Vaccines against Vector-borne Diseases: ~~Malaria~~, Dengue, Zika, and Chikungunya

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- Consulting Expert to WHO
- President, German Society for Travel Medicine

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Conflict of Interest Statement

Honoraria for consultancies, lectures and as principal investigator in studies from

Abbott, Astra Zeneca, Bavarian Nordic, Baxter, Boehringer Ingelheim, Clover Pharmaceuticals, Crucell, Dr. Falk, Emergent, GSK, Glenmark, Hermes Arzneimittel, Hoffmann LaRoche, Janssen Cilag, Medicago, Novartis Vaccines, Pfizer, r-biopharm, Sanofi Pasteur, MSD Sharp & Dohme, Sekizui-Virotech, Sigma Tau, Takeda, Themis Bioscience, Valneva

This presentation is not sponsored or monitored by anybody

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Vaccines against Vector-borne Diseases

Dengue

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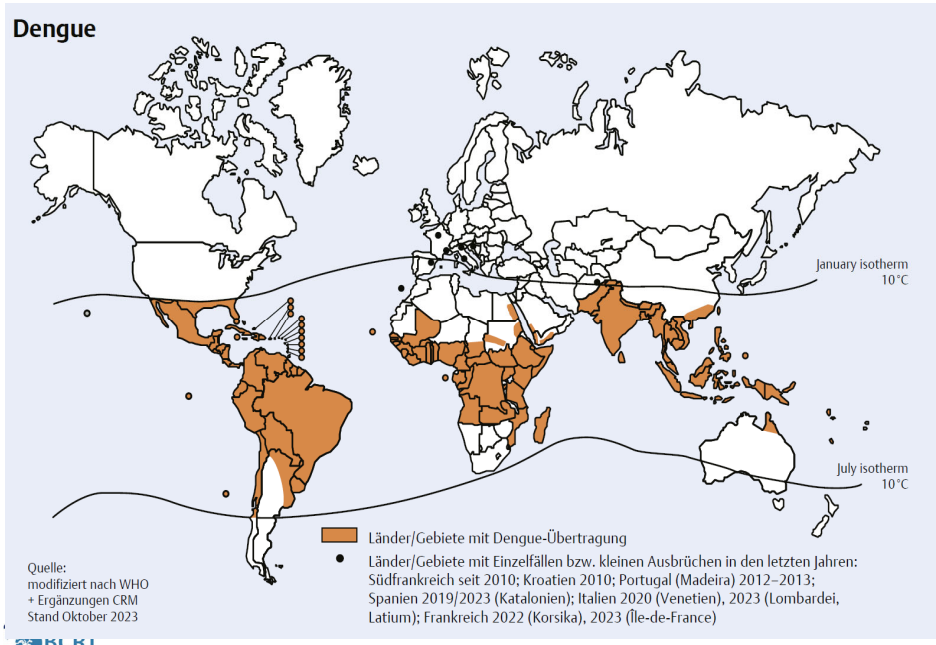
Rapid Increase of Dengue/DHF

Average Anual Reports to WHO

Jelinek T. Dengue-Fieber bei Reisenden. Thieme-Refresher Reisemedizin 2022; 12: 1–12

4



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Travelers with Dengue treated at the Mahidol University, Thailand

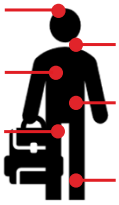
Retrospective analysis of travelers and foreign patients with DENV infection from a single hospital in Thailand between 2017 and 2021 (N=185)

Presentation/Symptoms

66% continuous fever
36% intermittent fever
58% chill

68% severe headache
3% seizure
2% stiff neck

77% muscle pain
34% retro-orbital pain
24% thigh pain



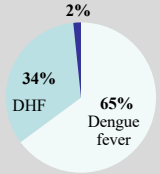
26% cough
24% sore throat
22% dyspnea

43% nausea
38% vomiting
24% diarrhea
18% stomachache

19% bleeding manifestation
18% rash
6% dysuria

58% male
41% female

Outcomes



Complications, such as transaminitis (15%), hypokalemia (4%), and hyponatremia (2%)

Average hospital stay of **<1 week**

Mortality of two patients (2%), due to multiple organ failure and co-infection

Approximately one in three travelers admitted to hospital with DENV infection developed severe dengue (DHF or shock syndrome)

- DENV, dengue virus; DHF, dengue hemorrhagic fever.
  Phothong P, et al. Presented at 6th Asia Dengue Summit, Bangkok, Thailand, 15–16 June 2023. Abstract 014.

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Most hospitalizations and severe dengue after secondary infections

Although most hospitalizations and severe dengue cases occur among secondary infections, some occur during 3rd and 4th infections

Dengue virus infection sequence	Percent of infections that proceed to disease outcome during follow-up		
	Symptomatic VCD – 2y	Hospital – 5y	Severe VCD – 5y
1	48.7 (43.5-53.8)	3.4 (2.2, 4.8)	0.5 (0.1, 1.1)
2	55.3 (51.4-59.8)	12.7 (11.6, 14.0)	2.6 (2.0, 3.2)
3	30.5 (27.1, 34.4)	3.3 (2.6, 3.9)	1.0 (0.7, 1.4)
4	30.5 (27.1, 34.4)	3.3 (2.6, 3.9)	1.0 (0.7, 1.4)

>85% of hospitalizations and severe disease in seropositive individuals

Sam Clifford and Stefan Flasche LSHTM, personal communication
Sridhar, NEJM 2018;379:327-40, Flasche et al, Plos Med 2016; 13(11):e1002181.

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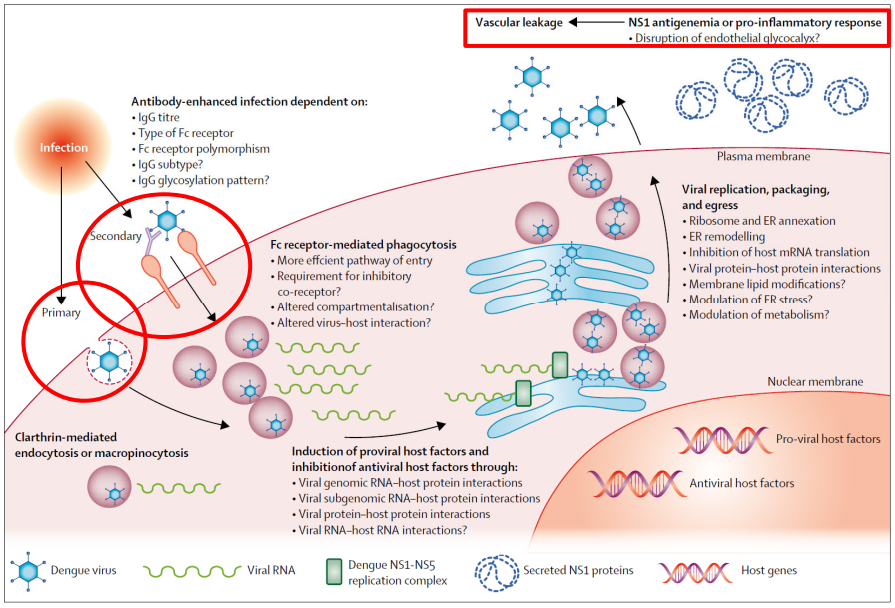
Pathogenesis of Complicated Dengue / Dengue Hemorrhagic Fever



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Source: Wilder-Smith et al. Dengue. Lancet 2019;393:350-63

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Viral factors: NS1 in immunopathology

- **NS1 can be considered as a virulence factor**
  - Interferes with complement activation
  - Binds to prothrombin and inhibits its activation
  - Binding to cells may enhance endocytosis and cytokine production, which may enhance DENV infection and increase vascular permeability
  - *Specific antibody response against NS1 appears to be protective against complications*

Avirutnan et al, J Immunol 187: 424 (2011)
Thiemmeca et al , J Immunol.97(10):4053 (2016)
Beatty. ScTrMed 7, 304, 304ra141 (2015)
Modhiran, ScTrMed 7, 304, 304ra142 (2015)

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•Medline Search 1995-2020

- 9 detailed reports of dengue with fatal outcome among travelers from non-endemic countries.
  - 8 were female.
  - median age was 32 years (range 21–63)
  - 7 primary DENV infections, 1 secondary infection, 1 data not reported.

–DENV-1 (n=2),
–DENV-2 (n=2),
–DENV-3 (n=3);
–DENV-1 or 2 (n=1),
–in one the serotype could not be determined.

Journal of Travel Medicine, 2021, 1–6
https://doi.org/10.1093/jtm/taab020
Advance Access Publication Date: 16 February 2021
Original Article

Original Article

Fatal outcomes of imported dengue fever in adult travelers from non-endemic areas are associated with primary infections

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Submitted 10 December 2020; Revised 28 January 2021; Editorial Decision 2 February 2021; Accepted 4 February 2021

Table 1. Overview of published cases of imported dengue with fatal outcomes ($n = 9$)

Year	Gender	Age	Country of residence	Country of dengue acquisition	Cause of Death	Time of death (DPSO)days	Dengue diagnosis and serotype		Primary/Secondary dengue infection		Ref.
									IgM	IgG	
1998	F	25	Netherlands	Thailand	Cerebral edema	6	RT-PCR	DENV-3	Prim.	1/128	1/16	20
2002	F	32	Finland	SE Asia	Cerebral hemorrhage	37	PRNT	DENV-1/2	Prim.	POS	NEG	13
2005	F	28	USA	Mexico	-	-	-	-	-	-	-	18
2005	F	30	Norway	Mexico	Subarachnoid hemorrhage	8	RT-PCR	DENV-2	Prim.	POS	NEG	14
2008	F	50	Norway	Thailand	DSS	7	RT-PCR	DENV-1	Prim.	POS	NEG	15
2009	M	54	Netherlands	Saint Martin	DSS	4	RT-PCR	DENV-2	Prim.	NEG	NEG	16
2009	F	21	Germany	Ecuador	Postoperative hemorrhage	11	RT-PCR	DENV-1	Sec.	1/20	1/2560	17
2012	F	63	USA	USA	Hemophagocytic lympho-histiocytosis	38	RT-PCR	DENV-3	Prim.	POS	-	19
2015	F	34	Australia	Papua New Guinea	Myocarditis/cerebral edema	6	RT-PCR	DENV-3	Prim.	POS	NEG	21

F = female, M = male, DSS = dengue shock syndrome, DPSO = days post symptom onset, RT-PCR = real-time reverse transcription polymerase chain reaction, PRNT = plaque reduction neutralization testing; DENV-x indicates dengue serotype; Prim. = primary; Sec. = secondary; POS = positive; NEG = negative; – = data missing.

