DENGUE E CHIKUNGUNYA: PROSPETTIVE VACCINALI

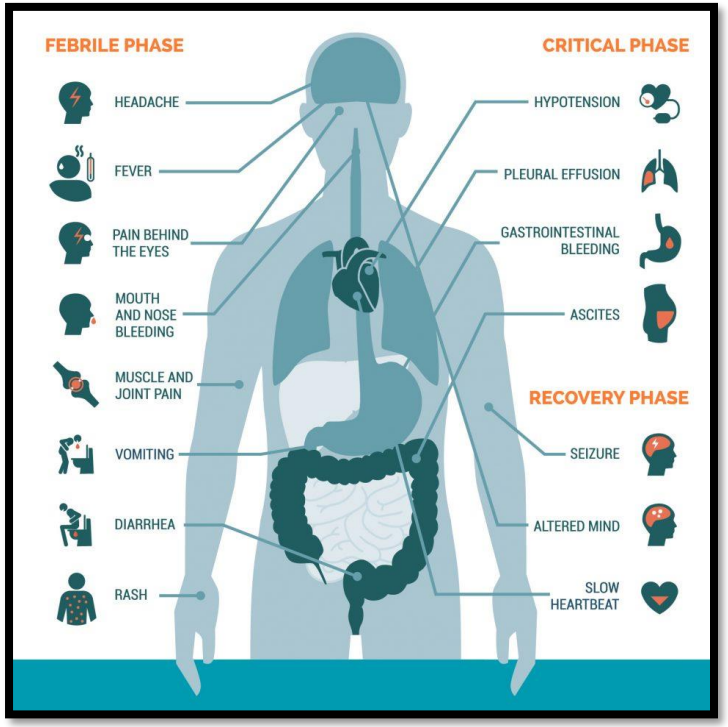
Lorenzo Zammarchi

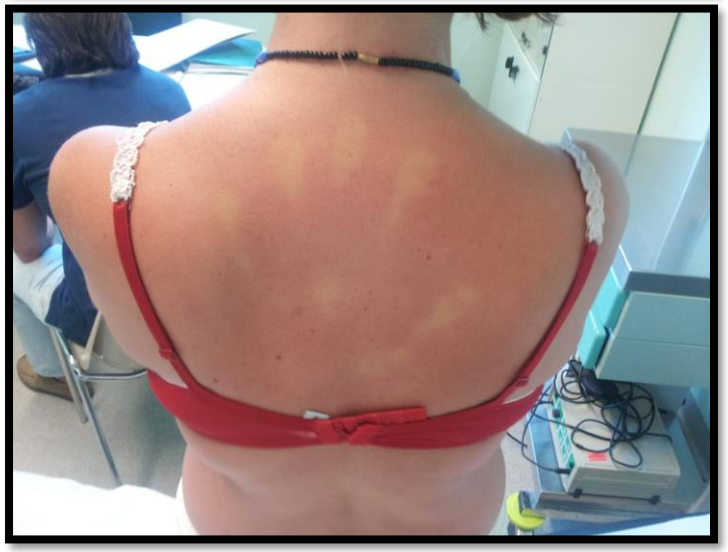
Dengue – Chikungunya

- Clinical features
- Virological and immunological aspects
- Epidemiology
- Vaccines approved / advanced

Dengue- clinical features

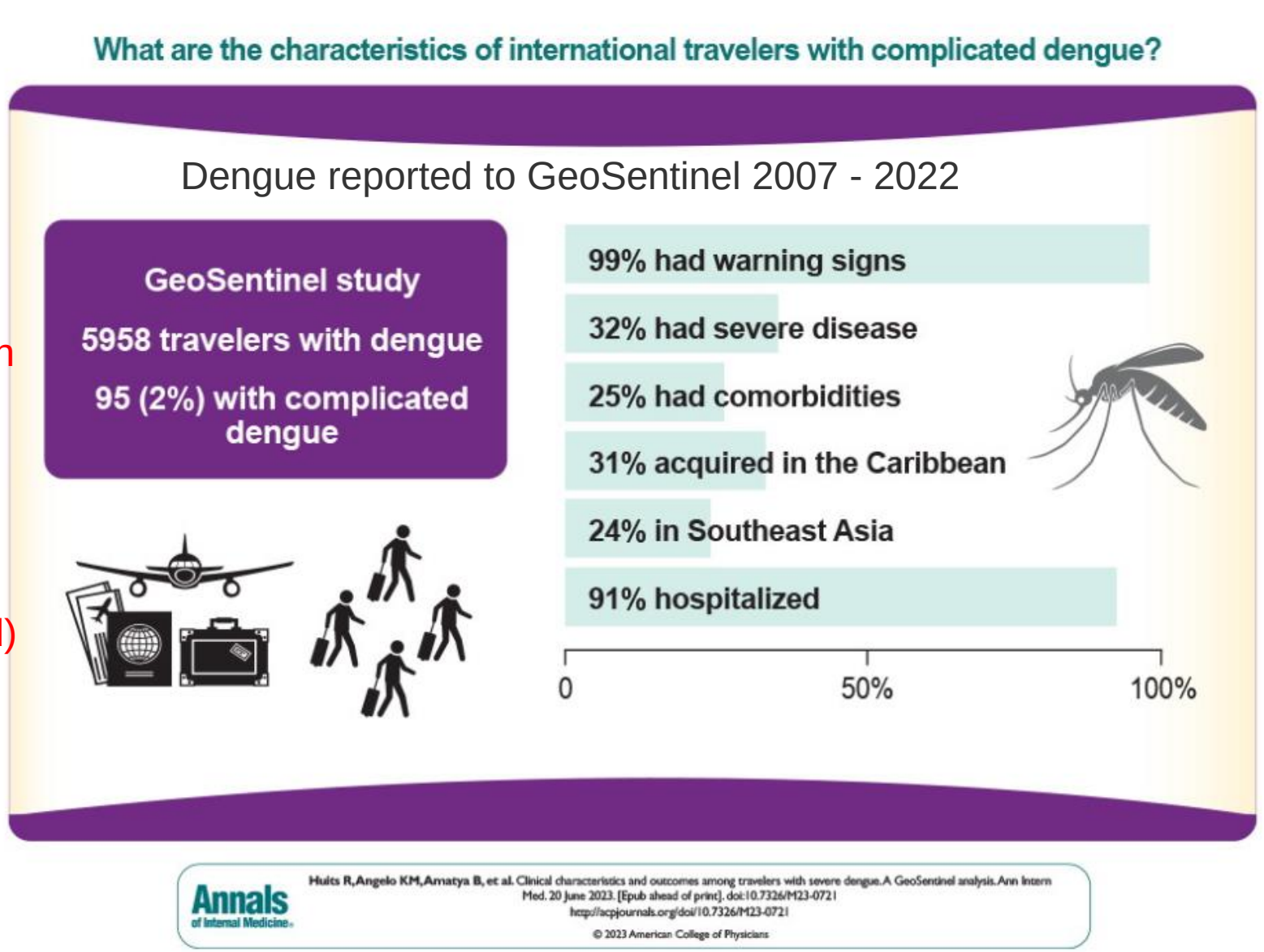
- Symptomatic infection 20%
- Febrile diseases with possibile complications:
  - Shock
  - Bleeding
  - Severe organ involvement (liver, CNS, hearth)
  - Severe perinatal infection
- Erythematous rash, leukopenia (neutropenia), thrombocytopenia, incresed transaminases, normal CRP
- Severe cases: 0.16% overall, up to 4%
- Case fatality rate: 0.046%, up to 0.35%
- Treatment is supportive





PAHO. Epidemiological Update for Dengue, Chikungunya and Zika in 2022. Updated: Jun 25 2023 1:00AM

- Median age 34 years
- 10-12% of cases in children <18y
- 48 (56%) female
- 32 (73%) primary infection
- 12 (27%) secondary infection
- 1 death (no dengue related)



ACCEPTED MANUSCRIPT

Atypical imported severe primary dengue presenting with neutrophilic leukocytosis and cardiac tamponade in a young female traveler

Iacopo Vellere, MD, Nicoletta Di Lauria, MD, Antonia Mantella, MbiolSci, Annalisa Cavallo, MD, Silvia Bresci, MD, Alessandro Bartoloni, MD, Lorenzo Zammarchi, MD

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Infection (2012) 40:441–443
DOI 10.1007/s15010-011-0208-3

CASE REPORT

Fatal dengue hemorrhagic fever imported into Germany

J. Schmidt-Chanasit · K. Tenner-Racz · D. Poppert · P. Emmerich · C. Frank · C. Dinges · R. Penning · A. Nerlich · P. Racz · S. Günther

Journal of Travel Medicine
International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide

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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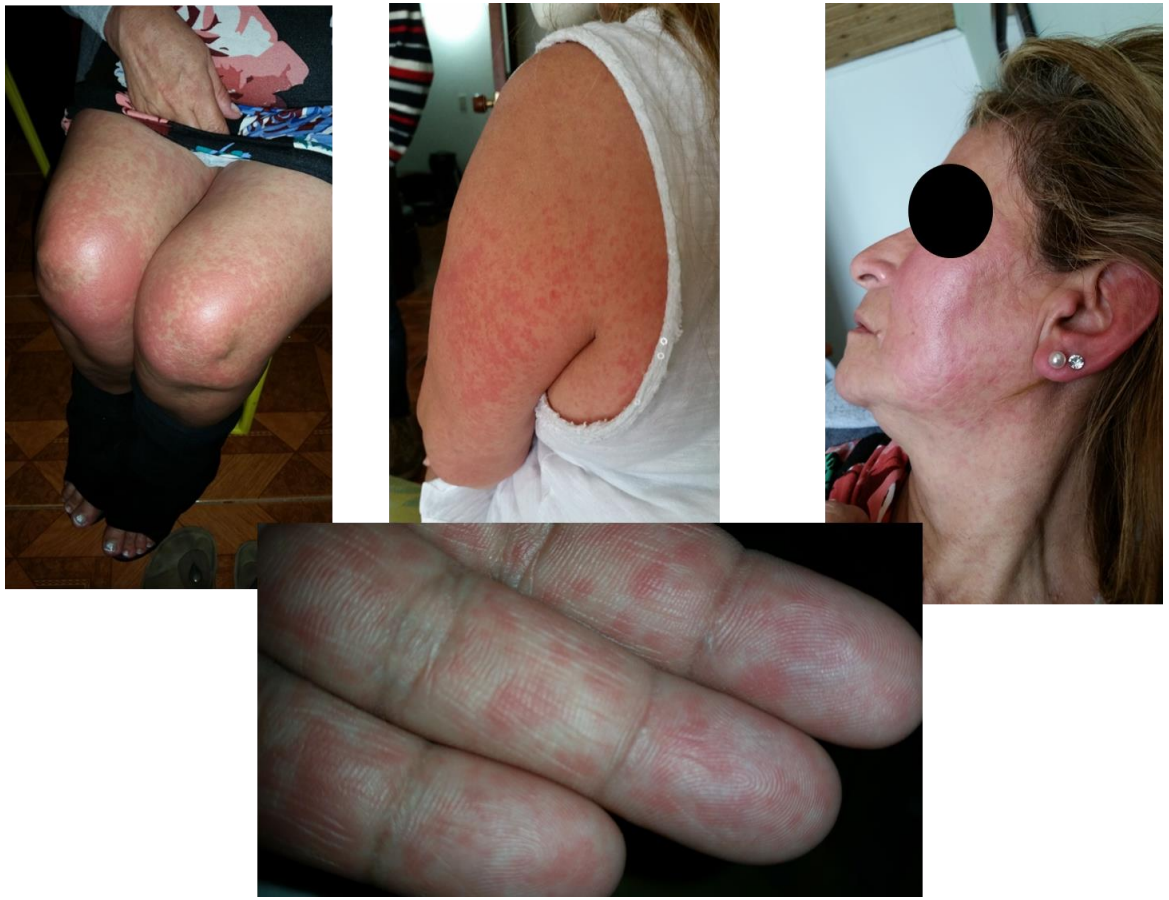
9 fatalities in travelers, 8 female, 7 with primary infection *[Huits R et al JTM 2021]*

