Dengue
da infezione tropicale a problema europeo?

Antonio Di Biagio

Genova, 11 giugno 2024

Conflitti di interesse

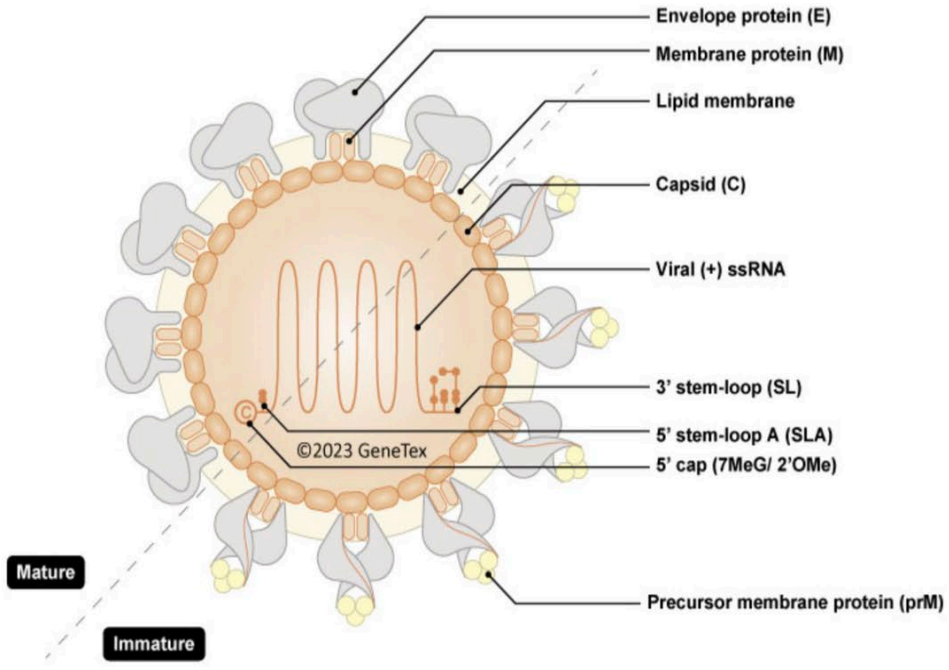
- **Nessun condizionamento nel preparare questa relazione**

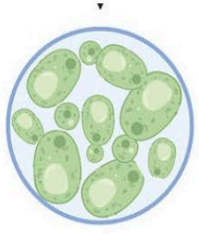
DENGUE VIRUS (DENV) 4 sierotipi

- **Trasmesso all'uomo attraverso un vettore (*Aedes spp*).**
- **Circa la metà della popolazione mondiale è oggi a rischio di dengue, circa 400 milioni di infezioni stimate che si verificano ogni anno**
- **Climi tropicali e subtropicali di tutto il mondo, soprattutto aree urbane e suburbane**
- **La Dengue rispetto a tutte le altre patologie trasmissibili nel periodo 2000-2013 è cresciuta del 400%**
- **La maggior parte delle infezioni sono asintomatiche, ma alcune possono essere gravi o mortali**

Dengue: il virus ed il ciclo vitale

Flaviviridae





Yeast (*Pichia pastoris*)

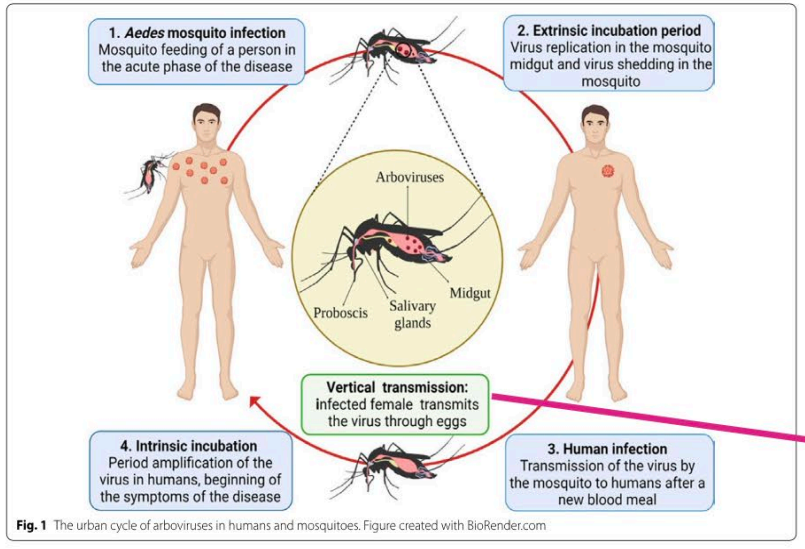
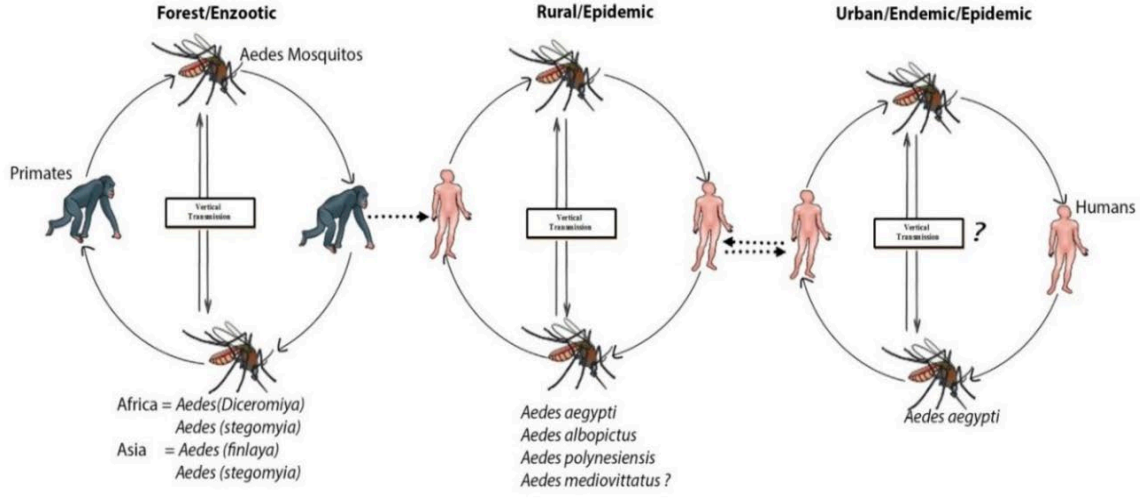


Fig. 1 The urban cycle of arboviruses in humans and mosquitoes. Figure created with BioRender.com

Gómez et al. Parasites & Vectors (2022) 15:287 https://doi.org/10.1186/s13071-022-05401-9

