification at timepoints)
  - In as-treated population (assessment at baseline and each post-baseline timepoint):
    - mean reduction (versus baseline) in viral load on Day 4 greater in AT-752 group (p= 0.0022)
    - median time to sustained resolution of fever 4 days in AT-752 group vs >5 days in the placebo group
    - reduction in oral temperature Day 4 timepoint greater in AT-752 group (treatment difference: 0.84°C; *P* = 0.0322)
    - trend toward faster platelet recovery in AT-752 group compared with placebo
    - fewer patients (proportionally) in AT-752 group underwent hospitalization for disease progression
- favorable safety and tolerability

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Am. J. Trop. Med. Hyg., 113(3), 2025, pp. 479–481
doi:10.4269/ajtmh.25-0362

Editorial

Another Dengue Antiviral Drug Bites the Dust Early: Where Does Dengue Therapeutic Drug Development Go from Here?

Swee Sen Kwek[1,2] and Jenny G. Low[1,2,3]*

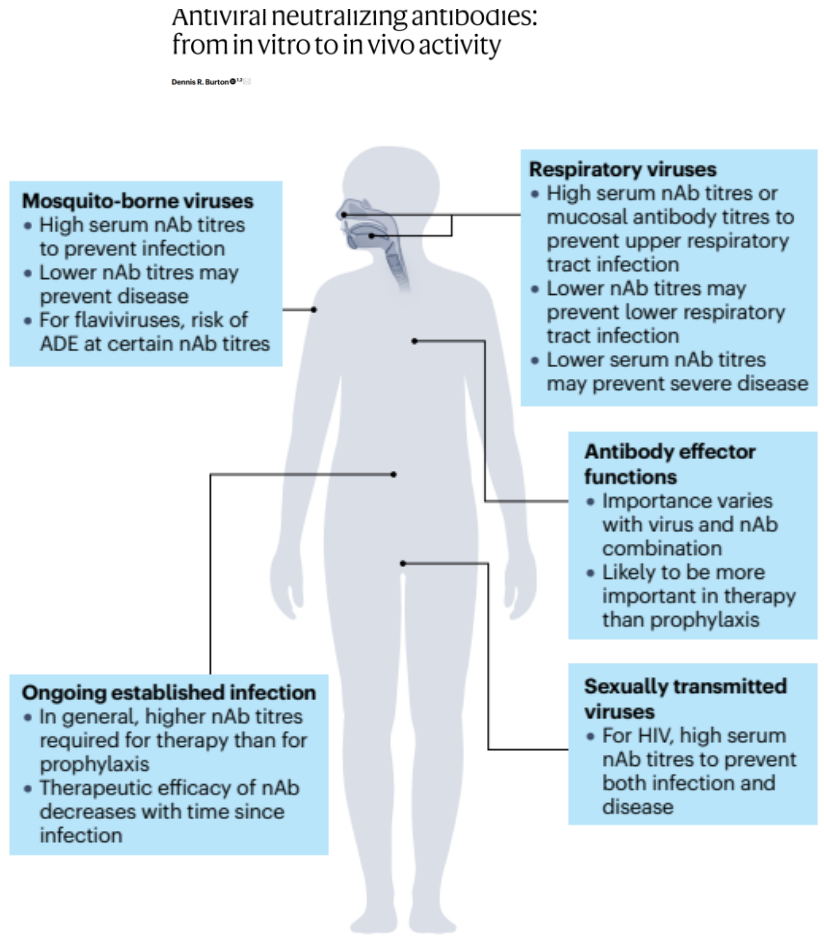
[1]*Department of Infectious Diseases, Singapore General Hospital, Singapore;* [2]*Programme in Emerging Infectious Diseases, Duke-National University of Singapore Medical School, Singapore;* [3]*Viral Research and Experimental Medicine Centre, SingHealth-Duke National University of Singapore Academic Medical Centre, Singapore*

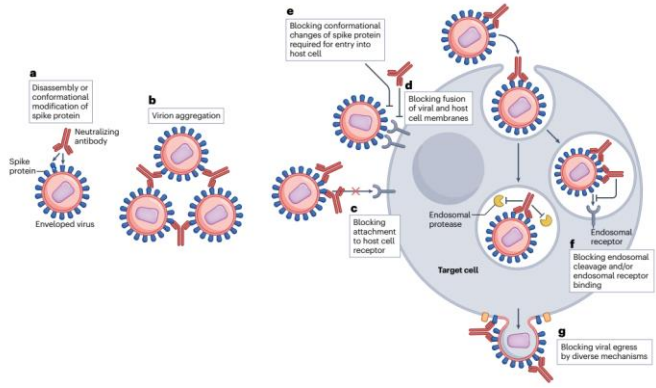
- early retirement of trial illustrates challenges of dengue antiviral studies
- narrow window for patient recruitment (non-specific febrile phase, overlap with other viral illnesses)
- subjective reporting of fever by patients is unreliable
- dengue distinguished from febrile illnesses via symptoms/lab findings later in course of infection
- trial intended to enroll patients with early dengue (first 48 hours), but viremia below limit of detection in 30% and rapid decline by Day 4
- limited sensitivity of diagnostic tools
- recruitment of trial patients tends to rely on point-of-care DENV NS1Ag test, but sensitivity low in first two days and in secondary dengue
- PCR-screening not practical