Chikungunya- clinical features

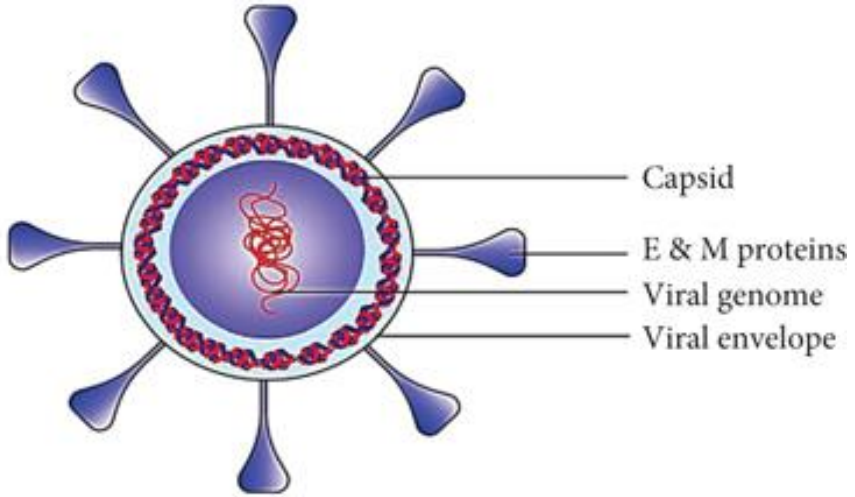
- Symptomatic infection 70%
- Febrile diseases with possibile complications:
  - Frequent debilitating long term arhtralgia/arthritis (up to 66% after 12 months)
  - Severe cases in extreme age groups
- Maculo-papular rash, slight increse of CRP
- Case fatality rate: 0.032%
- Treatment is supportive / symptomatic

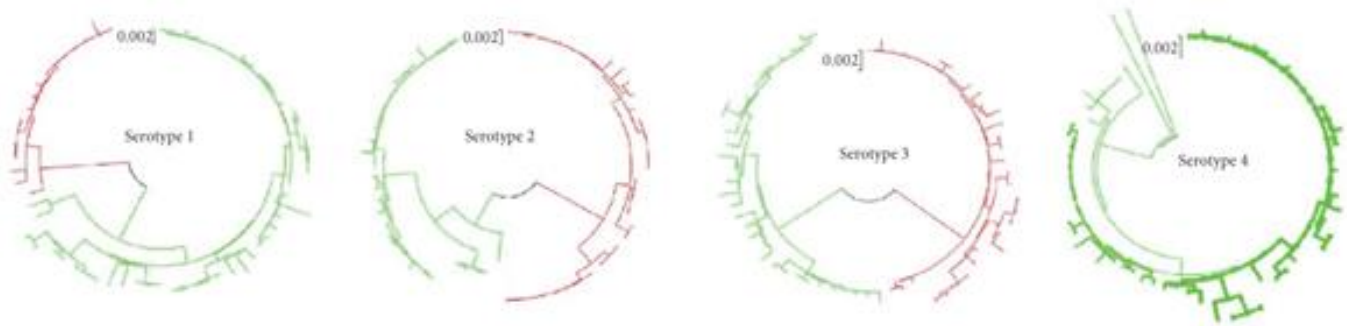


PAHO. Epidemiological Update for Dengue, Chikungunya and Zika in 2022. Updated: Jun 25 2023 1:00AM

Dengue- Virological aspects

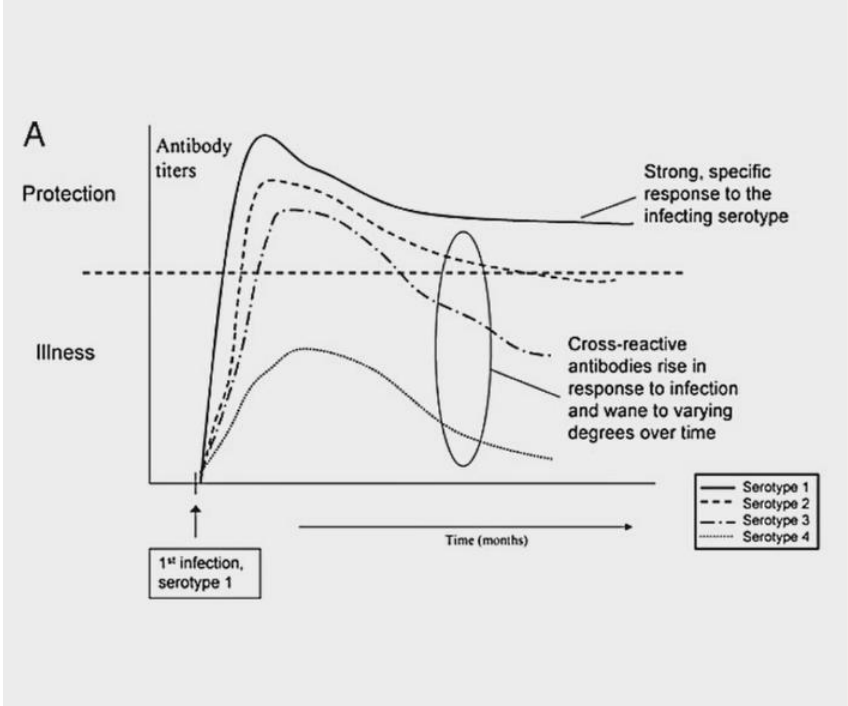
- Family Flaviviridae
- Genus *Flavivirus*
- 4 serotypes (DENV 1, 2, 3, 4)
- Transmission:
  - Vectorial *(Aedes* spp)
  - Mother-to-child
  - Transplant/transfusion
  - Needle injury
  - Sexual

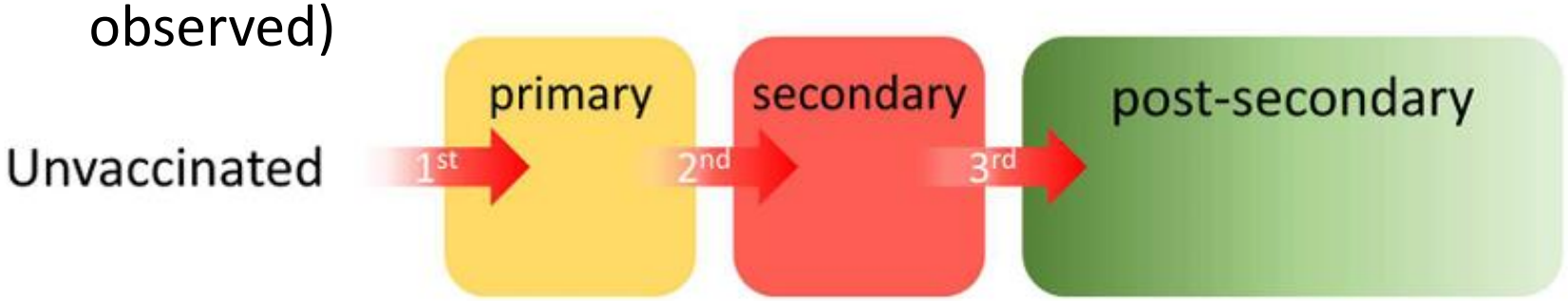


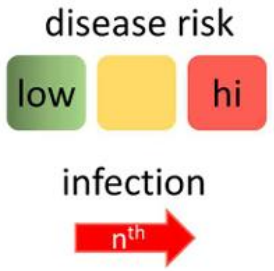


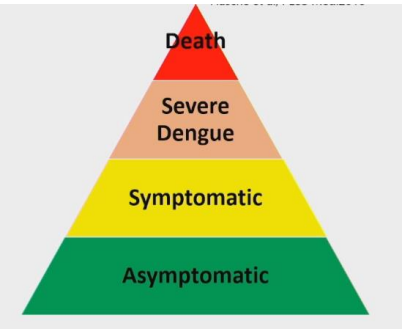
Dengue- Immunological aspects

- **Primary infection**:
  - no or mild disease
  - long-lived immunity to that serotype (homologous protection)
  - temporary (<30 months) cross-reactive immunity too the serotypes (heterologous protection)
- **Secondary infection**: increased risk (RR 2-3) of severe disease probably because antibody-dependent enhancement (ADE).
- **Post-secondary infections**: generally mild (rarely observed)