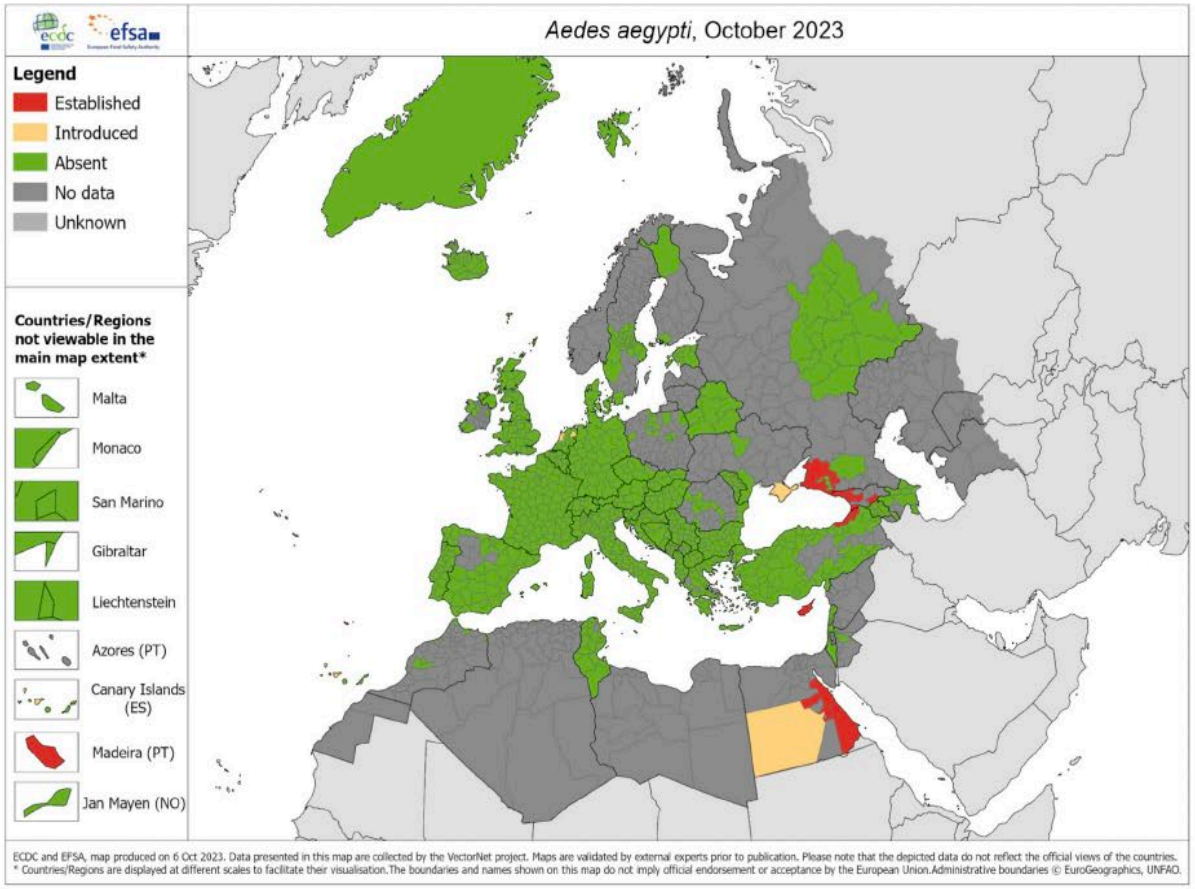
Aedes aegypti
Aedes albopictus

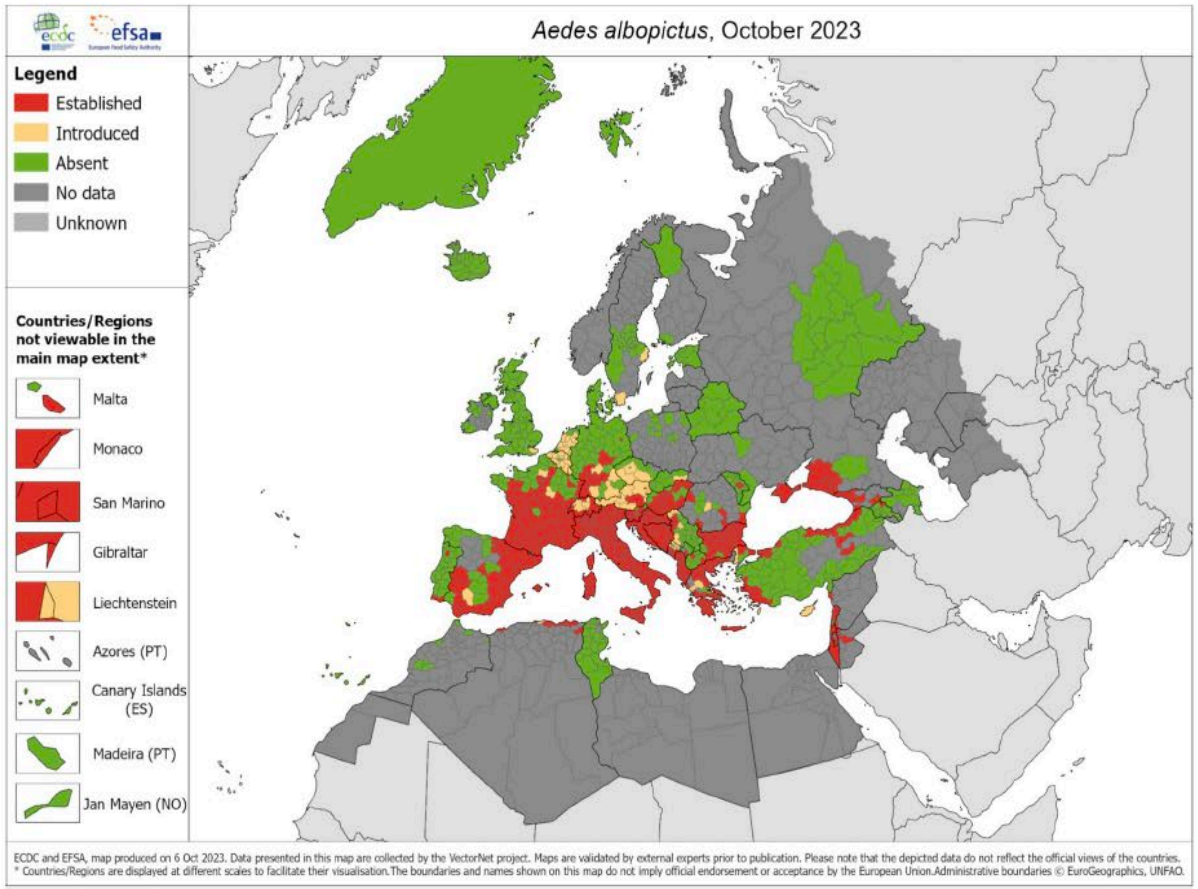
Aedes albopictus
Uova diapausanti
Resistono fino a -10°C
in climi temperati



Microorganisms **2019**, *7*, 296; doi:10.3390/microorganisms7090296

Dengue: i vettori in Europa





- depone uova resistenti all'essiccamento e al freddo (diapausanti; -10°C)
- ciclo di sviluppo larvale in piccoli contenitori con poca acqua stagnante
- pungono un'ampia varietà di ospiti, fra i quali l'essere umano.