Monoclonal antibodies

- Monoclonal antibodies as potential novel therapeutics or preventive agents (PrEP) for specific high-risk groups
- Needs:
  - against four DENV serotypes
  - not triggering ADE
  - efficacy even if high viremia or pre-existing antibodies
  - amenable to Fc region of antibodies engineering to optimize safety and pharmacological properties
- Two candidates of human antibodies in Phase 2 clinical evaluation:
  - VIS513
  - AV-1

nature reviews immunology https://doi.org/10.1038/s41577-023-00858-w





Farsiu et al, AMJTMH 2025; Terzi I et al, Virology, 2025; Burton DR, et al, Nat Rev Immunol. Nature Research; 2023.

VIS-513

An observer-blind, randomised, placebo-controlled, phase 1, single ascending dose study of dengue monoclonal antibody in healthy adults in Australia

Bhagwat Gunale, Nicholas Farinola, Chandrashekhar D Kamat, Cyrus S Poonawalla, Sambhaji S Pisal, Rajeev M Dhere, Claire Miller, Prasad S Kulkarni

Lancet Infect Dis 2024; 24: 639–49
Published Online February 23, 2024
https://doi.org/10.1016/S1473-3099(24)00030-6

- March- Dec 2019, 40 healthy adults, randomly assigned, no SAEs reported.
- 31 (91%) of 34 participants receiving dengue monoclonal antibody reported 143 adverse events
- Of these, 80 were treatment-related:
  - Headache (47%)
  - infusion reaction (32%)
  - lymphopenia (21%)
  - fatigue (15%)
  - pyrexia (12%)
- majority of adverse events were grade 1 or grade 2 in severity
- no anti-drug antibodies against dengue monoclonal antibody was detected

- recruitment completed for phase 2 trial of Dengushield (VIS-513, Serum Institute of India, CRTI 2021/07/035290), results awaited…..

Gunale et al, Lancet Inf Dis 2024; McBride et al, BMJ Public Health 2026

AV-1

Virology
Volume 612, November 2025, 110677

Neutralizing monoclonal antibodies against dengue virus: a scoping review of preclinical and clinical development

Irene Terzi [a], Dimitrios Dimitriadis [b], Melina Ntoga [b], Vasilios Petrakis [a c], Ioulia Dragoumani [b], Filothei Markatou [b], Petros Rafailidis [c]

Limited information publicly available regarding preclinical development, epitope specificity, and anti-DENV activity

- Phase 1 trial (NCT04273217)
- randomized, triple blind, placebo-controlled, single ascending dose study, conducted in healthy adults in the United States (ClinicalTrials.gov., 2020)
- 42 participants (18-45 years)
- single intravenous infusion of AV-1 at doses of 30 mg, 90 mg, 250 mg, 500 mg, or 1000 mg, or placebo
- Completed July 2021 (no serious adverse events)

- Phase 2 challenge trial (NCT06799741) recently started
- will evaluate AV-1's efficacy in at least 84 healthy adult volunteers
- randomized to AV-1 one day before or four days after being experimentally infected with mild, attenuated dengue virus strain (ClinicalTrials.gov., 2025a).
- subdivided into groups, 100 mg, 300 mg, or 900 mg, via a 60-min intravenous infusión
- aims to evaluate AV-1 influence on viral clearance, symptom severity, immune response, and define optimal dosing for future trials.

Terzi et al, Virology, 2025; McBride et al, BMJ Public Health 2026

Monoclonal antibodies: uncertainties

Sub-neutralising antibody concentration is associated with ADE of dengue virus infection

Neutralisation potency of dengue mAb not balanced across 4 dengue viruses→efficacy?

DENV mAb infusion associated with lymphopenia mainly in group receiving highest dose (12mg/Kg) of VIS513, may exacerbate DENV-associated lymphopenia

Accessibility and affordability?

DIGICOMPHOTO/ Science Photo Library

Published Online
February 23, 2024
https://doi.org/10.1016/
S1473-3099(24)00083-5

See Articles page 639

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Is a therapeutic dengue monoclonal antibody on the way?