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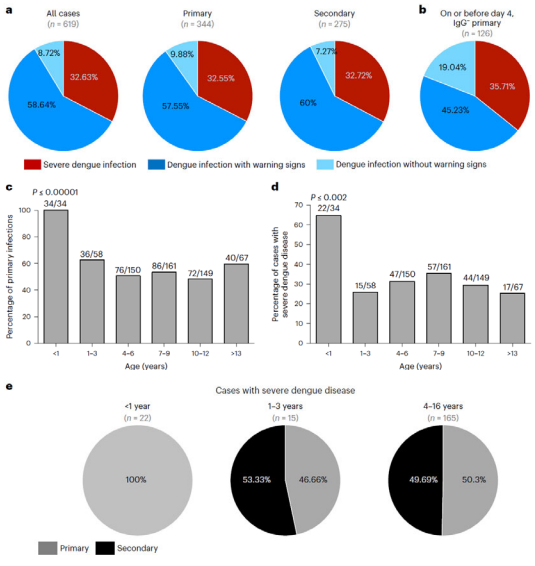
nature medicine

Brief Communication https://doi.org/10.1038/s41591-024-02798-x

Severe disease during both primary and secondary dengue virus infections in pediatric populations

Charu Aggarwal[1,16], Hasan Ahmed[2,16], Pragati Sharma[1], Elluri Seetharami Reddy[3], Kaustuv Nayak[1], Mohit Singla[4,5], Deepti Maheshwari[1], Yatiya M. Chawla[1], Harekrushna Panda[1], Ramesh Chandra Rai[6], Sivaram Gurubatty[7], Lalita Priyamvada[8], Siddhartha Kumar Bhaumik[9], Syed Faizl Ahamed[6], Rosario Vivek[6,7], Priya Bhatnagar[10], Prabhat Singh[1], Manpreet Kaur[1], Kritika Dixit[1], Sanjeev Kumar[6], Kamal Gottimukkala[1], Keshav Sahi[6], Prashant Bajpai[1], Gopinathan Pillai Sreekanth[6], Shobha Mamman[6], Anand Rajan[6], Valsan Philip Verghese[11], Asha Mary Abraham[6], Paresh Shah[6], Kalicharan Alagarasu[12], Tiameo Yu[13], Carl W. Davis[13], Jens Wrammert[8], Aftab Ansari[14], Rustom Antia[9], Sushil Kumar Kabra[1], Gunaprasad R. Medigeshi[10], Rafi Ahmed[15,16,17], Rakesh Lodha[1,16], Anita Shet[6,16] ✉, Anmol Chandele[10,16] ✉ & Raja Murali-Krishna[6,16,17] ✉



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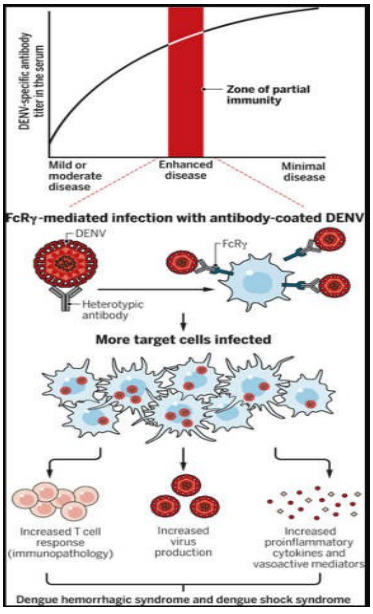
Issues with Dengue Vaccines

- Vaccine must be effective against all four serotypes
- After dengue infection with one serotype, there is (usually) lifelong protection against this serotype
- Second infection with a different serotype (heterotypic infection) poses a risk of severe dengue, presumably due to antibody-dependent enhancement (ADE)



Referenzen: [1] Saez-Llorens X, Biswal S, Borja-Tabora C, Fernando L, Liu M, Wallace D, et al. Effect of the Tetravalent Dengue Vaccine TAK-003 on Sequential Episodes of Symptomatic Dengue. Am J Trop Med Hyg. 2023;108(4):722-6.

Figure from: Feinberg MB, Ahmed R. Advancing dengue vaccine development. Science. 2017;358(6365):865-6.

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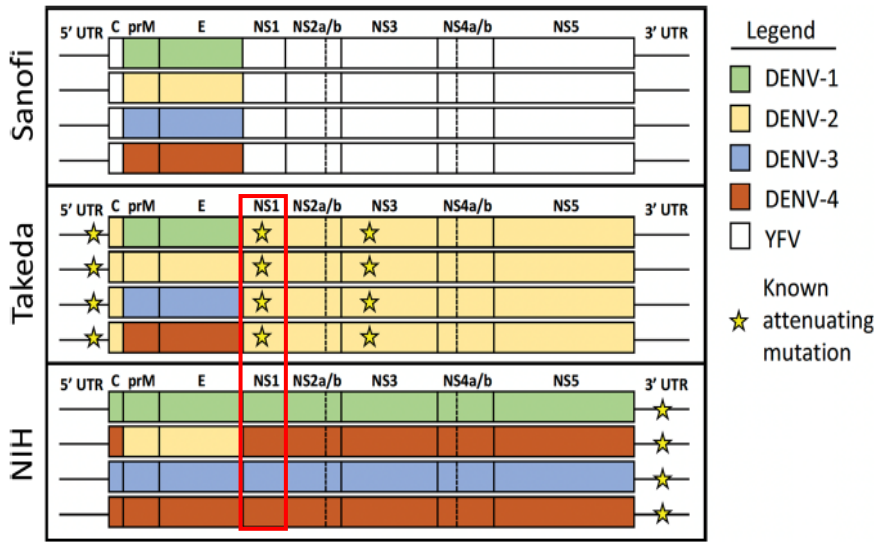
Vaccines against Dengue



Thomas SJ. Is new dengue vaccine efficacy data a relief or cause for concern? npj Vaccines (2023) 8:55; https://doi.org/10.1038/s41541-023-00658-2

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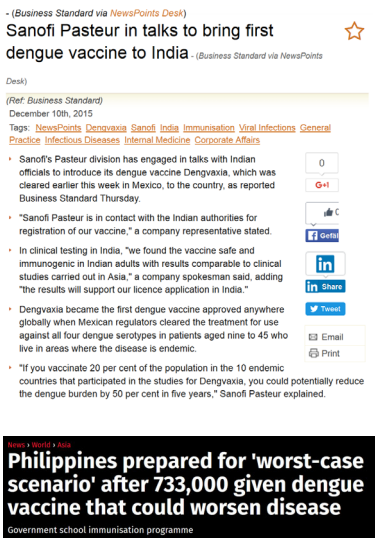
Dengue-Vaccine I



- (Business Standard via NewsPoints Desk)

Sanofi Pasteur in talks to bring first dengue vaccine to India - (Business Standard via NewsPoints Desk)

(Ref: Business Standard)

December 10th, 2015

Tags: NewsPoints Dengvaxia Sanofi India Immunisation Viral Infections General Practice Infectious Diseases Internal Medicine Corporate Affairs

- Sanofi's Pasteur division has engaged in talks with Indian officials to introduce its dengue vaccine Dengvaxia, which was cleared earlier this week in Mexico, to the country, as reported Business Standard Thursday.
- "Sanofi Pasteur is in contact with the Indian authorities for registration of our vaccine," a company representative stated.
- In clinical testing in India, "we found the vaccine safe and immunogenic in Indian adults with results comparable to clinical studies carried out in Asia," a company spokesman said, adding "the results will support our licence application in India."
- Dengvaxia became the first dengue vaccine approved anywhere globally when Mexican regulators cleared the treatment for use against all four dengue serotypes in patients aged nine to 45 who live in areas where the disease is endemic.
- "If you vaccinate 20 per cent of the population in the 10 endemic countries that participated in the studies for Dengvaxia, you could potentially reduce the dengue burden by 50 per cent in five years," Sanofi Pasteur explained.