Dengue: epidemiologia

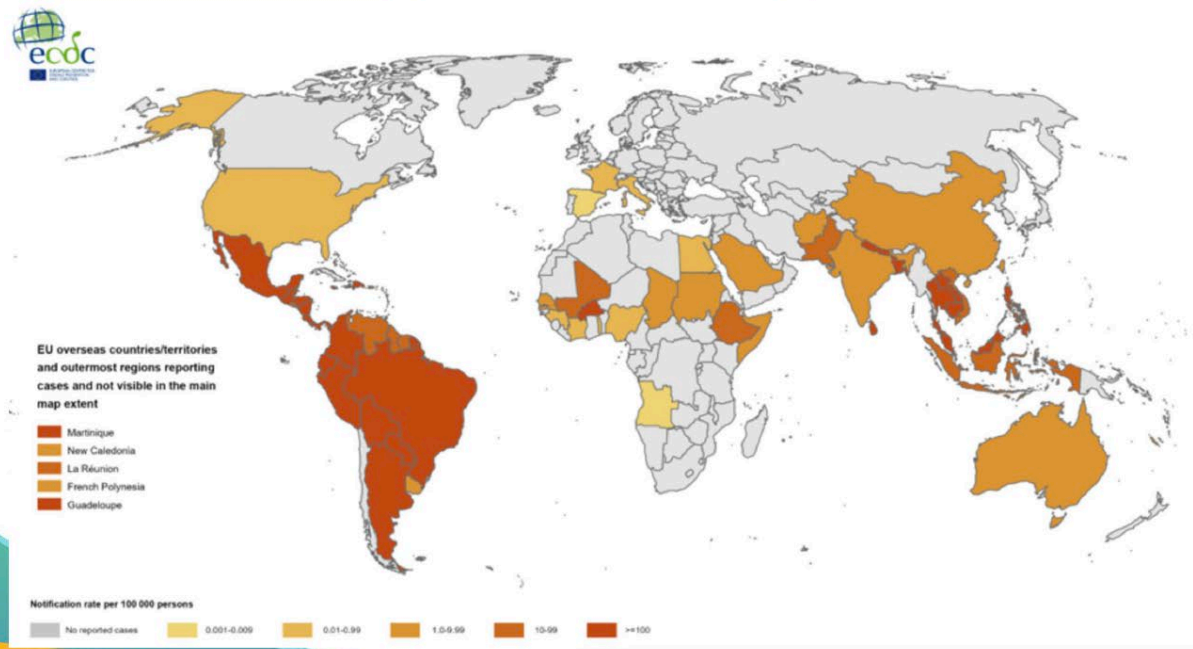
Situation update, March 2024

Since the beginning of 2024 **over two million dengue cases** and **over 500 dengue-related deaths** have been reported globally.

Most cases were reported in the WHO PAHO region with a cumulative number of 1 874 021 suspected cases reported until week 8 of 2024 (ending 25 February 2024).

According to the PAHO report of 7 March 2024, this is an increase of 249% compared to the same period in 2023.

Region with most cases	The Americas
Locally acquired cases in continental Europe (2023)	Italy, France, and Spain
Receptive areas of Europe: moderate transmission likelihood	environmental conditions become less favourable to vector activity and virus replication

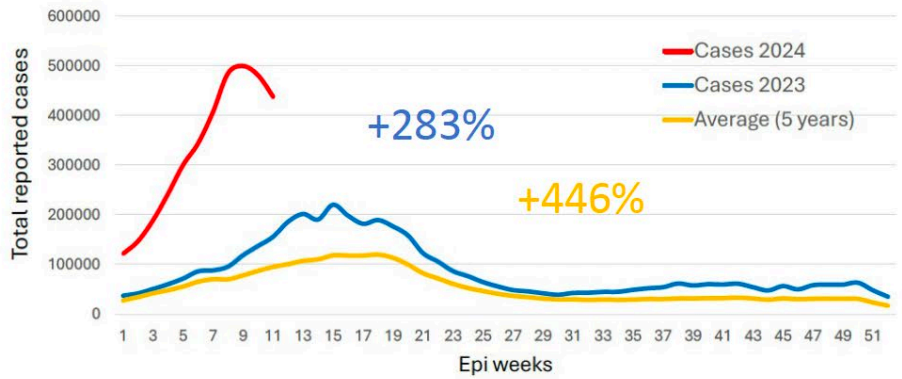


ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL Home

PAHO Pan American Health Organization World Health Organization

Report on the epidemiological situation of dengue in the Americas

Figure 1. Total number of suspected dengue cases as of EW 11 in 2024, 2023 and average of the last 5 years.Region of the Americas.



3.665.589 casi totali tra w1 e w11 2024
3.073 casi gravi (0.1%)
1.187 morti (case fatality rate 0.032%)

E. aegypti è ampiamente distribuita nelle Americhe.
Canada e Cile continentale non hanno dengue né vettore.

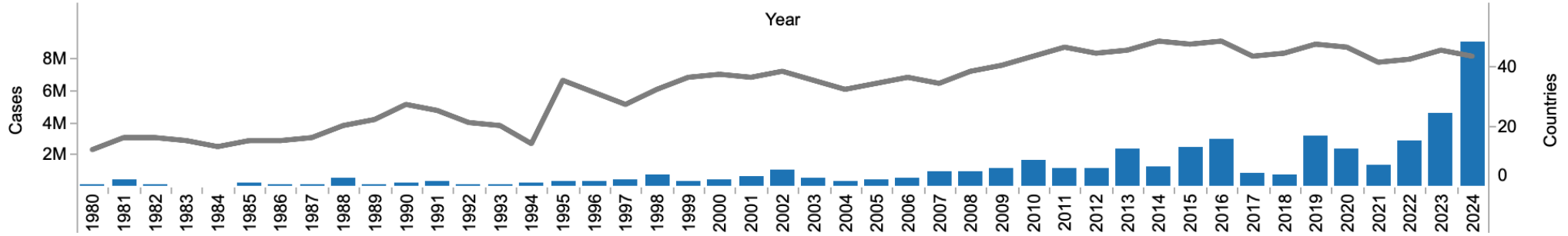
Continente Americano, 2024

system of mandatory notification that covers all of the national territory.