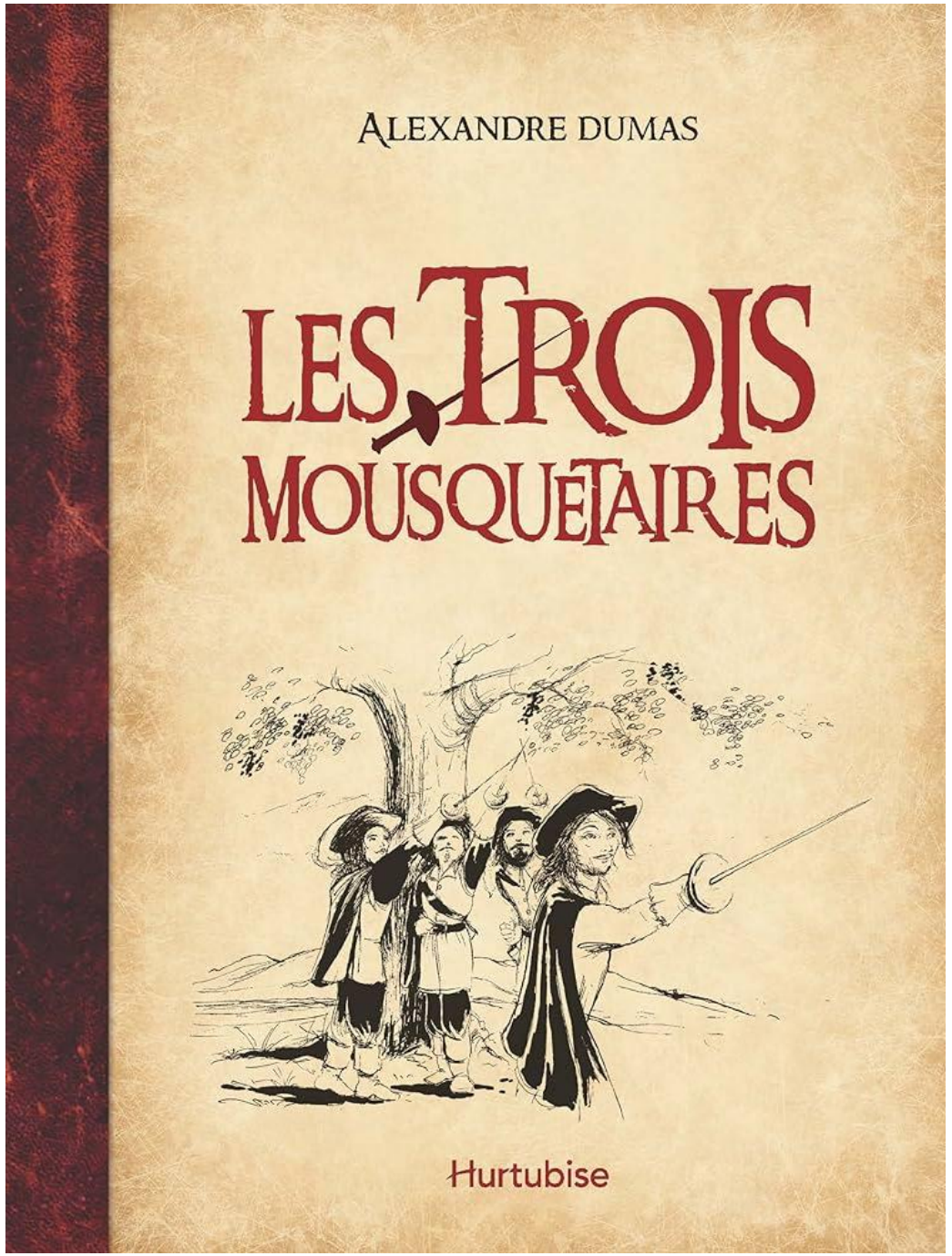
Repurposed drugs

- Some drugs repurposed and explored as host-directed therapies (HDT)
- May improve immune response and constrain host cellular factors in viral replication
- Aim to limit disease progression
- Phase 2, 3 trials ongoing for montelukast and dexamethasone
- **DEN-HOST** to evaluate host kinases, inflammation pathways, and cellular entry factors (baricitinib, dexamethasone, and N-acetylcysteine)
- (Repurposing drugs with anti-inflammatory properties such as chloroquine and ivermectin disappointing)

Pandemic Sciences Institute. International collaboration launches largest-ever therapeutics trial for patients hospitalised with dengue [Internet]. 2025 Available from: https://www.psi.ox.ac.uk/news-and-opinion/international-collaboration-launcheslargest- ever-therapeutics-trial-for-patients-hospitalised-with-dengue (accessed March 2026)