News › World › Asia

Philippines prepared for 'worst-case scenario' after 733,000 given dengue vaccine that could worsen disease

Government school immunisation programme

CYD-TDV (Dengvaxia®)

- Live vaccine against all 4 serotypes
- Backbone yellow fever vaccine virus, DEN 1-4 chimeras
- 3-shot-schedule: 0, 6, 12 months
- Very high immunogenicity
- Protection approx. 20% for non-immune people, approx. 60% after a dengue episode
- Caution for non-immune people: risk of DHF on contact with wild virus (signal after 2 years)
- Authorization in Europe
- Only used in French overseas territories

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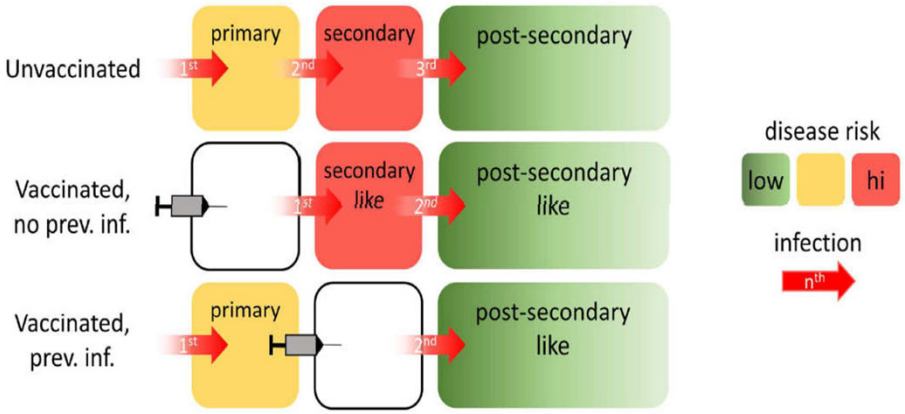
Dengvaxia®: Vaccination of sero-negative persons can induce complications similar to secundary infections



Flasche S, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. PLoS Med. 2016;13(11):e1002181.

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Dengue-Vaccine II

Takeda Dengue Vakzine, TAK-003 (Qdenga®)

- Live vaccination against all 4 serotypes
- Basis: attenuated dengue 2 vaccine virus, DEN 1, 3, 4-chimeras
- 2 shot-schedule: 0, 3 months
- Very high immunogenicity
- Protective efficacy total population 80.2%
- Protective effectiveness after 1st vaccination 81.1%
- Protection against hospitalisation: 90.4%
- No significant protection against dengue 4
- Significantly no protection against dengue 3 (in non-immune people)
- Few data for older adults
- Side effects at placebo level
- No signal for DHF in contact with wild virus (after >5 years of follow-up)

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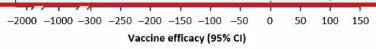
EXPLORATORY ANALYSIS: SEROTYPE LEVEL DATA UP TO 4.5 YEARS AFTER 2ND DOSE

		VCD or hospitalized VCD, n/N (cases per 100 person-years)		Vaccine efficacy (95% CI)
		Placebo (n=6687)	TAK-003 (n=13,380)	
VCD	Overall	547/6687 (8.2)	442/13,380 (3.3)	61.2 (56.0, 65.8)
	Seropositive	394/4854 (8.1)	295/9663 (3.1)	64.2 (58.4, 69.2)
	DENV-1	151/4854 (3.1)	133/9663 (1.4)	56.1 (44.6, 65.2)
	DENV-2	135/4854 (2.8)	54/9663 (0.6)	80.4 (73.1, 85.7)
	DENV-3	97/4854 (2.0)	96/9663 (1.0)	52.3 (36.7, 64.0)
	DENV-4	20/4854 (0.4)	12/9663 (0.1)	70.6 (39.9, 85.6)
	Seronegative	153/1832 (8.4)	147/3714 (4.0)	53.5 (41.6, 62.9)
	DENV-1	79/1832 (4.3)	89/3714 (2.4)	45.4 (26.1, 59.7)
	DENV-2	58/1832 (3.2)	14/3714 (0.4)	88.1 (78.6, 93.3)
	DENV-3	16/1832 (0.9)	36/3714 (1.0)	−15.5 (−108.2, 35.9)
	DENV-4	3/1832 (0.2)	12/3714 (0.3)	−105.6 (−628.7, 42.0)
Hospitalized VCD	Overall	142/6687 (2.1)	46/13,380 (0.3)	84.1 (77.8, 88.6)
	Seropositive	101/4854 (2.1)	29/9663 (0.3)	85.9 (78.7, 90.7)
	DENV-1	24/4854 (0.5)	16/9663 (0.2)	66.8 (37.4, 82.3)
	DENV-2	59/4854 (1.2)	5/9663 (<0.1)	95.8 (89.6, 98.3)
	DENV-3	15/4854 (0.3)	8/9663 (<0.1)	74.0 (38.6, 89.0)
	DENV-4	3/4854 (<0.1)	0/9663 (0.0)	100.0 (NE, NE)
	Seronegative	41/1832 (2.2)	17/3714 (0.5)	79.3 (63.5, 88.2)
	DENV-1	14/1832 (0.8)	6/3714 (0.2)	78.4 (43.9, 91.7)
	DENV-2	23/1832 (1.3)	0/3714 (0.0)	100.0 (NE, NE)
	DENV-3	3/1832 (0.2)	11/3714 (0.3)	−87.9 (−573.4, 47.6)
	DENV-4	1/1832 (<0.1)	0/3714 (0.0)	100.00 (NE, NE)



CI, confidence interval; DENV, dengue virus; DHF, dengue hemorrhagic fever; NE, not estimable; VCD, virologically confirmed dengue.
Tricou V *et al. Lancet Global Health* 2024; 12(2): e257–e270.

17

Long-term efficacy and safety of a tetravalent dengue vaccine (TAK-003): 4-5-year results from a phase 3, randomised, double-blind, placebo-controlled trial

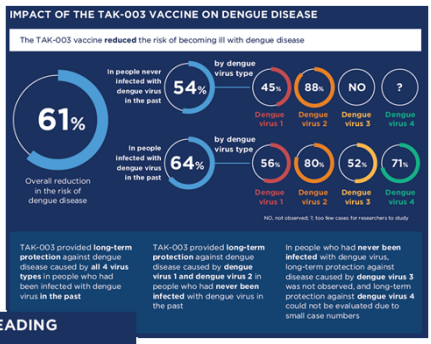
Vianney Tricou*, Delia Yu*, Humberto Reynales, Shibadas Biswal, Xavier Saez-Llorens, Chukiat Sirivichayakul, Pio Lopez, Charissa Borja-Tabora, Lulu Bravo, Pope Kosalaraksa, Luis Martinez Vargas, Maria Theresa Alera, Luis Rivera, Veerachai Watanaveeradej, Reynaldo Dietze, LakKumar Fernando, V Pujitha Wickramasinghe, Edson Duarte Moreira Jr, Asvini D Fernando, Dulanie Gunasekera, Kleber Luz, Ana Lucia Oliveira, Sooly Tuboi, Ian Escudero, Yanee Hutagaglung, Eric Lloyd, Martina Rauscher, Olaf Zent, Nicolas Folschweiller, Inge LeFevre, Felix Espinoza†, Derek Wallace†

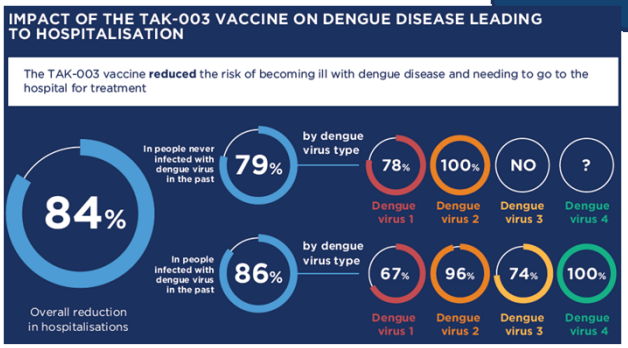
Summary

Background About half of the world's population lives in dengue-endemic areas. We aimed to evaluate the long-term efficacy and safety of two doses of the tetravalent dengue vaccine TAK-003 in preventing symptomatic dengue disease of any severity and due to any dengue virus (DENV) serotypes in children and adolescents.

Lancet Glob Health 2024; 12: e257–70

See Comment page e179





?, is used in the figure, this indicated that there were too few cases for researchers to study.
DENV, dengue virus; NO, not observed.
Tricou V, et al. *Lancet* 2024;12;e257–e270 (plain language summary).

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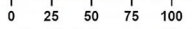
Dengue-Vaccine III

Butantan Dengue Vaccine (TV003)

- Live attenuated DEN1, 3, 4, DEN2 chimera with DEN4 backbone
- Single shot
- Currently in phase 3

Vaccine Efficacy (VE) through 2 years

	Butantan-DV Cases/ Total no.	Placebo Cases/ Total no.	Vaccine Efficacy[b]	(95% CI)
Any Serotype[a]				
Regardless of Serostatus	35/10215	100/5947	79.6%	(70.0, 86.3)
With Prior Exposure	8/4994	45/3023	89.2%	(77.6, 95.6)
Without Prior Exposure	26/4826	55/2690	73.6%	(57.6, 83.7)
DENV-1[c]				
Regardless of Serostatus	9/10215	50/5947	89.5%	(78.7, 95.0)
With Prior Exposure	1/4994	19/3023	96.8%	(81.0, 99.8)
Without Prior Exposure	8/4826	31/2690	85.6%	(69.1, 94.0)
DENV-2[c]				
Regardless of Serostatus	26/10215	50/5947	69.6%	(50.8, 81.5)
With Prior Exposure	7/4994	26/3023	83.7%	(63.1, 93.5)
Without Prior Exposure	18/4826	24/2690	57.9%	(20.8, 78.1)



- There were no cases of DENV-3 or DENV-4 during the first 2 years of follow-up of the study

2-Year Follow up postvaccination for each participant. Per-Protocol population.
[a]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.
[b] Participants with multiple dengue episodes were counted as single case.
[c] 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.

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Dengue-Vaccine IV

NIH Dengue Vaccine (TV005)

- Live attenuated DEN1, 3, 4, DEN2 chimera with DEN4 backbone
- Increased dose of DEN2 chimera (10^4 PFU, as opposed to 10^3 PFU in TV003)
- Single shot
- Currently in phase 2

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.

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The Journal of Clinical Investigation CLINICAL MEDICINE

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

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[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.