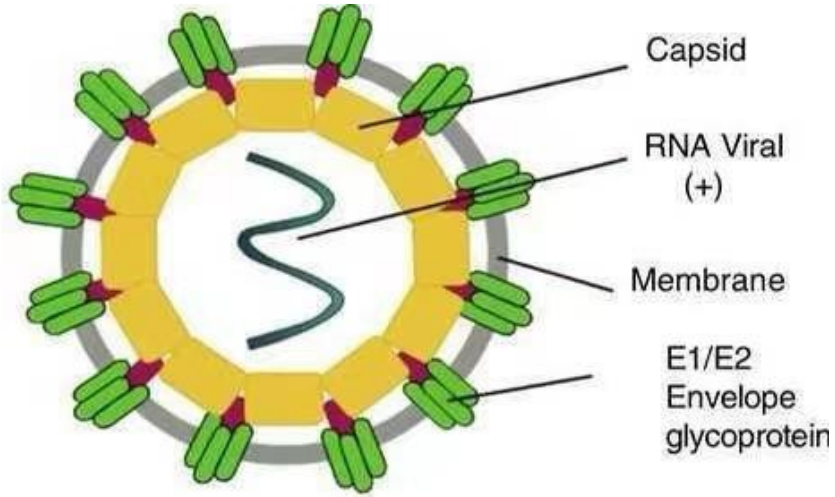




Flashe S PloS Medicine 2016

Chikungunya- Virological aspecs

- Family Togaviridae
- Genus *Alphavirus*
- 4 lineages
  - West African (WA)
  - Asian
  - East Central South Africa (ECSA)
  - Indian Ocean Lineage (IOL, derived from ECSA)
- Transmission:
  - Vectorial *(Aedes* spp)
  - Mother-to-child
  - Transplant/transfusion
  - Needle injury



Bartholomeeusen, K et al. Chikungunya fever. Nat Rev Dis Primers 2023

Chikungunya- Immunological aspects

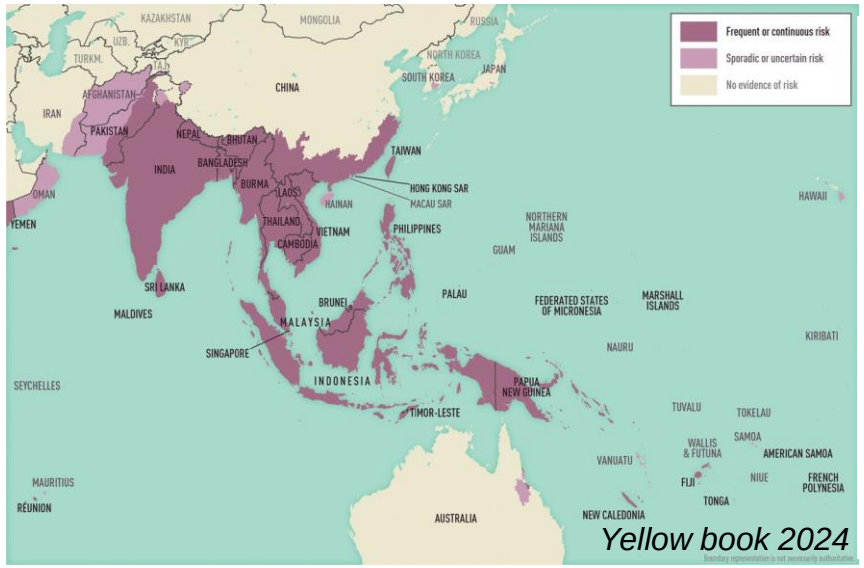
- CHIKV exhibits limited antigenic diversity and is not known to be capable of reinfection
- Prevalence of CHIKV ECSA neutralizing antibodies in a village with previous (19 years before) Asian CHIKV outbreak was 70%

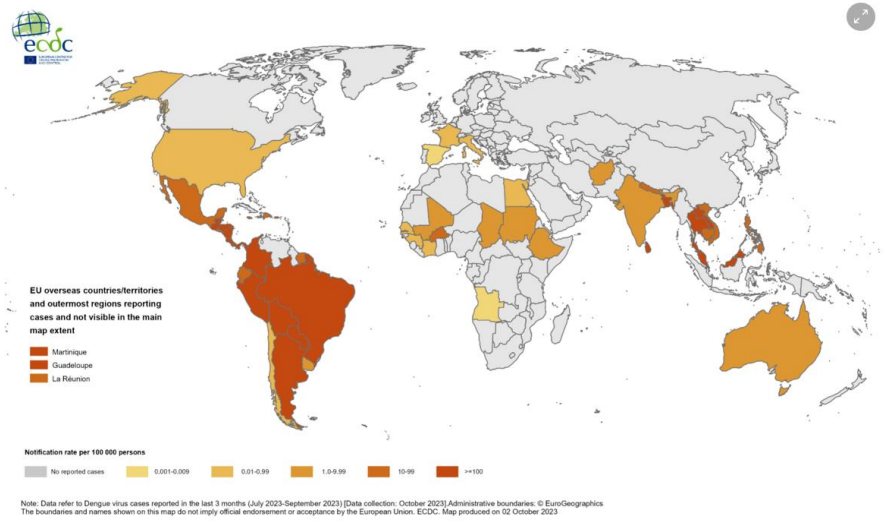
Nitatpattana et al. Virology Journal 2014
Erasmus et al. JID 2016

Dengue- Epidemiology

- 100-400 million **estimated** infections per year (underreporting)

- **Current situation (January – October 2023):**
  - **cases reported from 79 countries/territories globally**
  - **4.2 million reported cases**
  - **>3 000 dengue-related**
  - **Since Sept 2023 Peru is experiencing the largest outbreak of its history**

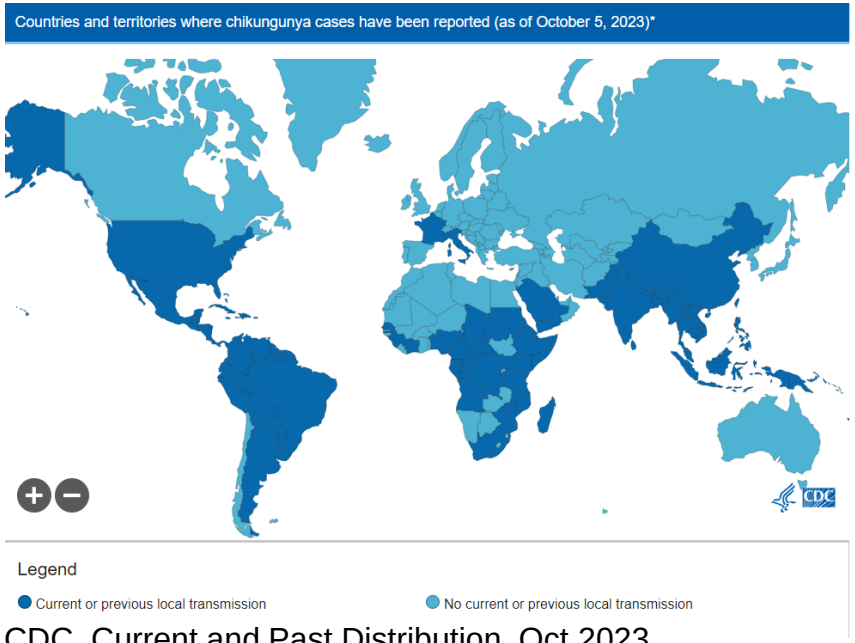




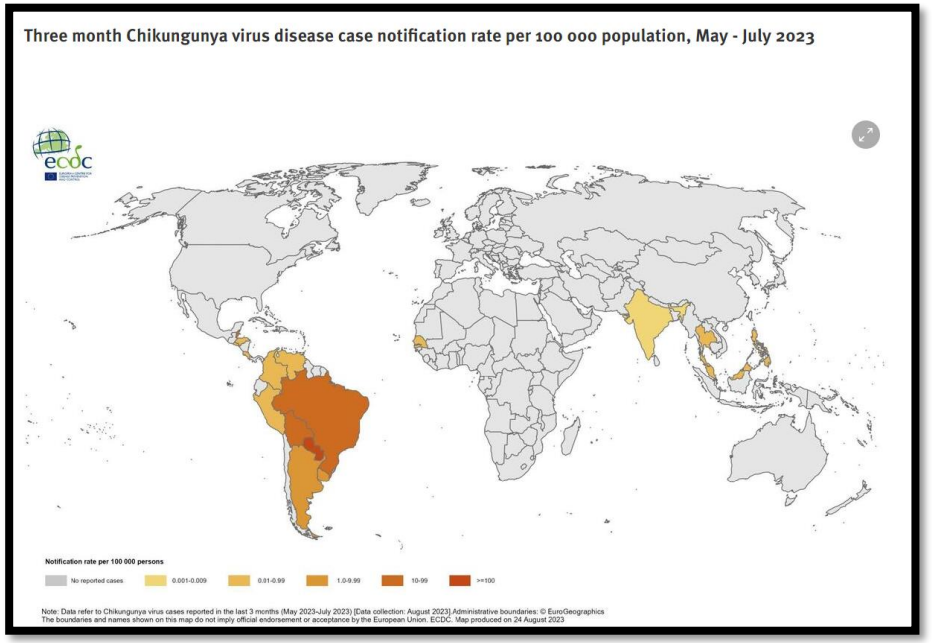
ECDC. Dengue Worldwide. https://www.ecdc.europa.eu/en/dengue-monthly. October 2023

Chikungunya- Epidemiology

- >100 countries report circulation of CHIKV
- >10 million cumulative cases of chikungunya fever today
- Current situation (January – August 2023):
  - 20 countries reported cases
  - >320,000 cases
  - >340 deaths