Dengue prevention

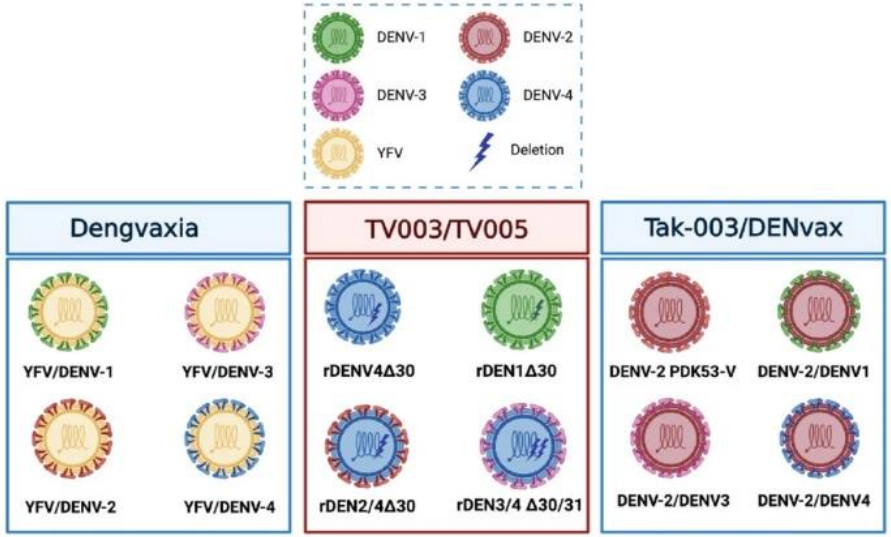
Vaccines



Vaccine development: “a bumpy road”

- Need to protect against four serotypes (essentially four viruses)
- Immune-mediated enhancement in severity/ antibody-dependent enhancement (associated mainly with secondary infections)

- Decades of dengue vaccine research……
- Licensure of three live-attenuated tetravalent dengue vaccines
- Each is recombinant of four chimeric components that target all four serotypes



Torres-Flores et al, BioDrugs, 2022

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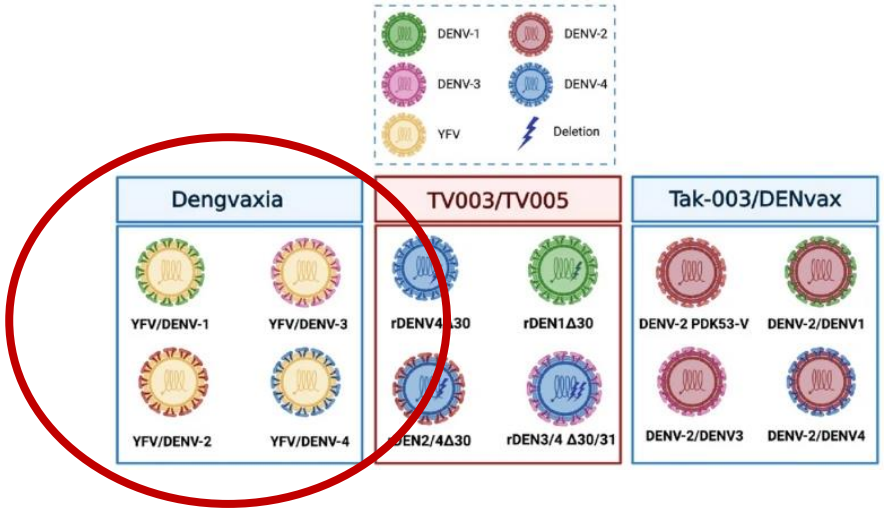

- CYD-TDV (Dengvaxia®, Sanofi)
- First vaccine to receive regulatory approval
- 3-dose series based on yellow fever backbone
- Phase 3 clinical trials (endemic and non-endemic areas), >30,000 participants
- Vaccine efficacies:
  - 59% against symptomatic virologically confirmed dengue (VCD)
  - 73% against dengue hospitalization
  - 79% against severe dengue
- Initially licensed in 2015 in Mexico, the Philippines, Brazil, El Salvador
- Post-licensure data: severe dengue in some vaccinated individuals who later infected with dengue
- Increased severity possibly due to live vaccine serving as primary dengue infection (ADE when second DENV)
- WHO SAGE: cause indeterminate but required pre-vaccination testing for dengue positivity
- Additionally, low demand led to interruption of manufacturing (September 2025)

Torres-Flores et al, BioDrugs, 2022; Capeding et al, Lancet, 2014; Villar et al, NEJM, 2014; Thomas et al, Hum Vaccin Immunother. 2013; WHO position paper, September 2018 - Recommendations. Vaccine. 2019