Dengue Cases

Year: 2024

Region	Total	Confirmed	Severe	Deaths
The Americas	8,991,508	4,344,779	8,915	4,157



Dengue: episodi di trasmissione autoctona EU

YEAR	COUNTRY	REGION	No of cases	MONTHS
2010	Croatia	Korčula Island and the Pelješac peninsula	10	August–October
2010	France	Alpes-Maritimes department	2	August–September
2013	France	Bouches–du-Rhône department	1	September-October
2014	France	Var and Bouches-du-Rhône departments	4	July-September
2015	France	Gard department	8	July–September
2018	France	Alpes Maritimes, Hérault, and Gard departments	8	September –October
2018	Spain	Catalonia region, Murcia region or province of Cádiz	6	August-October
2019	Spain	Catalonia region	1	September
2019	France	Alpes-Maritimes and Rhône departments	9	July-September

YEAR	COUNTRY	REGION	No of cases	MONTHS
2020	France	Hérault, Var, Alpes-Maritime, and Gard departments	13	July-October
2020	Italy	Veneto region	10	August
2021	France	Var and Hérault departments	2	July and September
2022	France	Pyrénées-Orientales, Hautes-Pyrénées, Haute-Garonne, Tarn et Garonne, Var, Alpes-Maritime, and Corsica departments	65	June-September
2022	Spain	Ibiza	6	August-October
2023	France	Île-de-France (3 cases), Bouches–du-Rhône (14 cases in 2 clusters), Pyrénées-Orientales (11 cases), Hérault (3 cases), Gard (9 cases), Alpes-Maritimes (3 cases) and Auvergne Rhône-Alpes (2 cases) departments.	45	July-October
2023	Italy	Lodi (41 cases), Rome (38 cases in the Rome metropolitan city and 1 case in Anzio) and Latina (2 cases) provinces.	82	End of July-November
2023	Spain	Catalonia (3 cases)	3	August-October

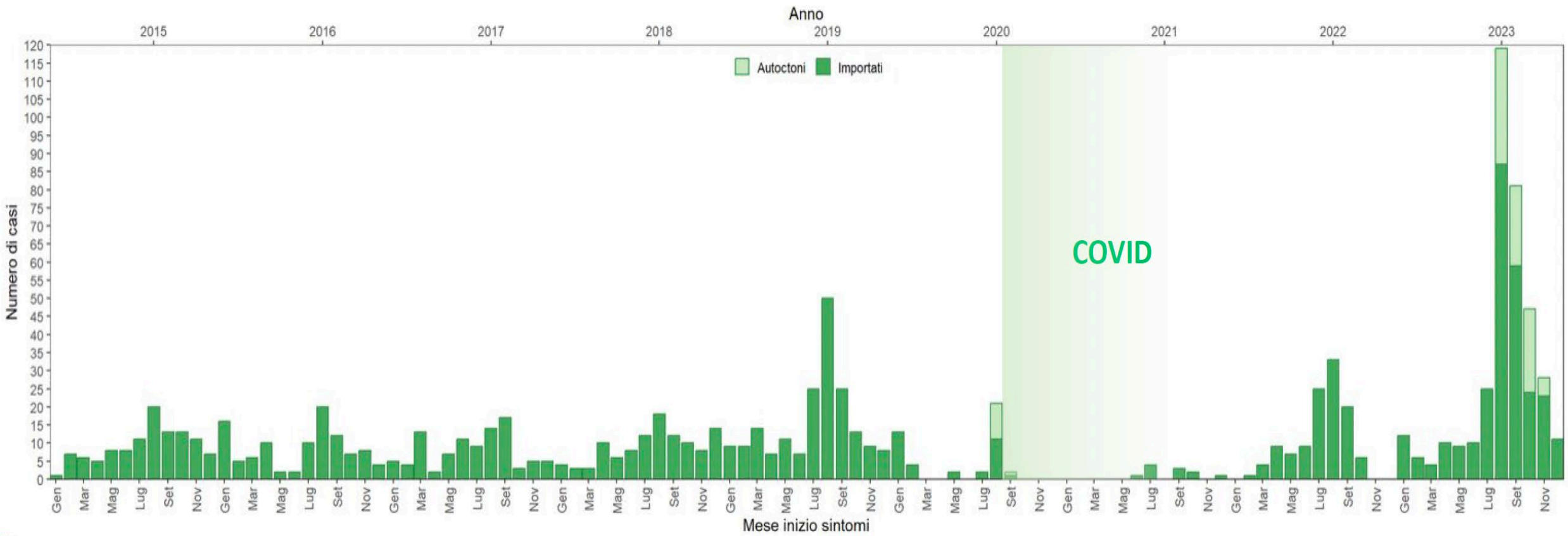
Del Manso M, Di Maggio E, Perego G, Petrone D, Mateo-Urdiales A, Caporali MG, Bella A, Venturi G, Di Luca M, Giannitelli S, Maraglino F, Ferraro F, Pezzotti P, Riccardo F; Arbovirosi in Italia - 2023