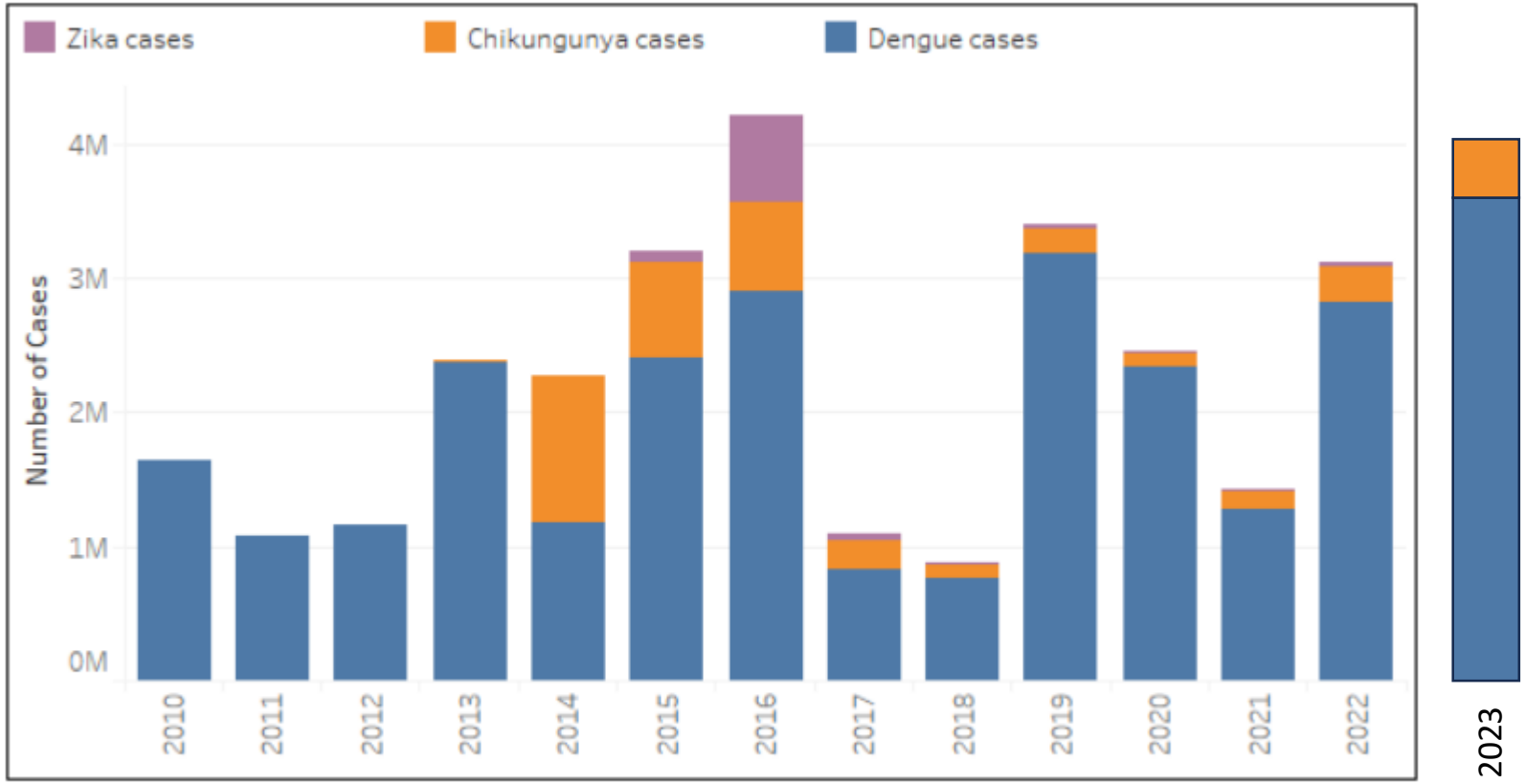
CDC. Current and Past Distribution, Oct 2023



ECDC. Chikungunya Worldwide. https://www.ecdc.europa.eu/en/chikungunya-monthly. October 2023

Dengue & Chikungunya epidemiology in the Americas

Figure 1. *Distribution of reported cases of dengue, chikungunya, and Zika by year. Region of The Americas. 2010-2022*



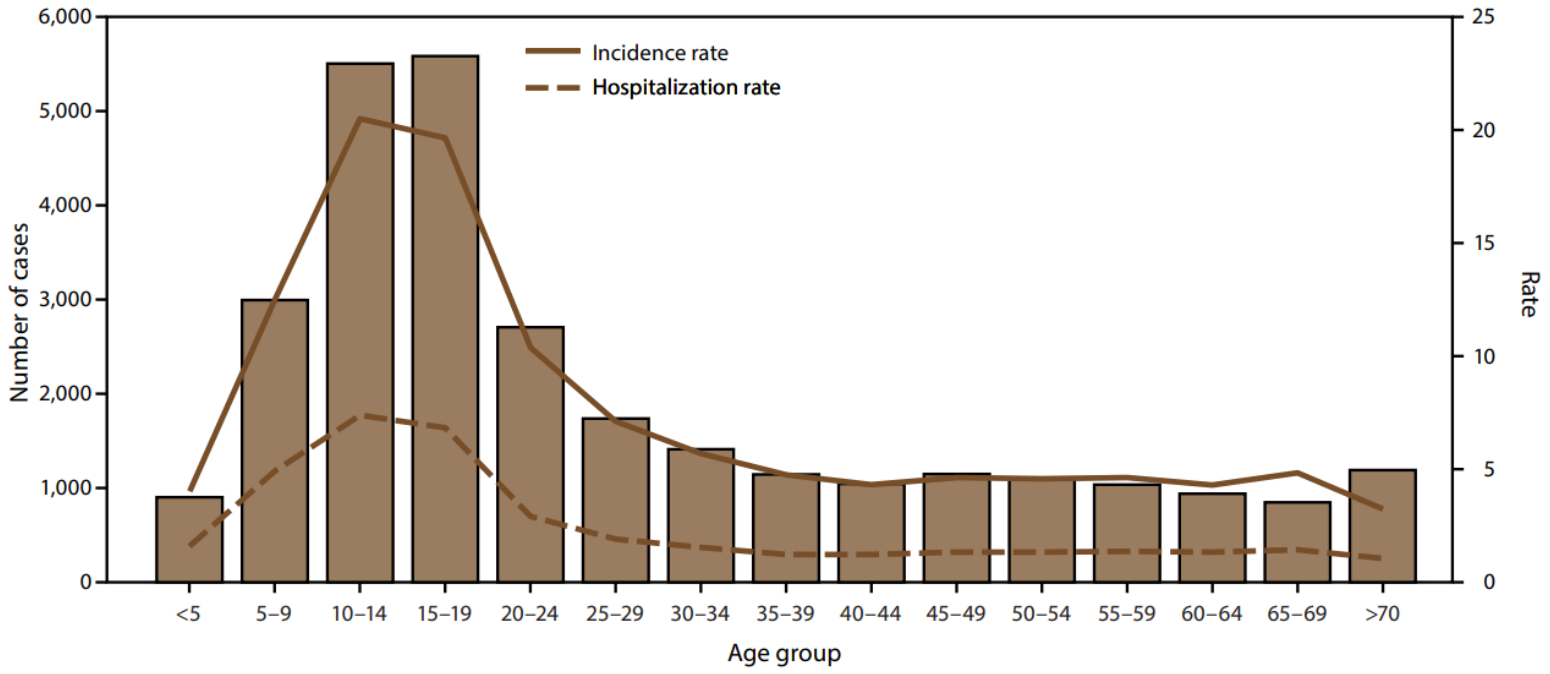
Source: *Data entered into the Health Information Platform for The Americas (PLISA, PAHO / WHO) by the Ministries and Institutes of Health of the countries and territories of the Region. Available at: https://www.paho.org/plisa*

- DENV:
  - tends to be endemic-epidemic
  - ≈50% of cases in 0-19 age group
  - Peak of the incidence and hospitalization rate between 10 and 19 years
- CHIKV cause periodic explosive outbreak in different areas involving all age groups
- In 2023:
  - >3,350,000 DENV cases (surpassed the 2019 record)
  - >330,000 CHIKV cases

https://www3.paho.org/data/index.php/en/mnu-topics/indicadores-dengue-en.html

Dengue epidemiology in Puerto Rico

FIGURE 3. Number of dengue cases, incidence rate,* and hospitalization rate, by age group — Puerto Rico, 2010–2020†



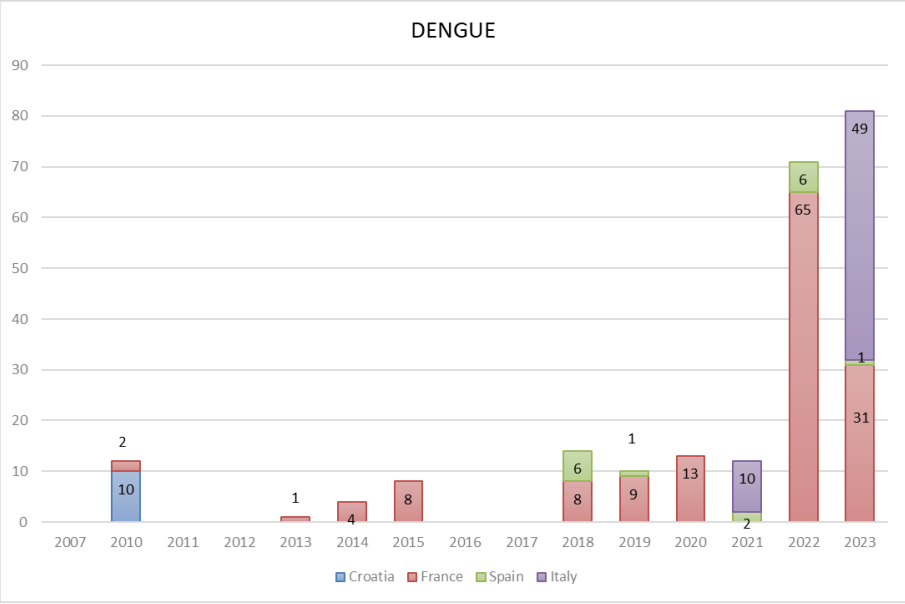
Source: ArboNet.
* Per 1,000 population using 2020 U.S. census population data.
† N = 29,862.

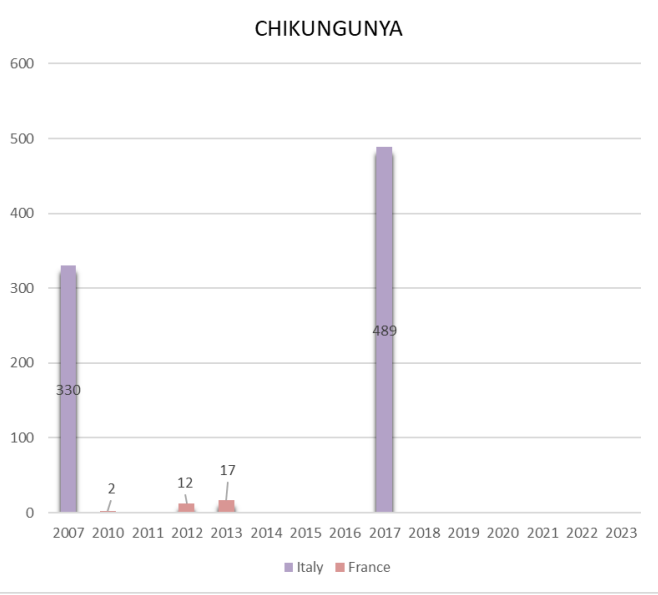
- Overall ≈50% of cases in age group 0-19
- Peak of the incidence and hospitalization rate between 10 and 19 years (when secondary infections occur)

Ryff KR et al. MMWR 2023

Dengue & Chikungunya locally acquired cases in Europe

- **1079** locally acquired cases in Mediterranean Europe
- **Italy**: 819 Chikungunya and 49 Dengue cases (81% of European cases)
- **France ***: 31 Chikungunya cases and 141 Dengue cases (16%)
- **Spain**: 16 Dengue cases (1%)
- **Croatia**: 10 Dengue cases (1%)





Source:
https://www.ecdc.europa.eu/en/all-topics-z/dengue/surveillance-and-disease-data/autochthonous-transmission-dengue-virus-eueea
Consulted on 9/10/2023

Source:
https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/chikungunya-virus-disease/surveillance-threats-and
Consulted on 9/10/2023

* 3 vector-borne locally acquired Zika virus cases in France (additional sporadic sexually transmitted Zika and Dengue cases were reported in several European countries)

Travel-related illness encountered at EuroTravNet clinics, the European surveillance sub-network of GeoSentinel, between March 1, 1998 and March 31, 2018

Research paper

Travel-related infections presenting in Europe: A 20-year analysis of EuroTravNet surveillance data

Table 1
Selected diagnoses reported between 1998 and 2018 (% of 103,739 patients).