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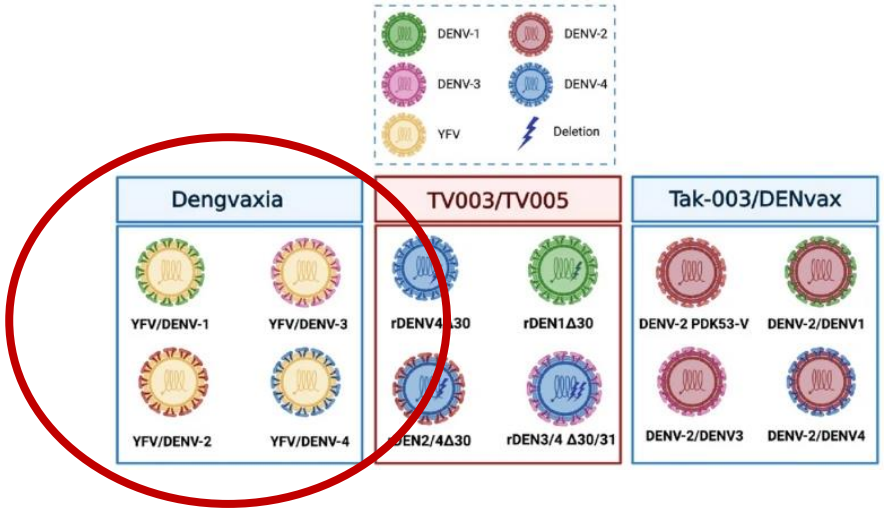

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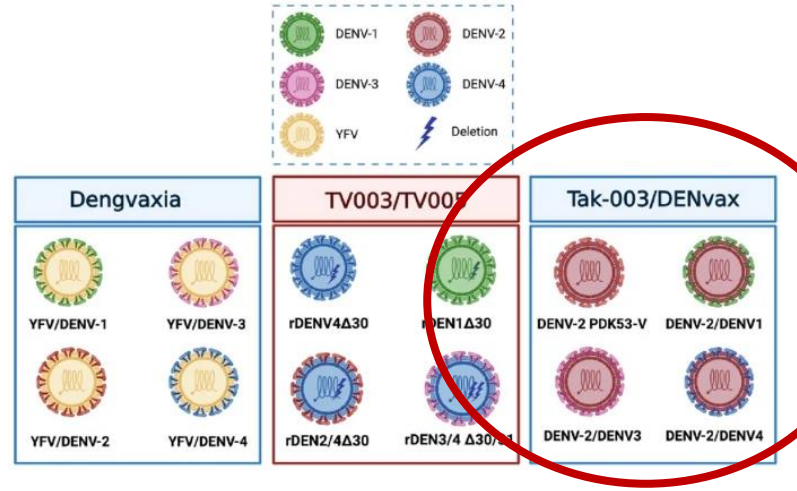

- TAK-003 (Qdenga®, Takeda)
- Licensed in 2022, first in Indonesia, now >40 countries.
- Based on DENV-2 backbone, 2-dose series (3-month interval)
- Phase 3 clinical trials, 20,000 participants
- Vaccine efficacies (11 months):
  - 80% against symptomatic VCD
  - 95% against dengue hospitalization
- VE higher in DENV-seropositive than DENV-seronegative participants (82% vs 75%)
- VE declined with time (4.5 years), long-term assessments following booster dose and follow up results support safety profile and persistent protection vs infection/hospitalization

Torres-Flores et al, BioDrugs, 2022; Biswal et al, NEJM, 2019; Rivera et al, CID, 2022; Tricou et al, Lancet 2024; Escudero et al, 2025

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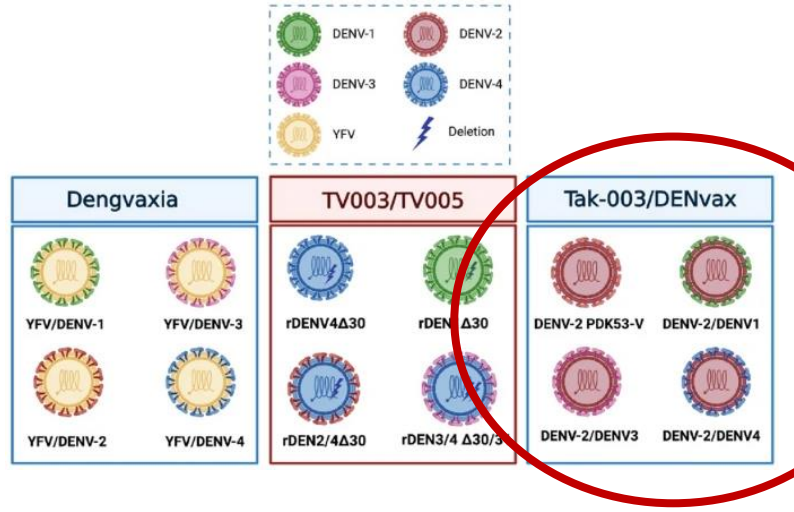