Data di ultimo aggiornamento: 09 gennaio 2024

Istituto Superiore di Sanità
EpiCentro - L'epidemiologia per la sanità pubblica

Dengue: trend in Italia 2015-2023

Mobilità della popolazione influenza l'epidemiologia



Dengue: epidemiologia in Italia 2023

Istituto Superiore di S
EpiCentro - L'epidemiologia pe

Arbovirosi in Italia 2023	Dengue	Zika Virus	Chikungunya	TBE	Toscana Virus

362
Casi*

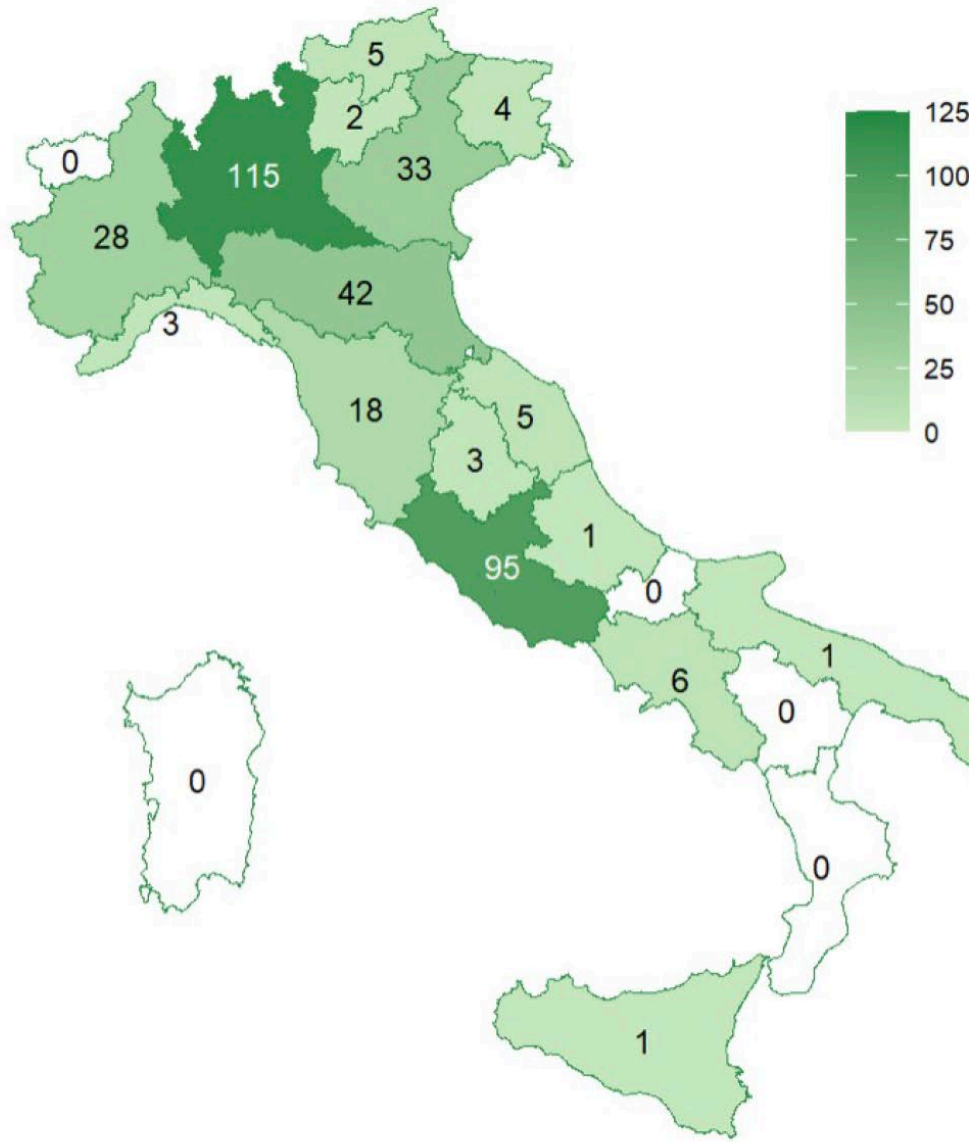
51.93% | 48.07%
Maschi | Femmine*

37 anni
Età mediana*

1
Decessi*

82 casi | 280 casi
Autoctoni | Importati*

*Dati dell'anno 2023 in fase di consolidamento



Dengue: outbreak 2020

RAPID COMMUNICATION

First autochthonous dengue outbreak in Italy, August 2020

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Lazzarini Luca , Barzon Luisa , Foglia Felice , Manfrin Vinicio , Pacenti Monia , Pavan Giacomina , Rassu Mario , Capelli Gioia , Montarsi Fabrizio , Martini Simone , Zanella Francesca , Padovan Maria Teresa , Russo Francesca , Gobbi Federico . First autochthonous dengue outbreak in Italy, August 2020. Euro Surveill. 2020;25(36):pii=20-01606. https://doi.org/10.2807/1560-7917.ES.2020.25.36.2001606

Article submitted on 31 Aug 2020 / accepted on 10 Sep 2020 / published on 10 Sep 2020

TABLE

Clinical and laboratory findings in outbreak (family cluster) of autochthonous dengue, Vicenza Province, Italy, July August 2020 (n=6)

Clinical, epidemiological and laboratory parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Date of symptom onset	30 Jul	16 Aug	16 Aug	16 Aug	18 Aug	18 Aug
Delay between sample collection and onset of symptoms (days)	27	10	6	10	8	8
Symptoms	Fever (38° C), arthralgia, myalgia, headache	Fever (39° C), arthralgia, myalgia, headache	Fever (38° C), arthralgia, upper limb itching	Fever (38° C)	Fever (38.5° C)	Fever (39° C)
Epidemiological link	Source case	Household contact of Case 1	Index case and household contact of Case 1	Household contact of Case 1	Household contact of Case 1	Household contact of Case 1
DENV RNA in blood[a]	Negative	DENV-1	DENV-1	Negative	DENV-1	DENV-1
DENV RNA in urine[a]	Negative	DENV-1	DENV-1	DENV-1	DENV-1	DENV-1
DENV RNA in saliva[a]	Negative	Negative	DENV-1	Negative	DENV-1	DENV-1
DENV NS1 antigen[b]	Negative	Positive	Positive	Negative	Positive	Positive
DENV IgM[c]	Positive	Positive	Negative	Positive	Positive	Positive
DENV IgG[c]	Positive	Negative	Negative	Negative	Negative	Negative

Lazzarini Luca , Barzon Luisa , Foglia Felice , Manfrin Vinicio , Pacenti Monia , Pavan Giacomina , Rassu Mario , Capelli Gioia , Montarsi Fabrizio , Martini Simone , Zanella Francesca , Padovan Maria Teresa , Russo Francesca , Gobbi Federico . First autochthonous dengue outbreak in Italy, August 2020. Euro Surveill. 2020;25(36):pii=20-01606. https://doi.org/10.2807/1560-7917.ES.2020.25.36.2001606

Dengue: outbreak 2022

RAPID COMMUNICATION

Outbreaks of autochthonous Dengue in Lazio region, Italy, August to September 2023: preliminary investigation

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3. Directorate for Health and Social Policy, Lazio Region, Rome, Italy
4. UOC Diagnostica generale, Istituto Zooprofilattico Sperimentale del Lazio e della Toscana "M. Aleandri", Rome, Italy
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13. The members of the group are listed under Collaborators

De Carli Gabriella, Carletti Fabrizio, Spaziante Martina, Gruber Cesare Ernesto Maria, Rueca Martina, Spezia Pietro Giorgio, Vantaggio Valentina, Barca Alessandra, De Liberato Claudio, Romiti Federico, Scicluna Maria Teresa, Vaglio Stefania, Feccia Mariano, Di Rosa Enrico, Gianzi Francesco Paolo, Giambi Cristina, Scognamiglio Paola, Nicastri Emanuele, Girardi Enrico, Maggi Fabrizio, Vairo Francesco, the Lazio Dengue Outbreak Group. Outbreaks of autochthonous Dengue in Lazio region, Italy, August to September 2023: preliminary investigation. Euro Surveill. 2023;28(44):pii=2300522. https://doi.org/10.2807/1560-7917.ES.2023.28.44.2300552