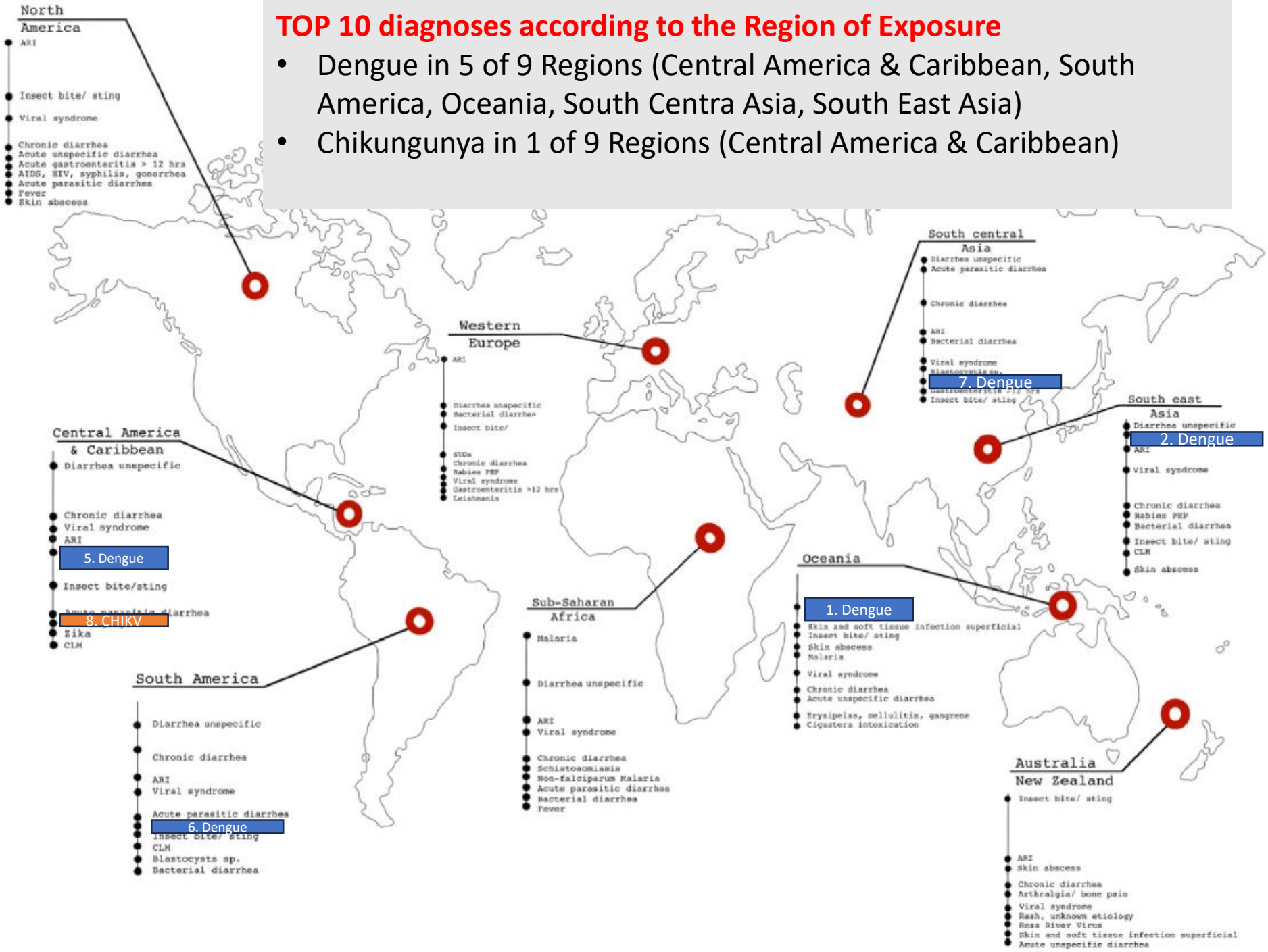
Diagnosis	1998–2002	2003–2007	2008–2012	2013–2018	Somers' D
Malaria	526 (8.4%)	872 (6.8%)	2340 (7.0%)	3457 (6.8%)	
Dengue	104 (1.7%)	308 (2.4%)	1133 (3.4%)	2176 (4.2%)	0.013*
Chikungunya	0	50 (0.4%)	86 (0.3%)	608 (1.2%)	0.007*
Zika, vector-associated	0	0	0	414 (0.8%)	0.007*
Zika, not vector-associated	0	0	0	6	
Ross River	0	0	5	14	
Yellow fever	0	0	0	5	
Japanese encephalitis	0	0	1	4	
Tick-borne encephalitis	0	5	4	4	
West Nile	0	1	3	3	
Rift Valley Fever	0	0	2	1	
Barmah Forest	0	0	0	1	
Murray Valley encephalitis	0	0	0	1	
*Other arbovirus infections***	0	3	4	6	
All arbovirus diagnoses	104 (1.7%)	364 (2.8%)	1236 (3.7%)	3191 (6.2%)	0.026*
Viral haemorrhagic fever	1	1	12	30	0.0003*
Animal exposure leading to rabies vaccination	41(0.7%)	222(1.7%)	602 (1.8%)	1823 (3.6%)	0.016*
Influenza A and B	0	9 (0.1%)	158 (0.5%)	469 (0.9%)	0.006*
Influenza-like-illness	18 (0.3%)	92 (0.7%)	551 (1.7%)	1295 (2.5%)	0.12*
Acute hepatitis A or B	58 (0.9%)	59 (0.5%)	123 (0.4%)	103 (0.2%)	−0.003*
Measles	4 (0.1%)	3 (0.0%)	21 (0.1%)	17(0.0%)	
Viral syndrome with or without rash	464 (7.4%)	1023 (7.9%	1851 (5.6%)	3225 (6.29%)	
Upper respiratory tract infection	265 (4.2%)	301 (2.3%)	660 (2.0%)	1008 (2.0%)	−0.005*
Total patients	6301	12,895	33,301	51,242	

+Somers' D only calculated when $N > 40$ and proportions are monotonically increasing or decreasing over time.
* =significant at 95% level.
** Others include sandfly fever/pappataci fever, sindbis fever, unspecified alphavirus, flavivirus and phlebovirus, unspecified arbovirus, 52 patients have 2 arboviral infections.

Grobusch MP et al Lancet Reg Health Eur. 2020

TOP 10 diagnoses according to the Region of Exposure

- Dengue in 5 of 9 Regions (Central America & Caribbean, South America, Oceania, South Centra Asia, South East Asia)
- Chikungunya in 1 of 9 Regions (Central America & Caribbean)



Contents lists available at ScienceDirect
The Lancet Regional Health - Europe
journal homepage: www.elsevier.com/lanepe

Research paper

Travel-related infections presenting in Europe: A 20-year analysis of EuroTravNet surveillance data

45 deaths in European returning travellers (1998-2018)

Diagnoses	Age	Sex	Region of exposure	Reason for Travel
ARDS, AIDS	28	Female	Caribbean	Tourism
Melioidosis	35	Male	Caribbean	Tourism
Fungal pneumonia	40	Female	Caribbean	Migration
Multi organ failure due to Salmonella species, sepsis	55	Male	Caribbean	Tourism
Pneumococcal meningitis	64	Female	Eastern Europe	VFR
Atypical/non-lobar pneumonia, Legionnaires' disease, acute renal failure	65	Male	Eastern Europe	Tourism
TB	82	Male	Eastern Europe	Migration
Pneumococcal pneumonia	77	Male	Middle East	Tourism
Pulmonary TB Disseminated/miliary TB, CNS tuberculoma	77	Female	Middle East	Migration
Pyogenic liver abscess, diabetes mellitus	34	Female	Not Ascertainable	Migration
Asymptomatic HIV, TB	37	Female	Not Ascertainable	VFR
Acute hepatic insufficiency after NSAID overdose	46	Male	Not Ascertainable	Tourism
Pulmonary embolism	52	Female	Not Ascertainable	Tourism
Cytomegalovirus, AIDS	55	Male	Not Ascertainable	Migration
Lobar pneumonia	84	Male	PlaneShip	Tourism
Yellow fever	43	Male	South America	Tourism
Extrapulmonary TB	40	Male	South Central Asia	Migration
Lobar pneumonia, Sepsis	75	Male	South Central Asia	VFR
Arterial dissection	38	Male	South East Asia	Business
HIV, acute infection (febrile), autoimmune disorders	47	Male	South East Asia	Tourism
Melioidosis[1]	53	Male	South East Asia	Tourism
Dengue DSS	53	Female	South East Asia	Tourism
Naegleria fowleri encephalitis	72	Female	South East Asia	Tourism
Severe and complicated malaria	26	Male	Sub-Saharan Africa	Military
Visceral Leishmaniasis, chronic Hepatitis B, sepsis	32	Male	Sub-Saharan Africa	Migration
TB, AIDS	33	Female	Sub-Saharan Africa	Migration
AIDS	34	Male	Sub-Saharan Africa	Migration
Severe and complicated malaria	40	Male	Sub-Saharan Africa	Business
AIDS, lobar pneumonia, sepsis	42	Female	Sub-Saharan Africa	Migration
Extrapulmonary TB, pulmonary TB	47	Male	Sub-Saharan Africa	VFR
P. falciparum malaria	48	Male	Sub-Saharan Africa	VFR
P. falciparum malaria, severe and complicated	53	Male	Sub-Saharan Africa	Business
P. falciparum malaria, severe and complicated	55	Female	Sub-Saharan Africa	Business
Severe and complicated malaria	57	Male	Sub-Saharan Africa	M/V/R/A
Granulomatous Amoebic Encephalitis (GAE)	60	Female	Sub-Saharan Africa	Tourism
Fungal pneumonia, sepsis	61	Female	Sub-Saharan Africa	Migration
Severe and complicated malaria	68	Male	Sub-Saharan Africa	Tourism
Viral syndrome (with/without rash)	6	Male	Western Europe	Tourism
Acute liver failure, leishmaniasis	56	Male	Western Europe	Tourism
Visceral leishmaniasis	59	Male	Western Europe	Tourism
Pneumococcal meningitis	65	Female	Western Europe	Tourism
Pyelonephritis, sepsis	67	Male	Western Europe	Tourism
Acute UTI, sepsis	78	Female	Western Europe	Tourism
ARDS, lobar pneumonia, sepsis	84	Female	Western Europe	Tourism
Lobar pneumonia, COPD, Parkinson's disease	86	Male	Western Europe	Tourism

- 7/45 *P. falciparum*
- 3/45 pneumococcal disease
- 1/45 Yellow-fever
- **1/45 Dengue**

Overall, malaria patients had a 2.5:1 risk ratio of dying from their disease compared to patients with all other diagnoses (7/7195 = 0.1% vs 38/96,544 = 0.04%).