- After 2023 licensure and incorporation into Brazil's universal vaccination program, concern from 24 reports of anaphylaxis (rate of 63.1 cases per million doses)
- Subsequent analyses on adverse events, rate lower
- WHO SAGE recommended TAK-003 for 6-16 years in dengue-endemic, high-transmission settings and others at risk (international travelers)
- 2-dose schedule challenges implementation in endemic areas and international travelers

Torres-Flores et al, BioDrugs, 2022; Percio et al, Vaccine 2024; Anschau et al, J Med Virol, 2025; WHO 2024; Freedman et al, JTM 2023; Steffen et al, JTM 2024

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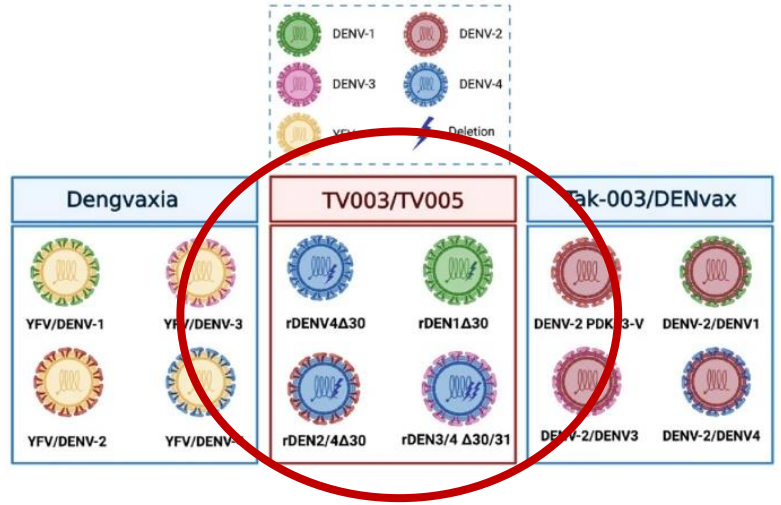


- TV003 (Butantan-DV; Instituto Butantan)
- Authorization for ages 12-59 years in Brazil (November 2025)
- Full-length attenuated DENV1, DENV-2, DENV-3, with recombinant attenuated DENV-4 virus that contains prM and E proteins of DENV-2
- Phase 3 clinical trial
  - overall 2-year VE of 80%: 74% among DENV-naïve and 89% among DENV-exposed
  - VE 90% against DENV-1; 70% against DENV-2;
  - lack of DENV-3 and DENV-4 precluded their VE determination
  - follow up 3.7 years VE against VCD 67% (DENV-3, DENV-4 not observed)

Torres-Flores et al, BioDrugs, 2022; Instituto Butantan https://ensaiosclinicos.gov.br/news/493; Wilder-Smith ewt al, Curr Op Inf Dis 2022; Huang et al, Exp Rev Anti-inf Ther 2021; Kallas et al, NEJM, 2024; Nogeira et al, Lancet Inf Dis 2024