TABLE

Epidemiological and laboratory characteristics of the three autochthonous dengue transmission events in the Lazio Region, Italy, 2023 (n = 7)

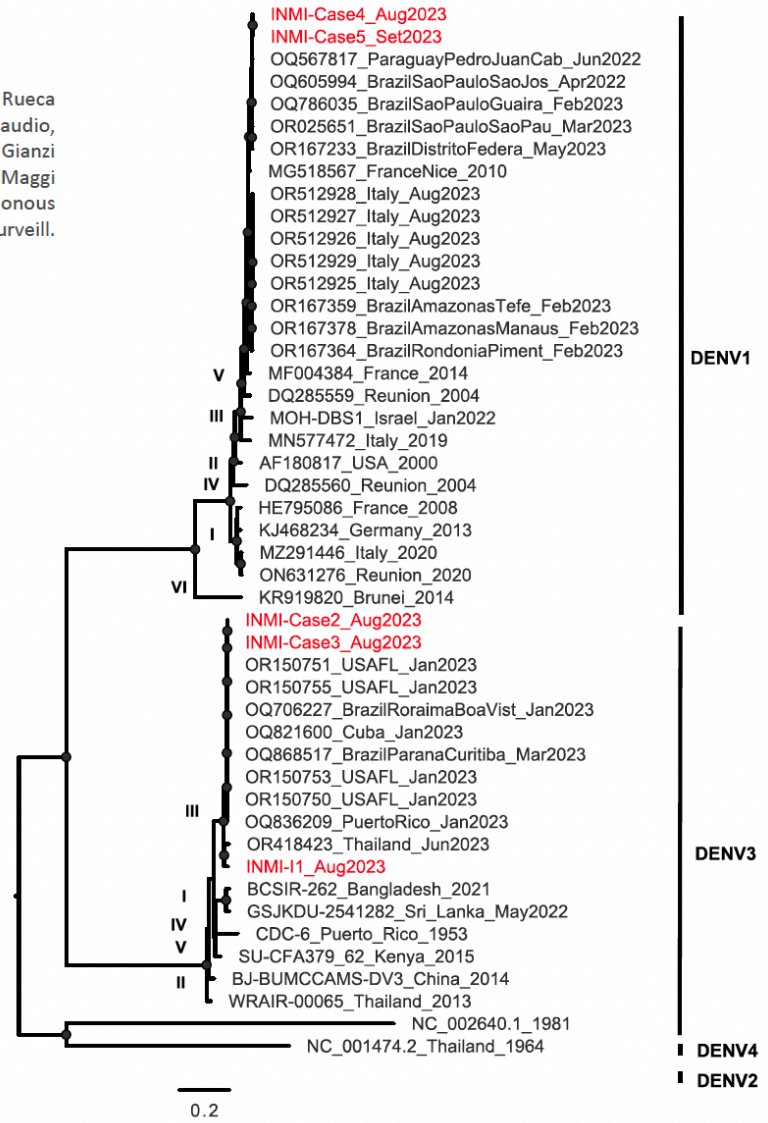
Epidemiological and laboratory parameters	DENV-1 cluster[a]				DENV-3 cluster		DENV-2
	Case 1	Case 4	Case 5	Case 6	Case 2	Case 3	Case 7
Date of notification	18 Aug	5 Sep	8 Sep	12 Sep	31 Aug	31 Aug	20 Sep
Epidemiological link with imported case	No	No	No	No	No	No	Yes
Laboratory results							
DENV NS1 antigen	NA	Negative	Positive	Positive	Positive	Positive	Positive
DENV IgG IC	Positive	Borderline	Positive	Negative	Negative	Negative	NA
DENV IgM IC	Positive	Borderline	Positive	Positive	Negative	Negative	NA
DENV IgG IF	Positive	Positive	Positive	NA	Weak reactivity	Weak reactivity	Positive
DENV IgM IF	Positive	Positive	Positive	NA	Weak reactivity	Weak reactivity	Positive
DENV RT-PCR (Cq at diagnosis)	31	32	23	27	22	24	36
DENV serotype	1	1	1	1	3	3	2

Cq: quantification cycle; DENV: dengue virus; IC: immunochromatography; IF: immunofluorescence; NA: not available.

[a] Only the first four cases in this cluster for whom phylogenetic analysis was completed are shown.

Twenty-five additional cases with no travel history have been reported in Rome and province of Rome and linked to the DENV-1 cluster as at 16 October.