Grobusch MP et al Lancet Reg Health Eur. 2020

Travel-related illness encountered at EuroTravNet clinics, the European surveillance sub-network of GeoSentinel, between March 1, 1998 and March 31, 2018

Vaccine-Preventable Diseases:

1. dengue (3721 patients)
2. animal exposures leading to rabies post-exposure prophylaxis (2688 patients)
3. chikungunya (744 patients)
4. seasonal influenza (636 patients)
5. hepatitis A (219 patients)
6. hepatitis B (125 patients)
7. varicella (78 patients)
8. pertussis (58)
9. measles (45)

8. mumps (25)
9. rubella (14)
10. TBE (13)
11. diphtheria (8)
12. yellow fever (5)
13. Japanese encephalitis (5)

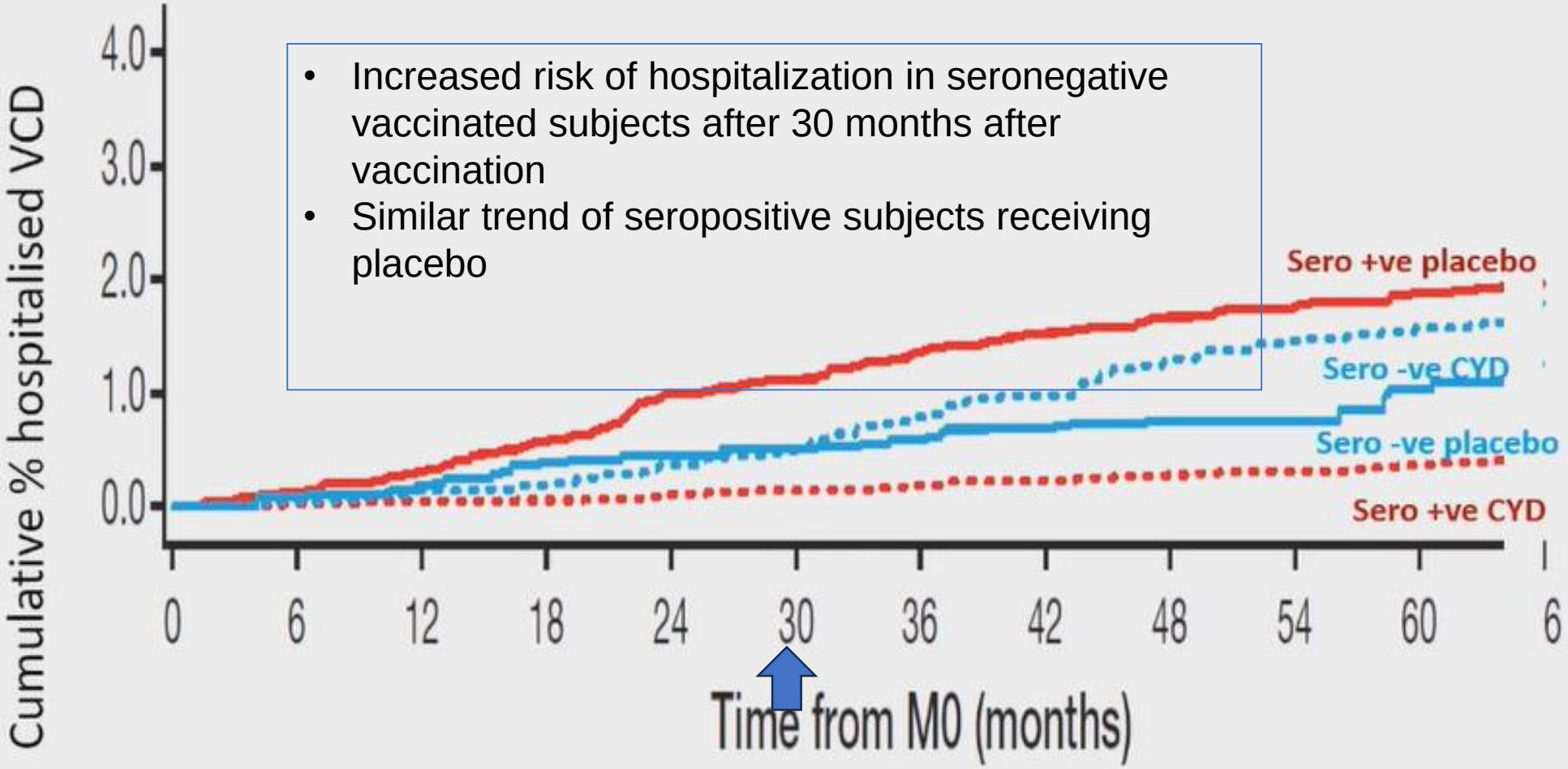
Grobusch MP et al Lancet Reg Health Eur. 2020

CYD-TDV (Dengvaxia by Sanofi Pasteur)- main features

- Live-attenuated chimeric tetravalent vaccine
- Yellow-fever virus backbone
- Dengue proteins: 8 (absence of NS1 antigen , which may have toxin like properties)
- Scheme: 3 doses over 12 months (0, 6, 12 months)
- Age range in phase 3 trial: 2-16y
- Effectiveness in seropositive:
  - ≈76% *versus* dengue of any severity
  - ≈90% *versus* severe dengue
- Seronegative subjects receiving the vaccine have a higher risk (similar to that of unvaccinated seropositive persons) of more severe illness and hospitalization due to dengue fever compared to unvaccinated seronegative persons

Dengvaxia: post-hoc results from the Phase 3 trials: Cumulative incidence of hospitalised dengue by serostatus

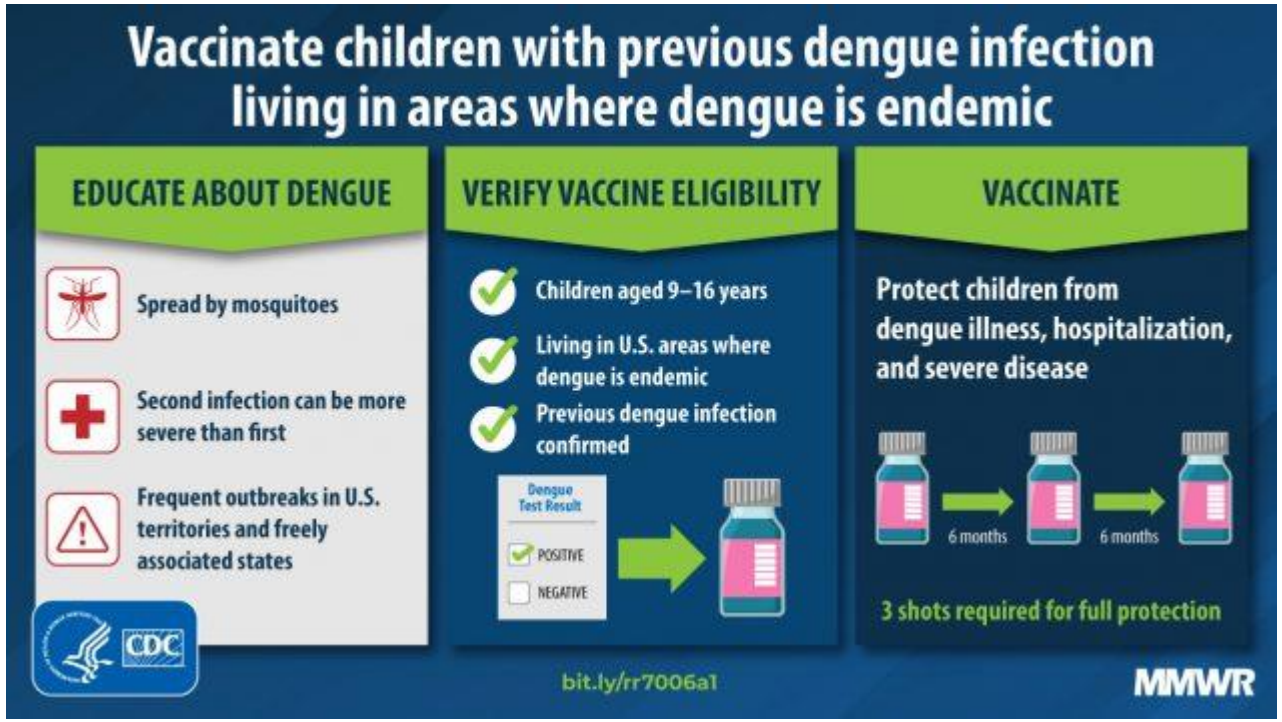
- Increased risk of hospitalization in seronegative vaccinated subjects after 30 months after vaccination
- Similar trend of seropositive subjects receiving placebo