BACKGROUND. Disease due to dengue viruses is a growing global health threat, causing 100–400 million cases annually. An ideal dengue vaccine should demonstrate durable protection against all 4 serotypes in phase III efficacy trials, however the lack of circulating serotypes may lead to incomplete efficacy data. Controlled human infection models help downselect vaccine candidates and supply critical data to supplement efficacy trials. We evaluated the efficacy of a leading live-attenuated tetravalent dengue vaccine candidate, TV005, against infection with a newly established dengue serotype 3 or an established serotype 2 challenge virus.

METHODS. Two randomized, controlled clinical trials were performed. In study 1, a total of 42 participants received TV005 or placebo (n = 21 each), and 6 months later, all were challenged with dengue 2 virus (rDEN2Δ30) at a dose of 10^5 PFU. In study 2, a total of 23 participants received TV005 and 20 received placebo, and 6 months later, all were challenged with 10^5 PFU dengue 3 virus (rDEN3Δ30). The study participants were closely monitored for safety, viremia, and immunologic responses. Infection, measured by post-challenge viremia, and the occurrence of rash and neutropenia were the primary endpoints. Secondary endpoints included safety, immunologic, and virologic profiles following vaccination with TV005 and subsequent challenge with the rDEN2Δ30 or rDEN3Δ30 strain.

RESULTS. TV005 was well tolerated and protected all vaccinated volunteers from viremia with DENV2 or DENV3 (none infected in either group). Placebo recipients had post-challenge viremia (100% in study 1, 85% in study 2), and all experienced rash following challenge with either serotype.

CONCLUSIONS. TV005 is a leading tetravalent dengue vaccine candidate that fully protected against infection with DENV2 and DENV3 in an established controlled human infection model.

TRIAL REGISTRATION. ClinicalTrials.gov NCT02317900 and NCT02873260.

FUNDING. Intramural Research Program, NIH (contract HHSN272200900010C).

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Qdenga®: Product Approval, Recommendations in Europe and by WHO

EMA
Authorization for the prevention of dengue fever from the age of 4y

SAGE-WHO
For endemic areas:
The vaccine to be considered for introduction in settings with high dengue disease burden and high transmission intensity to maximize the public health impact and minimize any potential risk in seronegative persons.
The vaccine to be introduced to children aged 6 to 16 years of age. Within this age range, the vaccine should be introduced about 1-2 years prior to the age-specific peak incidence of dengue-related hospitalizations. The vaccine should be administered in a 2-dose schedule with a 3-month interval between doses.
For travellers:

- Persons living in non-endemic countries who have previously been infected may benefit
- Frequent travellers, long-term travellers, migrants, and long-term expatriates have a higher likelihood of previous dengue infection
- The benefits of vaccination with TAK-003 are lower for travellers who have never experienced dengue infection
- Travellers need to be informed that the vaccine may not confer protection against DENV3 and DENV4 if they are seronegative, and that there is a potential risk of severe dengue if seronegative individuals are exposed to DENV3 and DENV4.
- Although pre-vaccination screening to determine serostatus is not required, where available its use could be considered to inform the assessment of risks and benefits.
- Protection starts 14 days after the first dose and has been demonstrated between the first and second dose; hence, the first dose can be given up to 14 days before travel to a dengue-endemic country.
- Until more data become available on efficacy-safety profiles, WHO recommends a lower age limit of 6 years and an upper limit of 60 years for travellers.

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- All travellers are at risk – no specific behaviour or destination
- Rate of asymptomatic cases is unknown
- Rate of complications is unknown, reasons are not clear
- Many cases develop in destination countries and are treated there
- Treatment is largely symptomatic, monoclonals may be game changers
- An effective protection against dengue is important
- Current advice to travelers to dengue endemic regions:
  - Avoid travel (unrealistic)
  - Mosquito bite protection (incomplete)
  - Vaccination (incomplete)
- But: not vaccinating puts travellers at risk of infection!

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Vaccines against Vector-borne Diseases

Chikungunya

23

CHIKV is a single-stranded RNA alphavirus[1]

Phylogenetic analysis has revealed 3 distinct strains[1,2]

- ✓ **West African**
- ✓ **East-Central-South African (ECSA)**
- ✓ **Asian**

- CHIKV is spread by the same mosquitoes that transmit dengue and Zika viruses.
- The symptoms of these diseases are similar, leading to misdiagnosis and delays in treatment in areas where they are common[3]

1. Da Cunha RV, Trinta, KS. Mem Inst Oswaldo Cruz, Rio de Janeiro. 2017;112:523-531.

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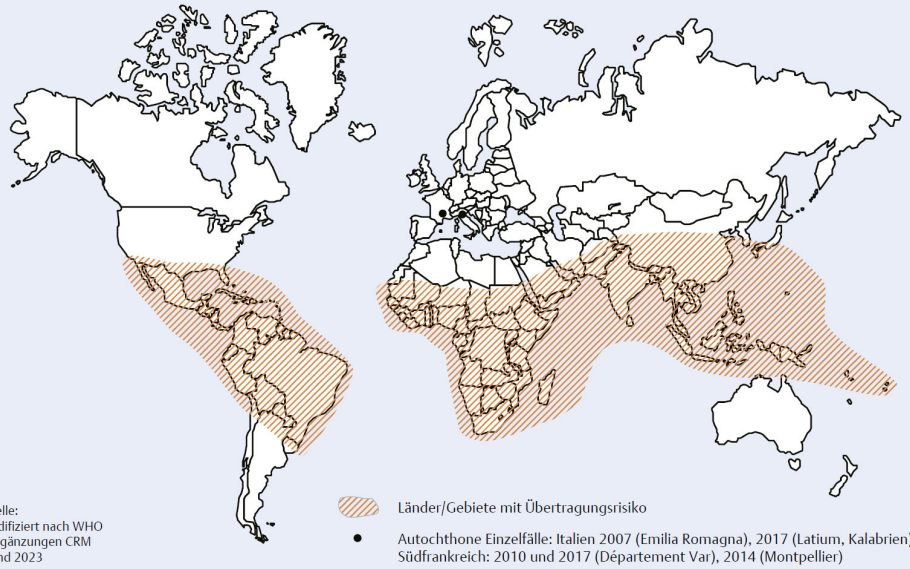
Chikungunya



Quelle:
modifiziert nach WHO
+ Ergänzungen CRM
Stand 2023

Länder/Gebiete mit Übertragungsrisiko

Autochthone Einzelfälle: Italien 2007 (Emilia Romagna), 2017 (Latium, Kalabrien); Südfrankreich: 2010 und 2017 (Département Var), 2014 (Montpellier)

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Chikungunya Disease Process

Acute Phase (up to 97%)[1]	Chronic Phase (4% to 78%)[5,6]
• Symptoms typically begin 3–7 days after being bitten by an infected mosquito[1] • Viremic for 5-10 days[2,3] • Acute symptoms typically resolve in 7–10 days[1] • Sub-acute post-viremic state (6-21 days) can occur[3,4] ➢ Persistent articular symptoms ➢ Tenosynovitis and bursitis	• Pattern similar to Rheumatoid Arthritis ➢ Characterized by peripheral spondylarthritis, undifferentiated arthritis, fibromyalgia, neuropathic chronic pain • Fatigue is other main persistent symptom, can last for months to years[7,8] • Risk factors for developing chronic symptoms:[6,9] ➢ >45 years of age ➢ high viral load during acute phase ➢ severe immunologic response in post-viremic phase

1. Staples et al. CDC Yellow Book 2020, Chapter 4. 2. Rudolph KE, et al. Am J Trop Med Hyg. 2014;90:882-891. 3 Suhrbier A et al. Nat Rev Rheumatol. 2012;8:420-429. 3. Thiberville SD et al. PLoS Negl Trop Dis. 2013; 2014;7:e2004-e2004. 4. Stalkowsky F et al. PLoS one 2009;4:e7603-e7603. 5. Rodríguez-Morales AJ et al . Arthritis Care Res 2016;68:849-58 6. Marti-Carvajal A et al. PLoS One 2017;12:e0179028 7. Manimunda SP, et al. Trans R Soc Trop Med Hyg 2010; 104: 392–99. 8. Soumahoro MK, et al. PLoS One 2009;4:e7800. 9. Zaid A et al. Arthritis Rheumatol 2018;70:484-95

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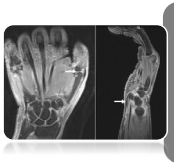
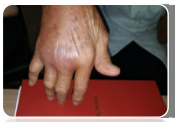
Chikungunya: Rheumatologic Disease

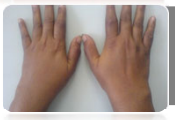
Post-CHIKV Rheumatism - 2 forms -	Effect of Arthritis/Polyarthritis	Impact on Quality of Daily Life
Mechanical musculoskeletal disorders	Long-term joint pain Stiffness after immobility[1,4] Multiple joints affected, ie, spine, shoulder, elbow, wrist, hand, hip, knee, ankles, feet	• Rising from chair • Walking • Picking up objects • Opening a bottle • Self care • Physical impact on leisure time and limitations on activity
Chronic inflammatory arthritis	Can be triggered by change in temperature and physical effort[5] May require surgery	



Carpitis and thumb arthritis (left) – Multiple tenosynovitis of fingers and wrist (right)[1]



2 years after CHIKV infection: Intense arthritis of metacarpophalangeal joints and wrist[3]



Symmetrical inflammatory polyarthritis[2]

1. Simon F., et al. Medicine: 2007;86:123-137. 2. Mohan A, et al. Indian J Dermatol. 2010; 55: 54–63. 3. Amaral J, et al. Viruses. 2019;11:289. 4. Tritsch S. et al. J Rheum. 2020;47:1267-74. 5. Schilte C. et al. PLOS Negl Trop Dis. 2013;7:e2137.