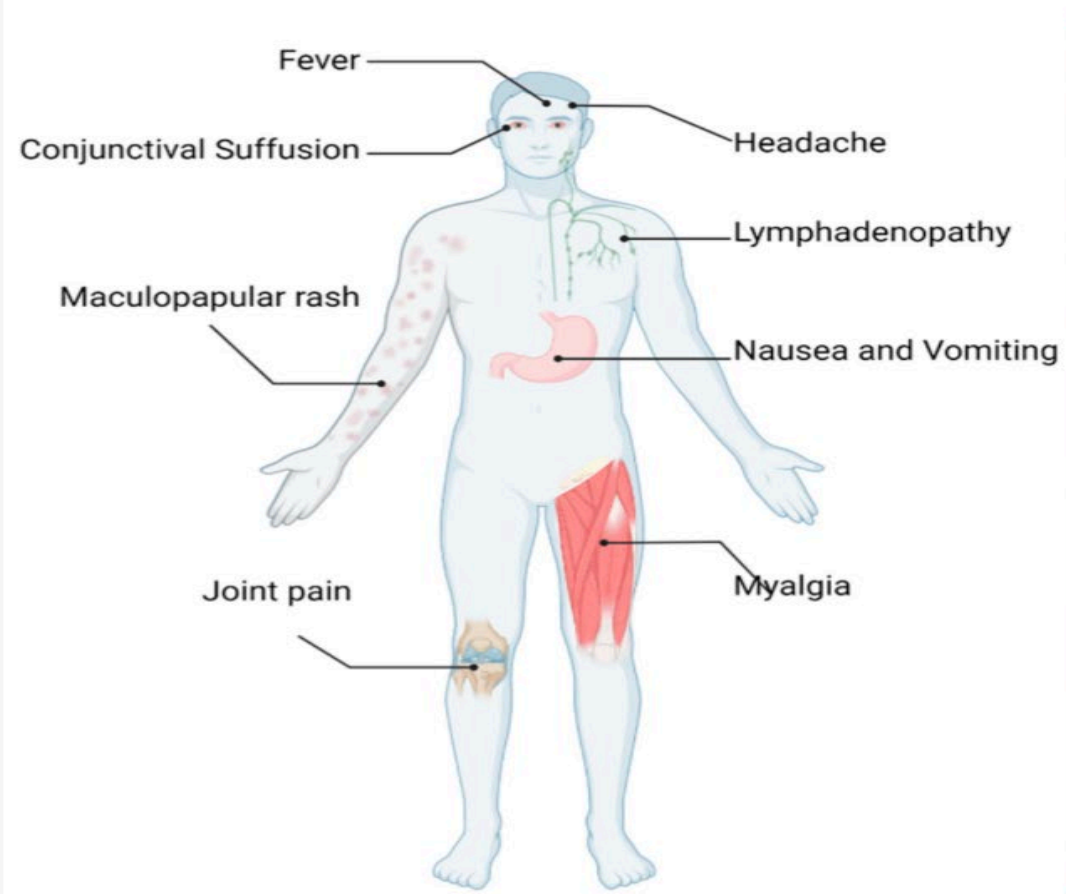
B. Whole genome sequencing

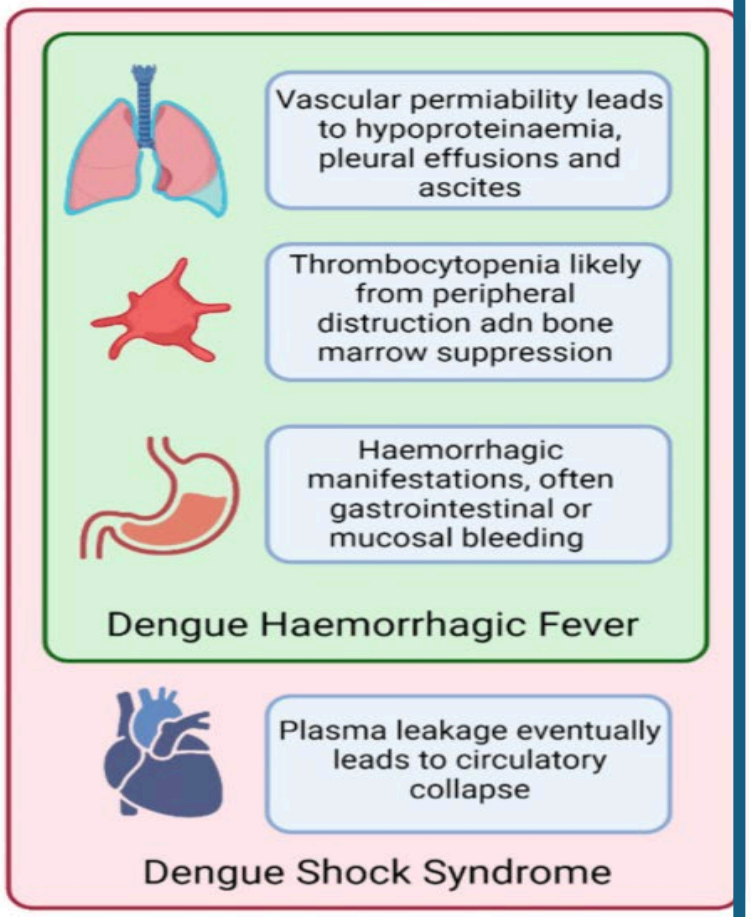


Più introduzioni virali contemporanee

Between 40% and 80% of dengue infections are asymptomatic.

Figure 1. Systemic effects of dengue and time course of infection.





Febrile Phase
Onset commonly 5-7 days after bite

Critical Phase
Onset 4-5 days after fever

PAHO Pan American Health Organization World Health Organization Americas Region

2010

Dengue case classification by severity

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
- Leucopenia
- 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 enlargement >2cm
- *Laboratory:* Increase in HCT concurrent with rapid decrease in platelet count