Prof. Annelies Wilder-Smith, CISTM18, Basel 24/5/2023

CYD-TDV (Dengvaxia by Sanofi Pasteur)- approval and recommendations

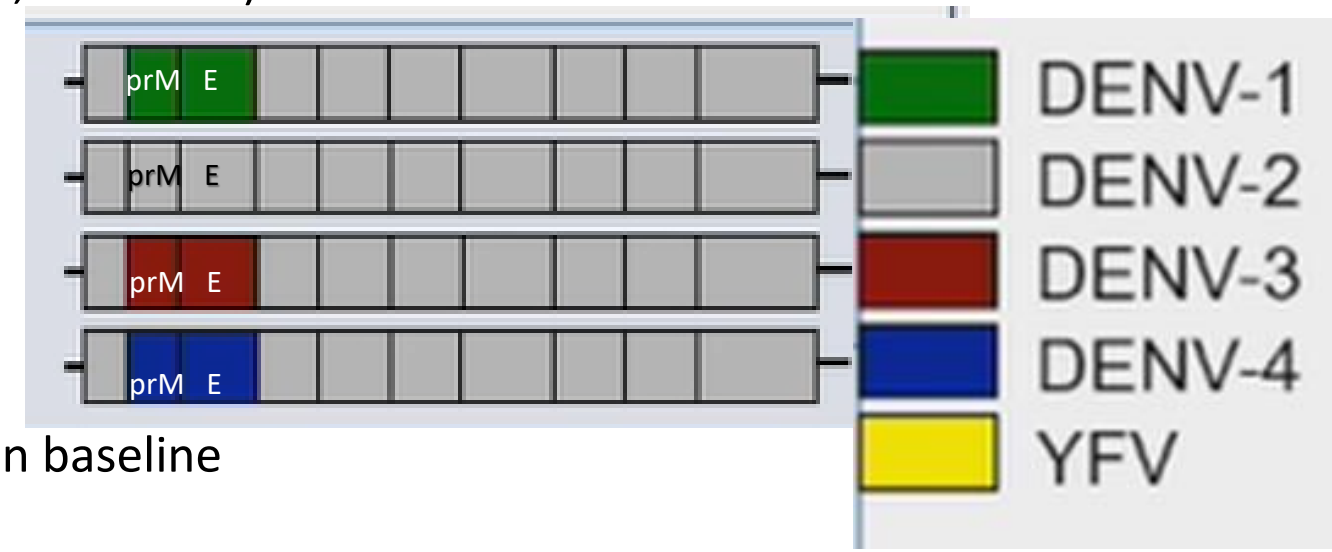
- U.S. FDA approved in persons aged 9-16 years who have laboratory confirmation of a previous dengue virus infection and live in a dengue-endemic area (**U.S. territories of American Samoa, Guam, Puerto Rico, and U.S. Virgin Islands**)
- Recommended by the Advisory Committee on Immunization Practices (ACIP) for children with previous dengue infection living in areas where dengue is endemic
- **Approved for use in approximately 20 dengue-endemic countries** but is not commercially available or in significant use in public health programs anywhere.
- **Dengvaxia is not approved nor recommeded for travelers living in nonendemic areas and visiting endemic areas; no supporting clinical data exist.**
- **Very low uptake due to high cost and complexity of test and vaccine strategy required**



Paz-Bailey G et al. MMWR 2021

TAK-003 (Qdenga by Takeda)- main features

- Live-attenuated chimeric tetravalent vaccine
- DENV-2 virus backbone
- Dengue proteins: 16 (including NS1 antigen)
- Storage: 2-8°C
- Scheme: 2 subcutaneous doses over 3 months (0, 3 months)
- Age range in phase 3 trial: 4-16y
- Effectiveness varies according to:
  - Baseline serostatus
  - DENV serotype
  - Time since vaccination
- No evidence of increased risk of hospitalization in baseline seronegative subjects
- No evidence of efficacy in baseline seronegative subjects against DENV-3 and DENV-4



TAK-003 (Qdenga by Takeda)- vaccine efficacy against Vaccine Confirmed Dengue (VCD) and hospitalization

Studied in ≈13,000 children and ≈ 800 adults versus ≈ 6000 controls (placebo)

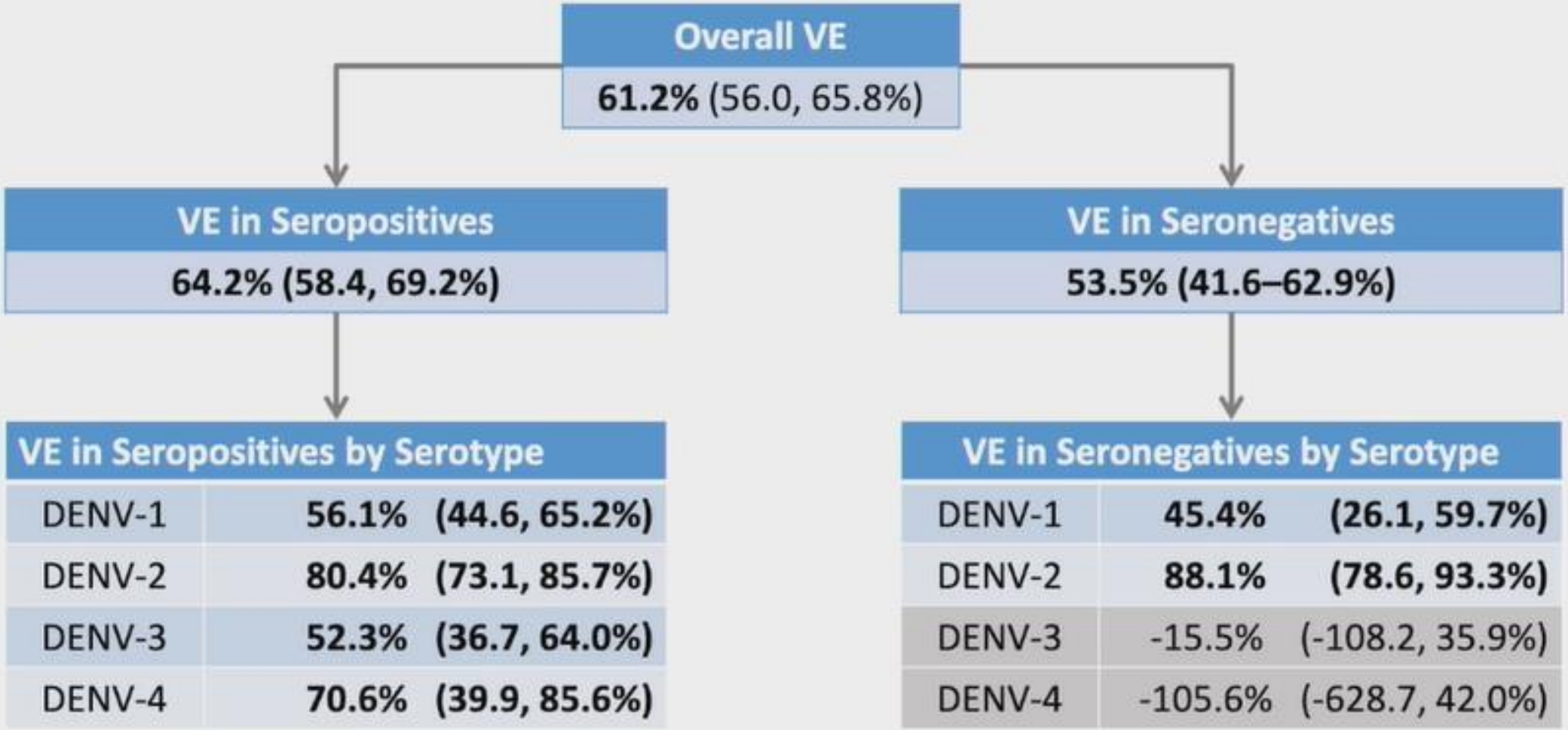
Vaccine efficacy against VCD by any serotype

- 80.2% at 12 months
- 61.2% at 54 months

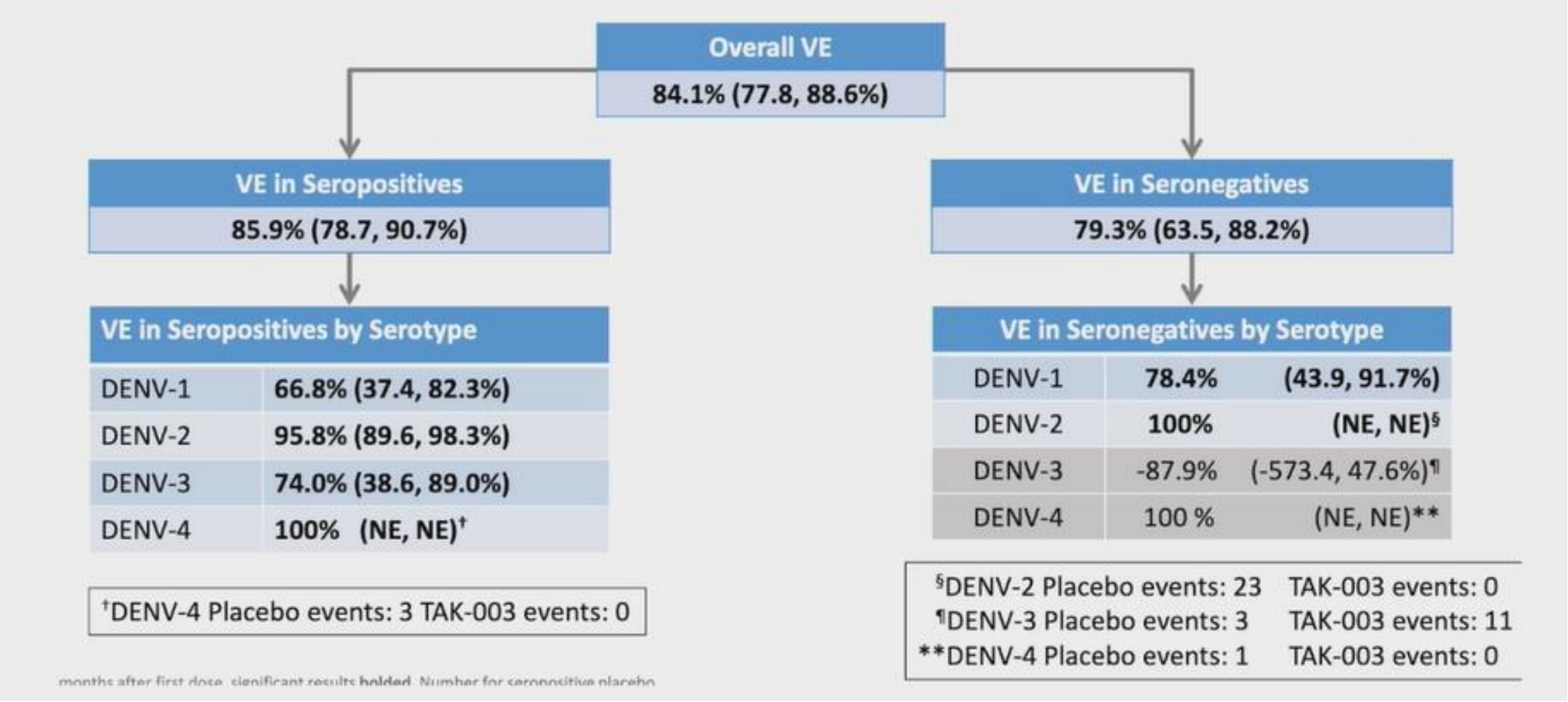
Vaccine efficacy against hospitalization by any serotype

- 90.4% at 18 months
- 84.1% at 54 months

TAK-003 (Qdenga by Takeda)- 54 months vaccine efficacy against VDC



TAK-003 (Qdenga by Takeda)- 54 months vaccine efficacy against hospitalization



TAK-003 (Qdenga by Takeda)- vaccine efficacy between the first and second doses

EXPLORATORY ANALYSIS OF VE AGAINST VCD BETWEEN THE FIRST AND SECOND DOSE (PPS)[1]

VCD in TAK-003 group, n	13
VCD in placebo group, n	34
VE against VCD, % (95% CI)	81.0 (64.1-90.0)

PRIMARY ENDPOINT ANALYSIS OF VE AGAINST VCD FROM 30 DAYS UP TO 12 MONTHS POST SECOND DOSE (PPS)[1]

VCD in TAK-003 group, n	61
VCD in placebo group, n	149
VE against VCD, % (95% CI)	80.2 (73.3-85.3)

PPS, per-protocol set; VCD, virologically confirmed dengue; VE, vaccine efficacy.