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Chikungunya: Persistent Rheumatologic Disease is Common

Outbreak	Year	Number of Patients	Observation Period	% Patients Affected	Post-Chik Chronic Disorders	Source
Réunion	2005	662	6 months	93.7	Rheumatic symptoms	Queyriaux et al. *Lancet Infect Dis* 2008
Italy	2007	250	12 months	66.5	Myalgia, asthenia or arthralgia	Moro et al. *J Infect* 2012
Réunion	2005	88	18 months	63.6	Persistent arthralgia	Borgherini G et al. *Clin Infect Dis* 2008
Italy	2007	180	36 months	60	Arthralgia	Schilte et al. *PloS Negl Trop Dis* 2013
Réunion	2005	147	15 months	57	Rheumatic symptoms	Sissoko et al. *PLoS Negl Trop Dis* 2009
Kerala, India	2007	1396	15 months	57	Polyarthralgia	Mathew et al. *Int J Clin Pract* 2011
Aruba	2014	248	>6 weeks >12 months	43.8 26.3	Chronic polyarthralgia	Huits et al. *PLOS One* 2018
French Guyana	2014	168	3 months 6 months	40.4 31.3	Rheumatic or musculoskeletal pain	Bonifay et al. *Eur J Clin Microbiol Infect Dis* 2018
South Africa	1975-1977	107	3-5 years	12	Residual joint symptoms such as stiffness, swelling, and pain	Brighton et al. *S Afr Med J* 1983

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Tropical Medicine and Infectious Disease

MDPI

Review

Cardiomyopathy and Death Following Chikungunya Infection: An Increasingly Common Outcome

Elizabeth M. Traverse [1], Hannah K. Hopkins [1], Vedana Vaidhyanathan [2] and Kelli L. Barr [1,*]

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[2] Central Libraries Research Engagements, Baylor University, Waco, TX 76706, USA; Vedana_vaidhyanathan@baylor.edu
* Correspondence: barrk@usf.edu; Tel.: +1-(813)-974-4480

Abstract: Chikungunya virus (CHIKV) is vectored by *Aedes aegypti* and *Aedes albopictus* mosquitoes and is found throughout tropical and sub-tropical regions. While most infections cause mild symptoms such as fever and arthralgia, there have been cases in which cardiac involvement has been reported. In adults, case reports include symptoms ranging from tachycardia and arrythmia, to myocarditis and cardiac arrest. In children, case reports describe symptoms such as arrythmia, myocarditis, and heart failure. Case reports of perinatal and neonatal CHIKV infections have also described cardiovascular compromise, including myocardial hypertrophy, ventricular dysfunction, myocarditis, and death. Myocarditis refers to inflammation of the heart tissue, which can be caused by viral infection, thus becoming viral myocarditis. Since viral myocarditis is linked as a causative factor of other cardiomyopathies, including dilated cardiomyopathy, in which the heart muscle weakens and fails to pump blood properly, the connection between CHIKV and the heart is concerning. We searched Pubmed, Embase, LILACS, and Google Scholar to identify case reports of CHIKV infections where cardiac symptoms were reported. We utilized NCBI Virus and NCBI Nucleotide to explore the lineage/evolution of strains associated with these outbreaks. Statistical analysis was performed to identify which clinical features were associated with death. Phylogenetic analysis determined that CHIKV infections with cardiac symptoms are associated with the Asian, the East Central South African, and the Indian Ocean lineages. Of patients admitted to hospital, death rates ranged from 26–48%. Myocarditis, hypertension, pre-existing conditions, and the development of heart failure were significantly correlated with death. As such, clinicians should be aware in their treatment and follow-up of patients.

Keywords: CHIKV; chikungunya; myocarditis; cardiomyopathy; cardiovascular

Citation: Traverse, E.M.; Hopkins, H.K.; Vaidhyanathan, V.; Barr, K.L. Cardiomyopathy and Death Following Chikungunya Infection: An Increasingly Common Outcome. *Trop. Med. Infect. Dis.* **2021**, *6*, 108. https://doi.org/10.3390/tropicalmed6030108

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Risk of death following chikungunya virus disease in the 100 Million Brazilian Cohort, 2015–18: a matched cohort study and self-controlled case series

Thiago Cerqueira-Silva, Julia M Pescarini, Luciana L Cardim, Clémence Leyrat, Heather Whitaker, Carlos Alexandre Antunes de Brito, Elizabeth B Brickley, Manoel Barral-Netto, Mauricio L Barreto, Maria G Teixeira, Viviane S Boaventura, Enny S Paixão

Summary

Background Chikungunya virus outbreaks have been associated with excess deaths at the ecological level. Previous studies have assessed the risk factors for severe versus mild chikungunya virus disease. However, the risk of death following chikungunya virus disease compared with the risk of death in individuals without the disease remains unexplored. We aimed to investigate the risk of death in the 2 years following chikungunya virus disease.

Methods We used a population-based cohort study and a self-controlled case series to estimate mortality risks associated with chikungunya virus disease between Jan 1, 2015, and Dec 31, 2018, in Brazil. The dataset was created by linking national databases for social programmes, notifiable diseases, and mortality. For the matched cohort design, individuals with chikungunya virus disease recorded between Jan 1, 2015, and Dec 31, 2018, were considered as exposed and those who were arbovirus disease-free and alive during the study period were considered as unexposed. For the self-controlled case series, we included all deaths from individuals with a chikungunya virus disease record, and each individual acted as their own control according to different study periods relative to the date of disease. The primary outcome was all-cause natural mortality up to 728 days after onset of chikungunya virus disease symptoms, and secondary outcomes were cause-specific deaths, including ischaemic heart diseases, diabetes, and cerebrovascular diseases.

Findings In the matched cohort study, we included 143 787 individuals with chikungunya virus disease who were matched, at the day of symptom onset, to unexposed individuals using sociodemographic factors. The incidence rate ratio (IRR) of death within 7 days of chikungunya symptom onset was 8·40 (95% CI 4·83–20·09) as compared with the unexposed group and decreased to 2·26 (1·50–3·77) at 57–84 days and 1·05 (0·82–1·35) at 85–168 days, with IRR close to 1 and wide CI in the subsequent periods. For the secondary outcomes, the IRR of deaths within 28 days after disease onset were: 1·80 (0·58–7·40) for cerebrovascular diseases, 3·75 (1·33–17·00) for diabetes, and 1·67 (1·25–14·09) for ischaemic heart disease, and there was no evidence of increased risk in the subsequent periods. For the self-controlled case series study, 1933 individuals died after having had chikungunya virus disease and were included in the analysis. The IRR of all-cause natural death within 7 days of symptom onset of chikungunya virus disease was 8·75 (7·18–10·66) and decreased to 1·59 (1·26–2·00) at 57–84 days and 1·09 (0·92–1·29) at 85–168 days. For the secondary outcomes, the IRRs of deaths within 28 days after disease onset were: 2·73 (1·50–4·96) for cerebrovascular diseases, 8·43 (5·00–14·21) for diabetes, and 2·38 (1·33–4·26) for ischaemic heart disease, and there was no evidence of increased risk at 85–168 days.

Interpretation Chikungunya virus disease is associated with an increased risk of death for up to 84 days after symptom onset, including deaths from cerebrovascular diseases, ischaemic heart diseases, and diabetes. This study highlights the need for equitable access to approved vaccines and effective anti-chikungunya virus therapeutics and reinforces the importance of robust vector-control efforts to reduce viral transmission.

Lancet Infect Dis 2024
Published Online February 9, 2024
https://doi.org/10.1016/S1473-3099(23)00739-9
See Online/Comment https://doi.org/10.1016/S1473-3099(24)00078-8

For the Portuguese translation of the abstract see Online for appendix 1

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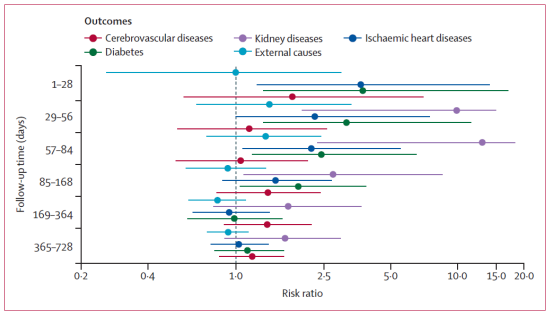

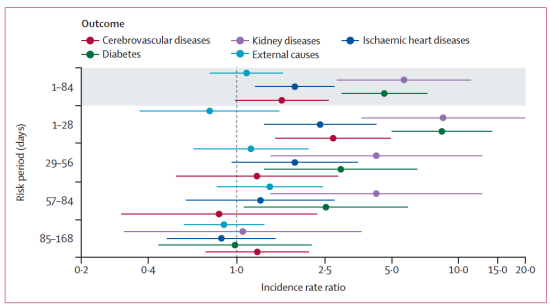

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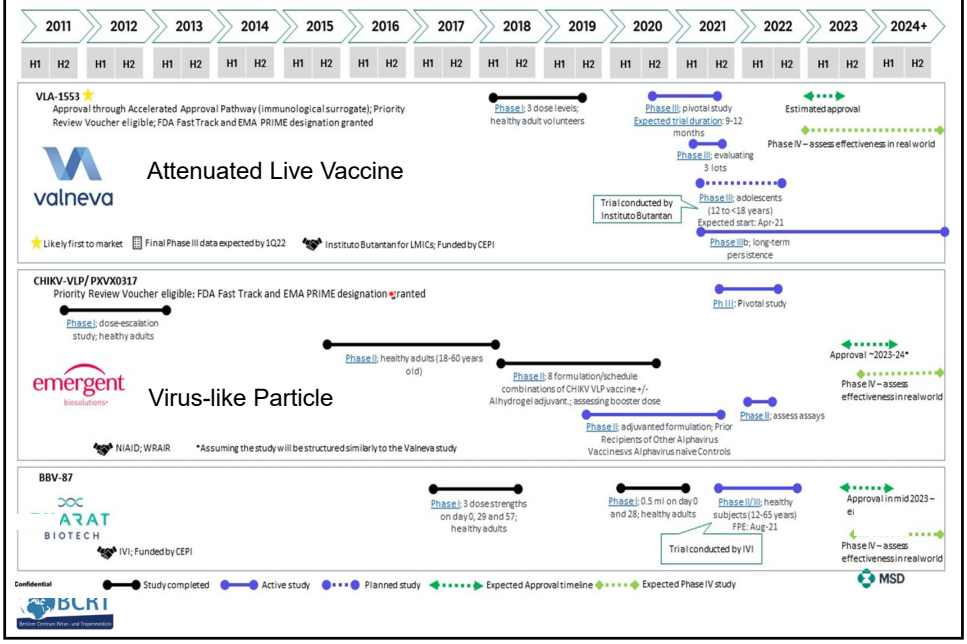
Chikungunya Pipeline