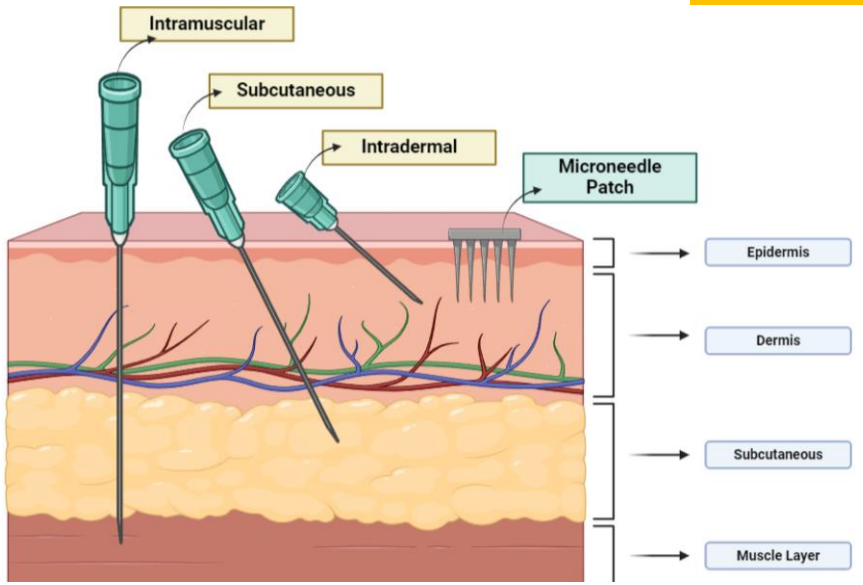
Additional dengue vaccine candidates

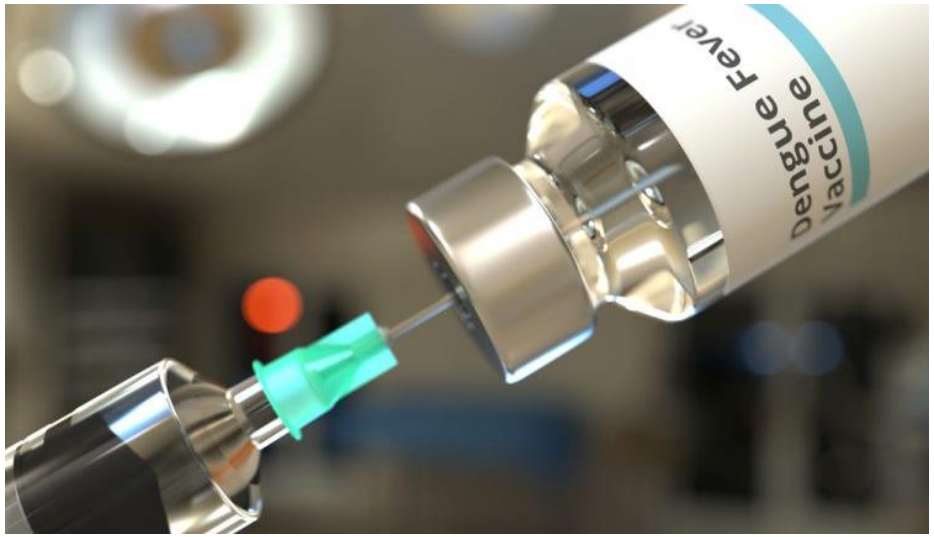
- Based on other vaccine platforms, including:
  - inactivated virus
  - subunit vaccine
  - DNA vaccine
  - viral vector vaccine
  - heterologous prime boost
- Development slower than for 3 recombinant live attenuated chimeric vaccines
- Large populations at risk and vulnerable populations where live vaccines usually contraindicated (e.g. immunocompromised persons, pregnant women), need for non-live vaccine platforms

Huang C-H, et al, Expert Rev Anti Infect Ther. 2021

The ideal vaccine?

- single dose
- non-live (for use in immunosuppressed patients and pregnant women)
- inducing rapid (10-14 days after vaccination) but long-term immunological response
- balanced response vs 4 serotypes (sero - and sero + individuals)
- delivered via low cost, low technical requirement delivery methods (self-administered microneedles)
- effective use in response to outbreaks and/or in remote low-resource settings





Mansoor et al, PharmSciTech 2022; Kumar et al, J Healthcare Q Res, 2024

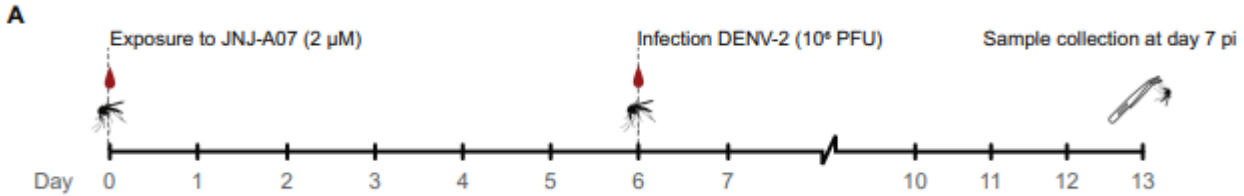
SCIENCE ADVANCES | RESEARCH ARTICLE

MICROBIOLOGY

Other approaches for prevention

The antiviral JNJ-A07 significantly reduces dengue virus transmission by *Aedes aegypti* mosquitoes when delivered via blood-feeding

Ana L. Rosales-Rosas[1], Sara Goossens[1], Winston Chiu[2], Atreyee Majumder[3], Alina Soto[1], Serge Masyn[4], Bart Stoops[5], Lanjiao Wang[1], Suzanne J. F. Kaptein[2], Olivia Goethals[4]†, Leen Delang[1]*†



- Reduction of DENV systemic infection in mosquitoes.
- Antiviral activity of JNJ-A07, pan-serotype DENV inhibitor, administered in blood meal to *Aedes aegypti* mosquitoes
- JNJ-A07 demonstrated activity in a mouse model where it blocked DENV-2 transmission by mosquitoes in preexposure and post-exposure settings
- JNJ-A07 persisted in mosquito bodies for 7 days after blood meal
- Further evaluation needed
- Interesting approach!! …..Evaluation of potential to control DENV outbreaks

Rosales-Rosas AL, et al, Sci Adv. 2024

Other approaches for prevention

- Vector control programs
- Environmental modifications to reduce vector habitat and spraying with insecticide
- Genetically modified mosquitoes that carry gene lethal to female larvae, male offspring pass gene to future generations, gradually decreasing mosquito populations
- Replacement of wild mosquitoes with *Wolbachia*-infected mosquitoes (with reduced vector competence) can prevent up to 77% dengue transmission and reduce dengue incidence