1. Biswal S, et al; TIDES Study Group. *N Engl J Med*. 2019;381(21):2009-2019.

TAK-003 (Qdenga by Takeda)- approval and recommendations

- Approved in subject aged 4 years and older by EMA in Dec 2022 and AIFA in Feb 2023
- Approved also in Germany, Sweden, Indonesia, Netherlands, Denmark, Brazil
- Pre-vaccine serological screening not requested
- Pre-vaccination selection based on history of dengue in the Netherlands and Denmark. Only for long term travelers in Germany.
- Commercialized in Italy at the end of September (price per dose 175 euro)
- WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommend to consider the introduction of the vaccine 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. SAGE recommended that the vaccine be introduced to children aged 6 to 16 years of age.

Highlights from the Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization
25-29 September 2023

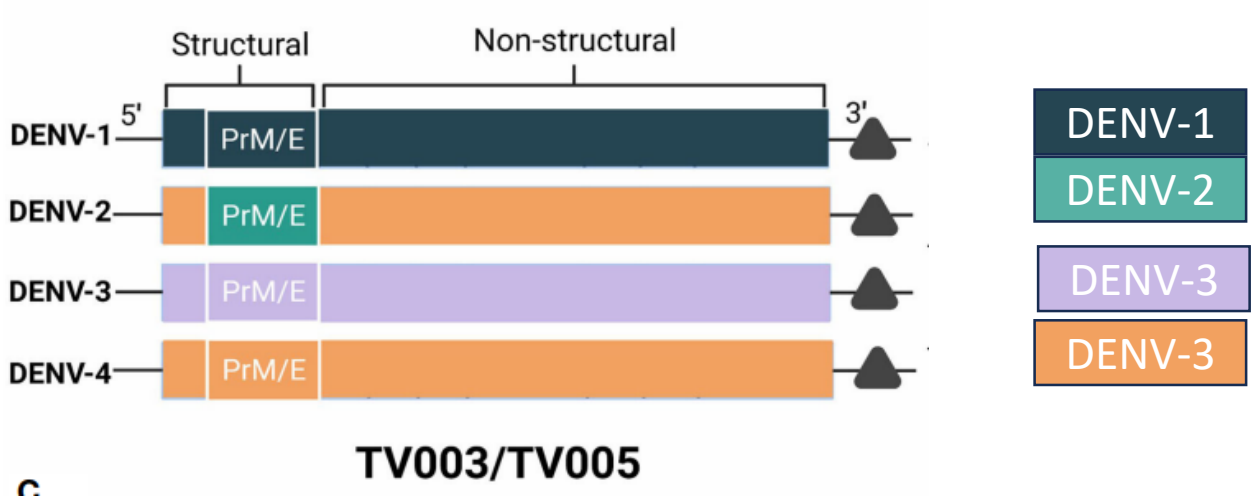
(The full report will be published in the Weekly Epidemiological Record on 1 December 2023, and only the wording of the full report should be considered final)

SAGE: The potential risk of enhanced disease due to serotypes 3 and 4 in seronegative vaccinated children cannot be ruled out.

TV003/TV005 by Butantan Institute (Brazil) financed by MSD and NIH

- Live-attenuated chimeric tetravalent vaccine
- **Single dose quadrivalent**
- Phase 3 trial expected to be completed in 2024 (five year follow-up)
- Comprises 3 full-length DENV (1, 3, 4) attenuated by one or more deletions
- The fourth component is a chimeric virus in which the prM and E proteins of DENV-2 replace those of DENV-4 background
- This vaccine carries the full-genomic backbone of three dengue serotypes, except for DENV2.

- **In participants who had already been infected before the study, the efficacy was 89.2%. In those who had never contracted the disease, protection was 73.5% [Press Release]**



VLA1553 Chikungunya vaccine by Valneva

- Most clinically advanced chikungunya vaccine candidate worldwide
- Seeking FDA approval in persons aged 18 years and above
- **Live-attenuated, single dose**
- **Immunogenicity as surrogate markers of efficacy**
- **Intramuscolar**
- **Based on ECSA genotype**

VLA1553-301 trial (March 2022):

- 4,115 adults aged 18 years and above across 44 sites in the U.S.
- Seroprotection 263 of 266 (98.9%) at 29 days
- Antibodies persistence at 6 months: 233 of 242 (96.3%)
- Highly immunogenic in elderly study participants (65 years of age

Lancet 2023

VLA1553 Chikungunya vaccine by Valneva- safety

	VLA1553 (n=3082)	Placebo (n=1033)	Total (n=4115)
Any adverse events	1926 (62·5%, 60·8–64·2) 6415	463 (44·8%, 41·8–47·9) 1071	2389 (58·1%, 56·5–59·6) 7486
Any related adverse events	1575 (51·1%, 49·3–52·9) 4621	322 (31·2%, 28·4–34·1) 647	1897 (46·1%, 44·6–47·6) 5268
Any related severe adverse events	62 (2·0%, 1·5–2·6) 70	1 (0·1%, 0·0–0·5) 3	63 (1·5%, 1·2–2·0) 73
Any serious adverse events	46 (1·5%, 1·1–2·0) 73	8 (0·8%, 0·3–1·5) 10	54 (1·3%, 1·0–1·7) 83
Any related serious adverse events	2 (0·1%, 0·0–0·2) 2	0 (0%, 0·0–0·4) 0	2 (0·0%, 0·0–0·2) 2
Any adverse events of special interest	10 (0·3%, 0·2–0·6) 26	1 (0·1%, 0·0–0·5) 2	11 (0·3%, 0·1–0·5) 28
Any adverse event with a frequency ≥10% in at least one study arm			
Headache	986 (32·0%, 30·3–33·7) 1028	160 (15·5%, 13·3–17·8) 178	1146 (27·8%, 26·5–29·2) 1206
Fatigue	886 (28·7%, 27·2–30·4) 893	137 (13·3%, 11·3–15·5) 139	1023 (24·9%, 23·5–26·2) 1032
Myalgia	750 (24·3%, 22·8–25·9) 758	82 (7·9%, 6·4–9·8) 84	832 (20·2%, 19·0–21·5) 842
Arthralgia	554 (18·0%, 16·6–19·4) 589	63 (6·1%, 4·7–7·7) 70	617 (15·0%, 13·9–16·1) 659
Injection site pain	413 (13·4%, 12·2–14·7) 519	101 (9·8%, 8·0–11·8) 122	514 (12·5%, 11·5–13·5) 641
Pyrexia	427 (13·9%, 12·7–15·1) 429	13 (1·3%, 0·7–2·1) 13	440 (10·7%, 9·8–11·7) 442
Nausea	359 (11·6%, 10·5–12·8) 364	63 (6·1%, 4·7–7·7) 64	422 (10·3%, 9·3–11·2) 428
Any serious adverse event with a frequency ≥0·2% in at least one study arm by system organ class			
Infections and infestations	9 (0·3%, 0·1–0·6) 9	3 (0·3%, 0·1–0·8) 3	12 (0·3%, 0·2–0·5) 12
Injury, poisoning, and procedural complications	8 (0·3%, 0·1–0·5) 15	1 (0·1%, 0·0–0·5) 1	9 (0·2%, 0·1–0·4) 16
Psychiatric disorders	7 (0·2%, 0·1–0·5) 8	2 (0·2%, 0·0–0·7) 4	9 (0·2%, 0·1–0·4) 12
Cardiac disorders	5 (0·2%, 0·1–0·4) 7	0 (0%, 0·0–0·4) 0	5 (0·1%, 0·0–0·3) 7

Data are n (%, 95% CI) N. For each category, participants were included only once, even if they experienced multiple events in that category. Related adverse events are those recorded as probably related or possibly related on the eCRF. Adverse events of special interest counts are for the overall event and the adverse event of special interest symptom count includes a count of all symptoms contributing to the event. Two-sided exact Clopper-Pearson 95% CIs are presented. eCRF=electronic case report form. n=number of participants. N=number of events.

Table 3: **Overall summary of adverse events (safety population)**

- 17% (n=520) any arthralgia
- 0.5% (n=15) duration >11 days
- Longest duration: 182 days

Table 2 | Chikungunya virus vaccine candidates

Vaccine	Type	Chikungunya virus lineage	Chikungunya virus strain	Advantages	Limitations	Status	Refs.
VLA1553	Live-attenuated virus	East Central South African	La Réunion Island, 2006	Rapid immune response (<14 days); single dose	Transient arthralgia and fever; cannot use in pregnancy or immunocompromised; durability >1 year unknown	Phase III study, complete; FDA license application started August 2022	Wressnigg et al.[201], Roques et al.[202]
PXVX0317	Virus-like particle plus adjuvant	West African	Senegal, 1983	Rapid immune response (<14 days); durable immune response (2 years); thermostable; single dose; platform safe in pregnancy and immunocompromised	Requires an adjuvant	Phase III study, ongoing	Chang et al.[204], Goo et al.[205], Bennett et al.[206]
V184	Measles vector	East Central South African	La Réunion Island, 2006	Platform based on the highly safe, effective and durable measles vaccine; also boosts measles immunity	May require 2 doses; durability >224 days unknown; cannot use in pregnancy or immunocompromised	Phase III study, not started	Reisinger et al.[209], Ramsauer et al.[210]
BBV87	Inactivated virus plus adjuvant	East Central South African	India, 2006	Thermostable; platform safe in pregnancy and immunocompromised	Phase I data not published yet; requires 2 doses; requires an adjuvant	Phase II/III study, ongoing	CEPI press release[220]

Conclusions

- The two dengue vaccine approved may have a role in the setting of endemic areas
- Their use in travelers is not well defined [*The potential risk of enhanced disease due to serotypes 3 and 4 in seronegative vaccinated children cannot be ruled out.]*
- The first CHIKV vaccine will be probably available soon , however it is associated to some degree of immediate side effect and it is contraindicated in immunosuppressed patients and during pregnancy
- Recommendation on the use of these vaccines in the setting of travel medicine are welcome.

Grazie per l’attenzione!