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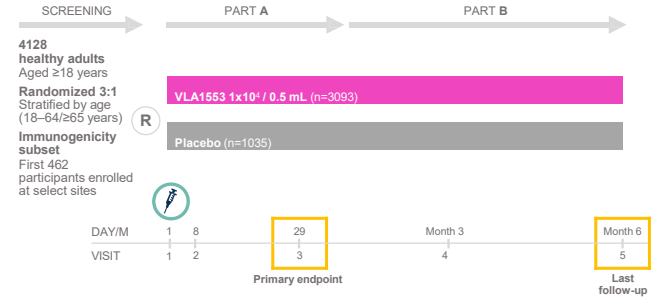
Phase 3 trial: A pivotal, multicenter, randomized, placebo-controlled trial (VLA1553-301)[1,2]

STUDY DESIGN



Primary immunogenicity endpoint:

- Proportion of participants achieving seroresponse (CHIKV-specific neutralizing antibody titers of $\mu PRNT_{50}$ ≥150) at 28 days post vaccination
  - FDA agreed upon non-acceptance threshold of 70%

Secondary immunogenicity endpoints:

- Immune response as measured by CHIKV-specific neutralizing antibody titers, determined by µPRNT assay
- Proportion of participants with a seroresponse*/seroconversion

Secondary safety endpoints:

- Frequency and severity of unsolicited AEs within 28 days post vaccination
- Frequency and severity of solicited injection-site and systemic reactions within 10 days post vaccination
- Frequency, severity and relatedness of any AE or serious AE during the entire study period

*Defined as a 50% plaque reduction in a µPRNT.

AE = adverse event; CHIKV = chikungunya virus; FDA = Food and Drug Administration; µPRNT = micro plaque reduction neutralization test; M = month; R = randomization.

1. Schneider M, et al. Lancet. 2023;401(10394):2138-2147. 2. ClinicalTrials.gov NCT04546724. Available at: https://clinicaltrials.gov/ct2/show/ NCT04546724. Accessed: October 2023.

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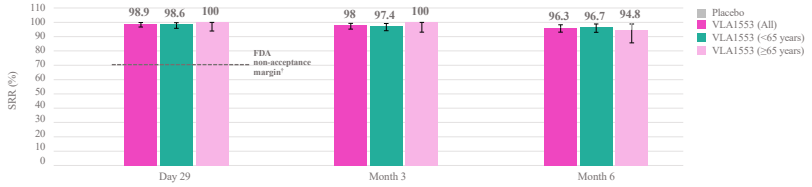
The pivotal trial of vaccine candidate VLA1553 met its primary endpoint[1]

- VLA1553 induced a seroresponse* in **98.9% of participants after 1 month**, exceeding the FDA threshold[†1]
- High SRR of **96.3% was maintained at 6 months**[1]
- Seroresponse was **unaffected by age** (98.6% in participants aged <65 years and 100% in ≥65 years at Day 29)[1]

SRR in baseline seronegative subjects (per-protocol population)[1,2]



*Defined as CHIKV neutralizing antibody titer ≥150 by $\mu PRNT_{50}$. †The lower bound of the 95% CI for the SRR at Day 29 in the VLA1553 group needed to exceed 70% neutralizing antibody titers determined using $\mu PRNT_{50}$ assay.
CHIKV = chikungunya virus; CI = confidence interval; FDA = Food and Drug Administration; $\mu PRNT_{50}$ = 50% micro plaque reduction neutralization test; SRR = seroresponse rate.
1. Schneider M, et al. Lancet. 2023;401(10394):2138-2147. 2. VALNEVA Data on file (unpublished data).

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Safety and immunogenicity of a single-shot live-attenuated chikungunya vaccine: a double-blind, multicentre, randomised, placebo-controlled, phase 3 trial

Martina Schneider, Marivic Narciso-Abraham, Sandra Hadl, Robert McMahon, Sebastian Toepfer, Ulrike Fuchs, Romana Hochreiter, Annegret Bitzer, Karin Kosulin, Julian Larcher-Senn, Robert Mader, Katrin Dubischar, Oliver Zoihsl, Juan-Carlos Jaramillo, Susanne Eder-Lingelbach, Vera Buerger, Nina Wressnigg

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See Comment page 2090

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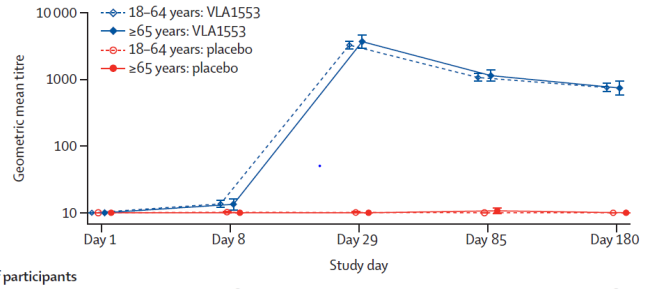
Correspondence to: Dr Martina Schneider, Valneva Austria, 1030 Vienna, Austria martina.schneider@valneva.com

Summary

Background VLA1553 is a live-attenuated vaccine candidate for active immunisation and prevention of disease caused by chikungunya virus. We report safety and immunogenicity data up to day 180 after vaccination with VLA1553.

Methods This double-blind, multicentre, randomised, phase 3 trial was done in 43 professional vaccine trial sites in the USA. Eligible participants were healthy volunteers aged 18 years and older. Patients were excluded if they had history of chikungunya virus infection or immune-mediated or chronic arthritis or arthralgia, known or suspected



Number of participants					
18–64 years: VLA1553	207	198	207	194	184
18–64 years: placebo	73	70	73	69	68
≥65 years: VLA1553	59	53	59	52	58
≥65 years: placebo	23	23	23	22	23

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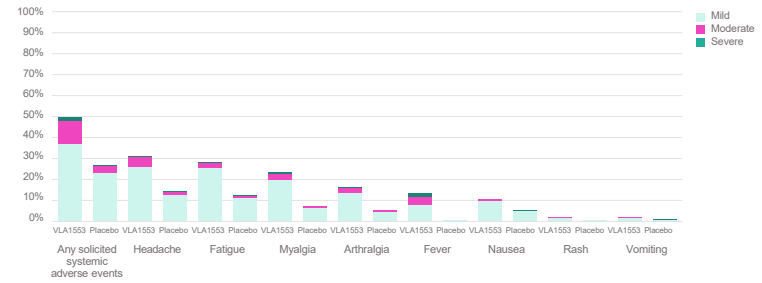
Vaccine candidate VLA1553 was generally well tolerated across all age groups, with most AEs classified as mild/moderate[1]

Solicited systemic adverse events by maximum severity*[1]



*Safety and tolerability of the vaccine were assessed in the safety population. Participant eDiaries were used for the collection of daily oral body temperature, solicited injection-site and systemic adverse events up to 10 days post vaccination. Participants with solicited AEs after vaccination with VLA1553, and placebo by maximum severity.

AE = adverse event.

1. Schneider M, et al. Lancet. 2023;401(10394):2138-2147.

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Phase 3 safety, immunogenicity, and lot-consistency study of CHIKV VLP in healthy adults and adolescents[1]

Randomized, placebo-controlled, double-blind, parallel-group design with four treatment groups

Participants were randomized in a 2:2:2:1 ratio within each age stratum (12 to <18, 18 to <46, and 46 to <65 years) to receive one of three consecutively manufactured lots of adjuvanted CHIKV VLP vaccine (40 µg of CHIKV VLP plus 300 µg aluminium hydroxide adjuvant) or placebo as follows:

Dose groups[2]:

Group 1: CHIKV VLP lot 104 (n=919)

Group 2: CHIKV VLP lot 105 (n=948)

Group 3: CHIKV VLP lot 106 (n=927)

Group 4: Placebo: n=464

Study population
Healthy adolescent and adult participants 12 to <65 years of age

Study centers
Multicenter study
47 sites in the US

Number of participants
3258

Study duration
6 months (183 days)

CHIKV, chikungunya virus; VLP, virus-like particle; n, number of participants.

1. NCT05072080. ClinicalTrials.gov. 2. A nested lot consistency sub study was performed in adult participants 18 to <46 years of age in the CHIKV VLP treatment groups (groups 1-3).

Data presented at ESCMID Global 2024, data not yet published in a peer-reviewed article

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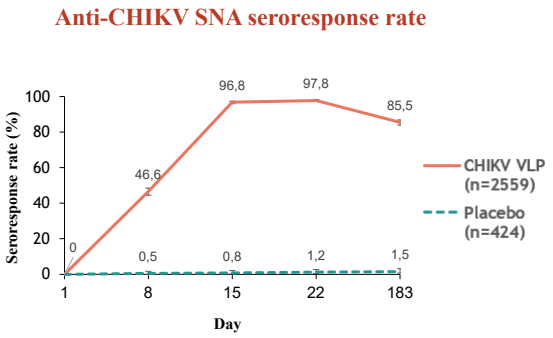
Anti-CHIKV sero-response rate over time (immunogenicity evaluable population)



Note: Values below lower limit of quantitation (LLOQ=15) are assigned the value LLOQ/2=7.5.