Paz-Bailey G, e al, International Journal of Infectious Diseases, 2025; Spinner SAM, et al, Front Bioeng Biotechnol. 2022; Hilgenboecker K, et al, FEMS Microbiol Lett. 2008; Hoffmann AA,et al, Nature. 2011

Research Gaps, Future Research Directions

Improve detection of outbreaks, advance modeling of disease burden

Understand temperature and precipitation patterns, predict vector activity, inform public health and vector control responses

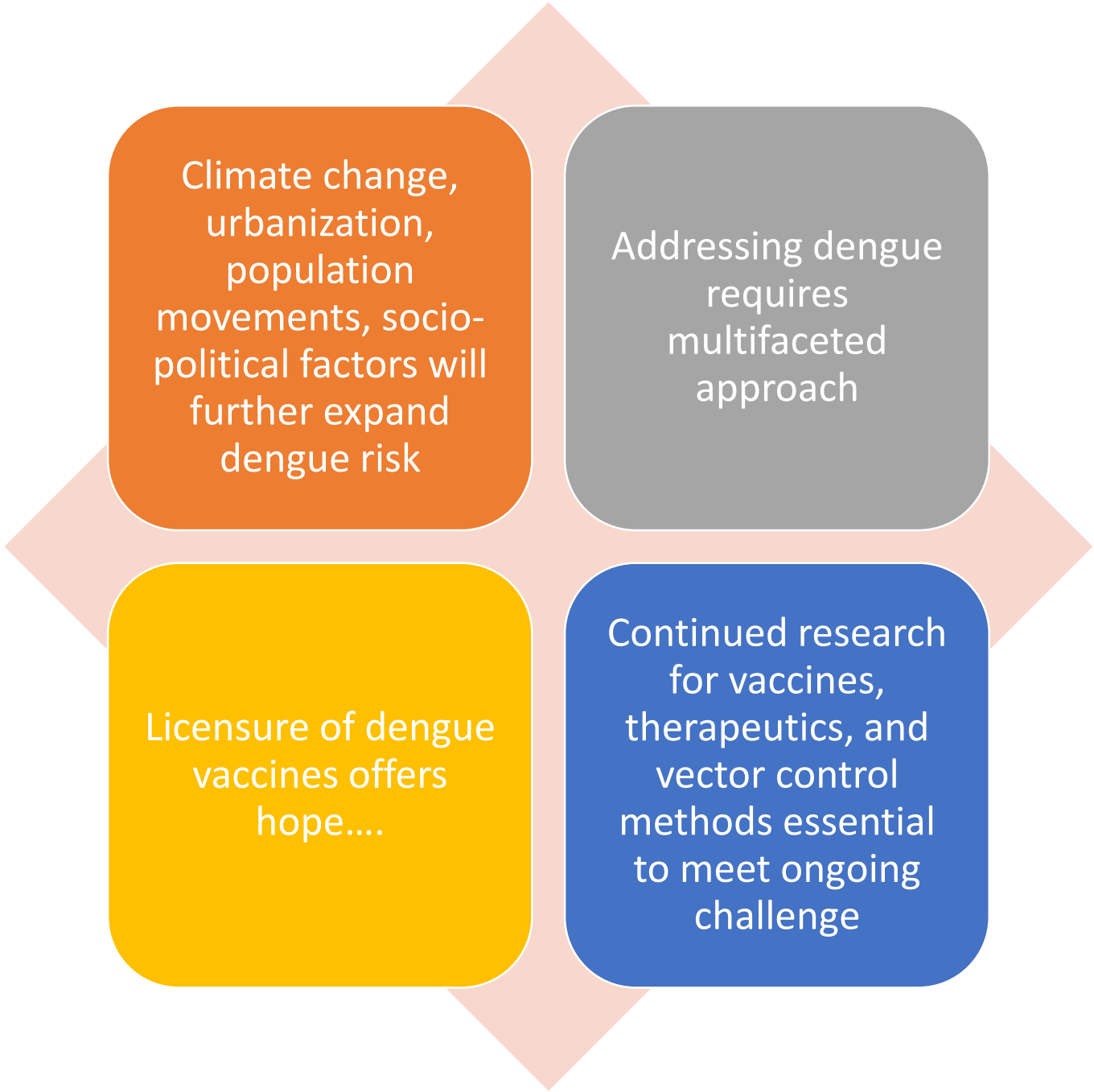
Triage to identify patients at high risk of severe disease (may benefit from antiviral or host-directed therapeutic interventions)

Effective and accessible antiviral as proposed by WHO TPP not yet available, collaborative initiatives underway

mAbs: VIS513 most advanced, broad neutralization, good safety, imminent Phase 3 testing; challenge trial for AV-1 expected

Efforts to develop immunization tools without the limitations of live attenuated vaccines

Conclusions



Thank you-Gracias

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