CHIKV, chikungunya virus; CI, confidence interval; GMT, geometric mean titer; IEP, immunogenicity-evaluable population; SNA, serum neutralizing antibody; VLP, virus-like particle. Seroresponse rate (considered the presumptive seroprotection rate) was defined as the percentage of participants who achieve a CHIKV-luc neutralization titer (NT_{80}) ≥100. Values below lower limit of quantitation (LLOQ=15) are assigned the value LLOQ/2=7.5."

Data presented at ESCMID Global 2024, data not yet published in a peer-reviewed article

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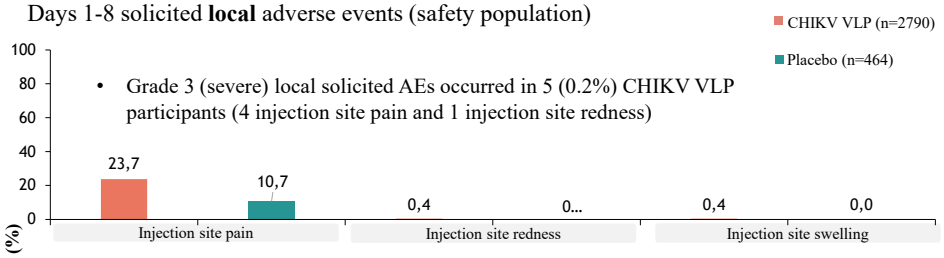
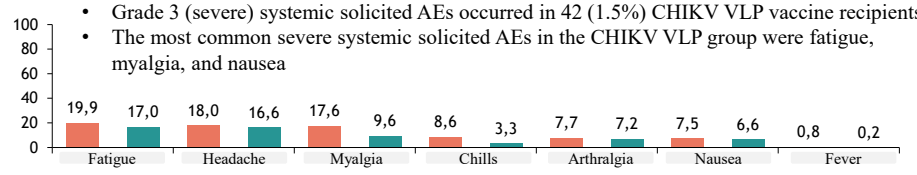
CHIKV VLP vaccine solicited adverse events in adolescents and adults 12-<65

Days 1-8 solicited **local** adverse events (safety population)



- Grade 3 (severe) local solicited AEs occurred in 5 (0.2%) CHIKV VLP participants (4 injection site pain and 1 injection site redness)

Days 1-8 solicited **systemic** adverse events (safety population)



- Grade 3 (severe) systemic solicited AEs occurred in 42 (1.5%) CHIKV VLP vaccine recipients
- The most common severe systemic solicited AEs in the CHIKV VLP group were fatigue, myalgia, and nausea

AE, adverse event; CHIKV, chikungunya virus; VLP, virus-like particle.

Data presented at ESCMID Global 2024, data not yet published in a peer-reviewed article

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Approval of VLA1553 (Ixchiq®) in the USA

FDA NEWS RELEASE

FDA Approves First Vaccine to Prevent Disease Caused by Chikungunya Virus

For Immediate Release:

November 09, 2023

Español (https://www.fda.gov/news-events/press-announcements/la-fda-aprueba-la-primera-vacuna-para-prevenir-la-enfermedad-causada-por-el-virus-del-chikungunya)

Today, the U.S. Food and Drug Administration approved Ixchiq, the first chikungunya vaccine. Ixchiq is approved for individuals 18 years of age and older who are at increased risk of exposure to chikungunya virus.

The chikungunya virus is primarily transmitted to people through the bite of an infected mosquito. Chikungunya is an emerging global health threat with at least 5 million cases of chikungunya virus infection reported during the past 15 years. The highest risk of infection is in tropical and subtropical regions of Africa, Southeast Asia, and parts of the Americas where chikungunya virus-carrying mosquitos are endemic. However, chikungunya virus has spread to new geographical areas causing a rise in global prevalence of the disease.

The most common symptoms of chikungunya include fever and joint pain. Other symptoms may include a rash, headache, and muscle pain. Some individuals may experience debilitating joint pain that persists for months or even years. Treatment includes rest, fluids, and over-the-counter medications for pain and fever.

"Infection with chikungunya virus can lead to severe disease and prolonged health problems, particularly for older adults and individuals with underlying medical conditions," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "Today's approval addresses an unmet medical need and is an important advancement in the prevention of a potentially debilitating disease with limited treatment options."

Ixchiq is administered as a single dose by injection into the muscle. It contains a live, weakened version of the chikungunya virus and may cause symptoms in the vaccine recipient similar to those experienced by people who have chikungunya disease.

The safety of Ixchiq was evaluated in two clinical studies conducted in North America in which about 3,500 participants 18 years of age and older received a dose of the vaccine with one study including about 1,000 participants who received a placebo. The most commonly reported side effects by vaccine recipients were headache, fatigue, muscle pain, joint pain, fever, nausea and tenderness at the injection site.

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Chikungunya Vaccination for U.S. Travelers Decision Tree

Healthcare provider should assess a traveler's risk for chikungunya virus infection based on planned itinerary:

1. All travelers to countries at risk for chikungunya should take precautions to avoid mosquito bites.
2. For some travelers aged ≥18 years with higher risk itineraries, chikungunya vaccine might be indicated.

Traveling to a country or territory where there is a chikungunya outbreak[1]?

- **Yes** → **Chikungunya vaccine RECOMMENDED.**
- **No** → **Traveling to a country or territory without an outbreak but with evidence of chikungunya virus transmission among humans within the last 3 years[1] and in one of these groups?**
  1. Aged >65 years, particularly those with underlying medical conditions, who are likely to have at least moderate exposure[2] to mosquitoes? OR
  2. Staying for a cumulative period of 6 months or more?

  → **Yes** → **Chikungunya vaccine MAY BE CONSIDERED.**

[1]CDC posts information on countries and territories with outbreaks or evidence of chikungunya virus transmission among humans during the last 5 years at https://www.cdc.gov/chikungunya/geo/index.html.

[2]Moderate exposure could include travelers who might have at least 2 weeks (cumulative) of exposure to mosquitoes in indoor or outdoor settings. It does not include travelers who might have limited exposure to mosquitoes (e.g., business travelers likely to be mainly in mosquito-protected indoor settings).

Made available by CDC on May 15, 2024.

Factors to assess when considering use of chikungunya vaccine

Assess likelihood of exposure to chikungunya virus

Evaluate level of disease activity at destination

- Is there an *outbreak*? Is there evidence of *recent chikungunya virus transmission*?

Assess duration of travel or residence and likelihood of future travel to areas with transmission

- Longer duration travel increases the likelihood a traveler might be exposed to an infected mosquito or future outbreak
- Current and future travel plans should be considered as this will impact cumulative infection risk

Discuss likelihood of exposure to *Aedes* species mosquitoes and of adherence to prevention measures

- *Aedes* species mosquito mostly bite during the day, can bite indoors and outdoors, and are most numerous in urban areas
- Traveler willingness to use preventive measures (e.g., mosquito repellent, protective clothing) will influence risk
- Risk will be lower for travelers mainly in mosquito-protected indoor settings (e.g., buildings with air conditioning or window screens)

Assess risk factors for severe disease outcomes

Consider age of traveler

- Adults aged >65 years, infants aged <1 year, and neonates have a higher risk for rare but severe disease presentations
- Older age (e.g., >65 years) is a risk factor for long-term arthralgia after infection

Review underlying medical conditions of traveler

- Certain medical conditions (e.g., diabetes, cardiac disease, hypertension) increase the risk for severe disease
- Pre-existing joint problems are a risk factor for long-term arthralgia after infection

Assess traveler preferences

Explore individual's personal values

- Travelers likely have differing risk tolerance for the possibility of acquiring chikungunya or the possibility of an adverse event after vaccination

CS 348783-A May 10, 2024 11:33 AM

https://www.cdc.gov/chikungunya/hcp/vaccine/index.html

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Vaccines against Vector-borne Diseases

Zika

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Zika-Virus

- ✓ Flavivirus
- ✓ First isolated in 1947 from a rhesus monkey at a research station in the Zika Forest in Entebbe/Uganda
- ✓ Occurs naturally in tropical Africa
- ✓ Transmitted by mosquitoes of the genus Aedes, especially Ae. Aegypti
- ✓ In 2009, human infection with Zika virus was reported for the first time outside Africa and Asia, namely on the Yap Islands of Micronesia
- ✓ The largest outbreak up to date occurred in 2016 in Latin America
- ✓ Symptoms: skin rash, fever, joint pain, conjunctivitis and, more rarely, muscle pain, headaches, vomiting
- ✓ The skin rash lasts an average of six days, other symptoms disappear earlier.
- ✓ Guillain-Barré-Syndrome may occur as complication
- ✓ Viremia during pregnancy leads to viral neurotropy in newborn: brain damage and microcephaly
- ✓ Zika can be transmitted by sex

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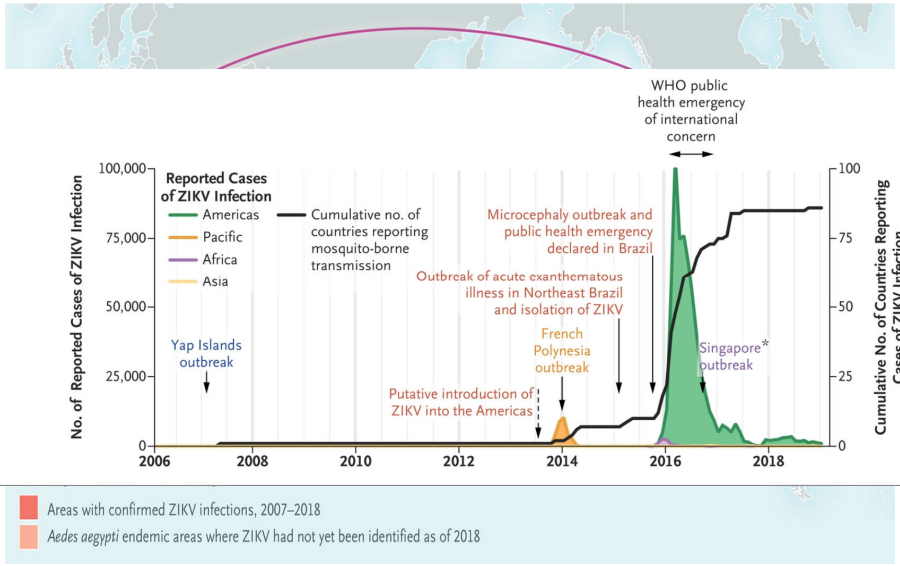
Global Spread of Zika-Virus



Musso D et al. Zika Virus Infection - After the Pandemic. N Engl J Med 2019 Oct 10;381:1444-1457

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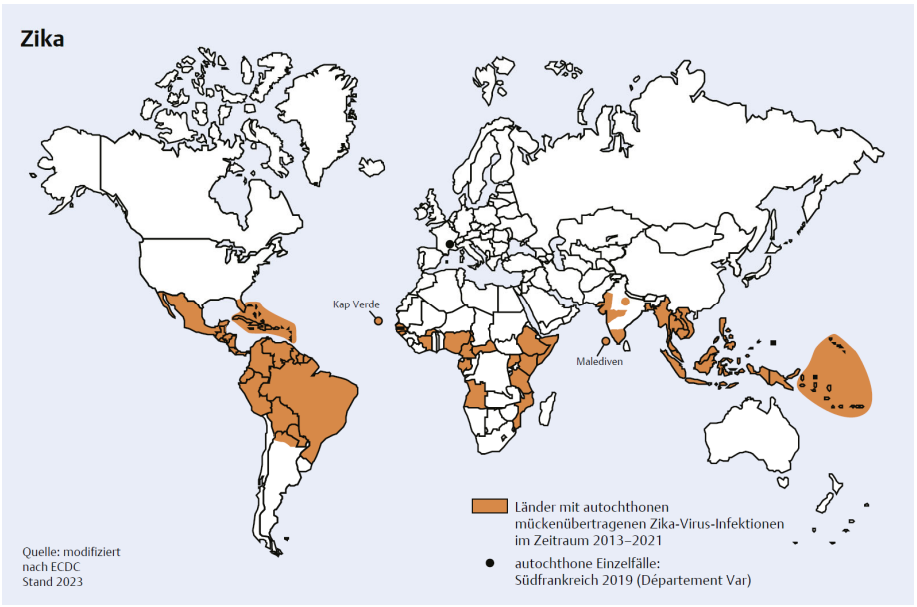

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Clinical features of dengue, Zika and chikungunya viral infection

Features	Zika	Dengue	Chikungunya
Fever[1]	++	+++	+++
Rash[1]	+++	++	++
Joint pain[1]	++	+	+++
Conjunctivitis[1]	++	-	-
Muscle pain[1]	+	+++	+
Headache[1]	+	++	++
Hemorrhage	Rare	++	Rare[2]
Shock[1]	-	+	-
Guillain-Barré syndrome	Rare[3]	Very rare[4]	Very rare[5]
Neurological infection	Rare	+	+
Case fatality rate	Very rare[6] (Except fetal loss)	<1%[7]	0.1%[8]

1. Rabe, *et al.* Zika Virus – What Clinicians Need to Know? Clinical Outreach and Communication Activity (COCA) Call, January 2016, Atlanta, GA
2. World Health Organization. Guidelines for Prevention & Control of Chikunyunga Fever. 2009
3. Gold, *et al. Jama Neurol* 2016;73:905–6
4. Fragoso, *et al. Arq Neuropsiquiatr* 2016;74:1039–40
5. Villamil-Gómez, *et al. Enferm Infecc Microbiol Clin* 2016;34:140–1
6. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=38229&lang=en Accessed 25/10/2017
7. Shepherd. Dengue, Prognosis. Updated 2017. Available at: https://emedicine.medscape.com/article/215840-overview#a6 Accessed 02/11/2017
8. Mavalankar, *et al. Emerg Infect Dis* 2008;14:412–15

Source: ECDC

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Zika Vaccine Candidates in Clinical Trials

Vaccine type	Vaccine name	Antigen	Phase	Developer(s)	Adjuvant
Inactivated vaccines	ZPIV	Whole virus	I	NIAID/WRAIR/BIDMC	Alum
	PIZV/TAK-426	Whole virus	I	Takeda Pharmaceuticals	Alum
	VLA1601	Whole virus	I	Valneva Austria GmbH	Alum
	BBV121	Whole virus	I	Bharat Biotech International	Alum
DNA vaccines	VRC5288	prM/E	I	NIAID, VRC	None
	VRC5283	prM/E	II	NIAID,VRC	None
	GLS-5700	prM/E	I	GeneOne Life Science/Inovio Pharmaceuticals	None
Live-attenuated vaccine	rZIKV/D4Δ30–713	rZIKV/D4Δ30–713	I	NIAID	None
mRNA vaccines	mRNA 1325	prM/E	II	Moderna Therapeutics	None
	mRNA 1893	prM/E	II		None
Viral vectored vaccines	MV-ZIKA-RSP	prM/E	I	Themis Bioscience GmbH	None
	MV-ZIKA	prM/E	I	Themis Bioscience GmbH	None
	ChAdOx1 ZIKA	CprME/NS	I	University of Oxford	None
	Ad26.ZIKV.001	ZIKV M-Env	I	Janssen Vaccines and Prevention B.V.	None

Abbreviations: ZPIV, ZIKV purified inactivated vaccine. PIZV, purified inactivated Zika virus vaccine. VRC, Vaccine Research Center. prM, premembrane. E, envelope. WRAIR, Walter Reed Army Institute of Research. NIAID, National Institute of Allergy and Infectious Diseases (USA). BIDMC, Beth Israel Deaconess Medical Center. ChAdOx1, Chimpanzee adenovirus Oxford 1. MV, measles virus vaccine.

Peng ZY et al. A review on Zika vaccine development. Pathgens and Disease. 2024:82;ftad036

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Potential Advantages and Disadvantages of Various Zika Vaccine Candidates

Vaccine type	Advantages	Disadvantages	Principle of generation
Inactivated vaccines	High safety for immunosuppressed people. Better stability for storage.	Low immunogenicity Need adjuvants or multiple doses to enhance immunity.	Composed of viral particles along with other pathogens that were cultured.
Live-attenuated vaccines	Persistent immune response without adjuvants or multiple doses.	Not recommended for immunosuppressed people or gravidas because of potential hazards.	Reduce the virulence of a pathogen while maintaining its activity.
DNA vaccines	Better stability for storage. Better perform vaccine design by adding or deleting.	Low immunogenicity. Low therapeutic efficacy due to the degradation of DNA.	An antigen from a pathogen is cloned and inserted into the DNA plasmid.
mRNA vaccines	Provide a better safety profile because of less insertional mutations.	Low-temperature storage owing to instability. Need to boost immunization.	Synthesized with the virtually desired sequence.
Viral vectored vaccines	Induce stronger immune responses.	Not recommended for immunocompromised persons or gravidas.	Insert genes encoding the proteins of pathogenic microorganisms into the vector.

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Peng ZY et al. A review on Zika vaccine development. Pathgens and Disease. 2024:82;ftad036

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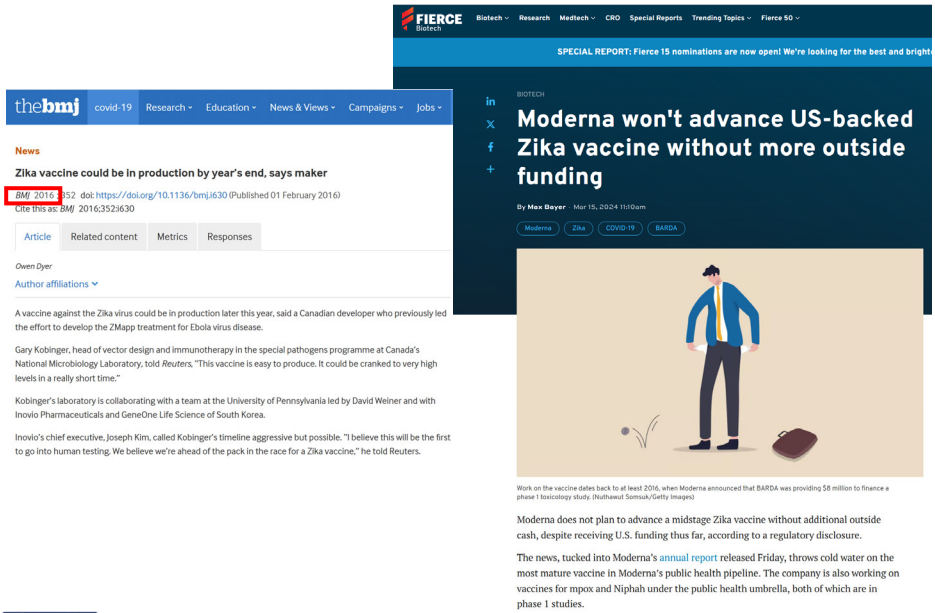

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