** Requiring strict observation and medical intervention*

Criteria for severe dengue

1. Severe plasma leakage leading to:
- Shock (DSS)
- Fluid accumulation with respiratory distress

2. Severe bleeding
as evaluated by clinician

3. Severe organ involvement
- Liver: AST or ALT>=1000
- CNS: Impaired consciousness
- Heart and other organs

utorità sanitaria internazionale >

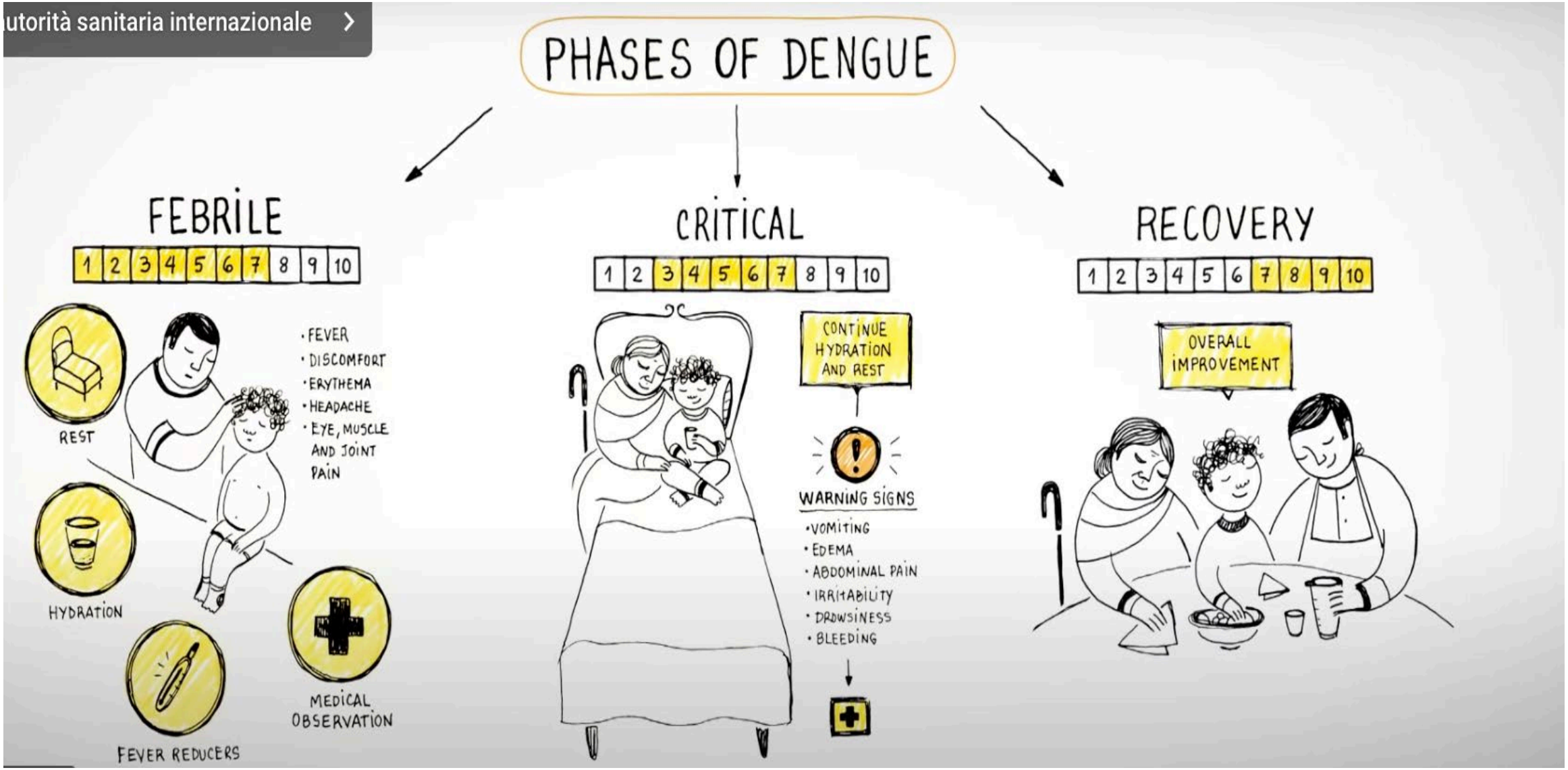


PHOTO QUIZ

Philip A. Mackowiak, Section Editor

Fever in a Returned Traveler: An "Off the Cuff" Diagnosis

(See pages 1074–5 for Answer to Photo Quiz)

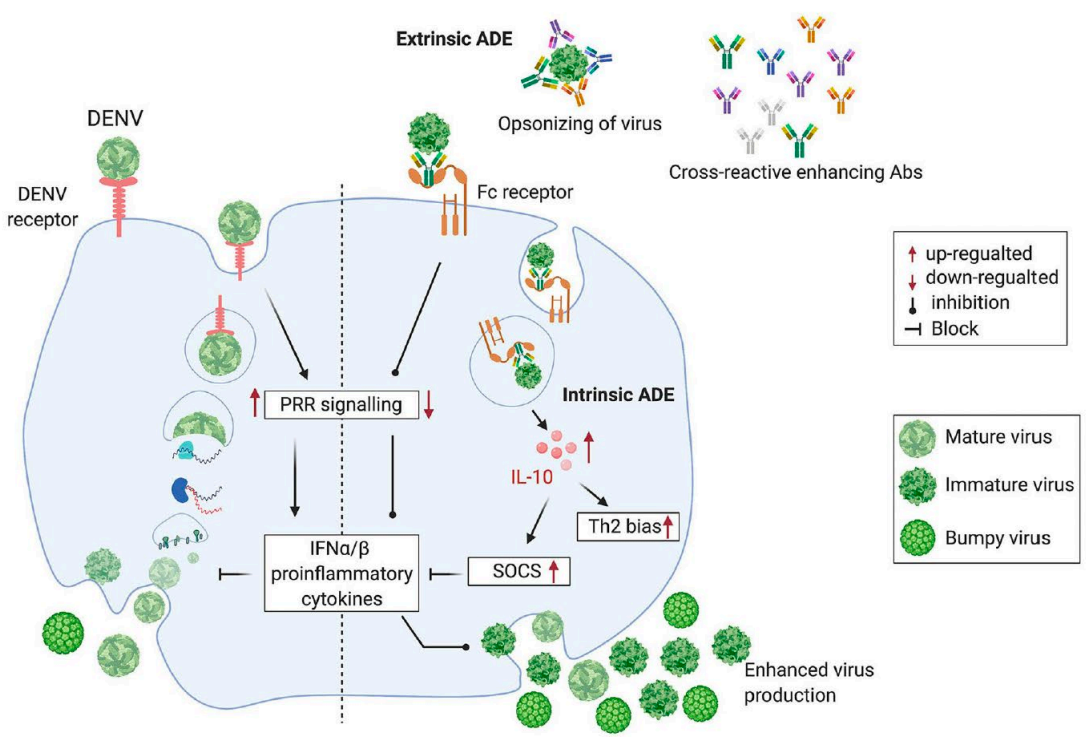
Figure 1

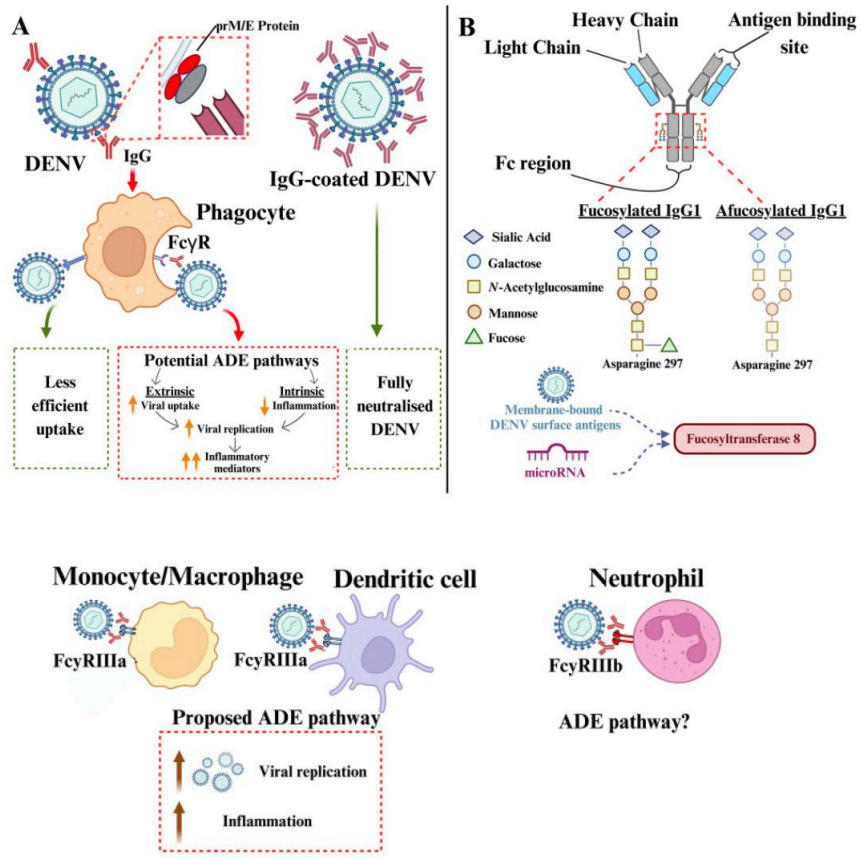
New linear petechial eruptions were noted on her
right arm immediately after the blood pressure cuff was deflated

SECONDA INFEZIONE

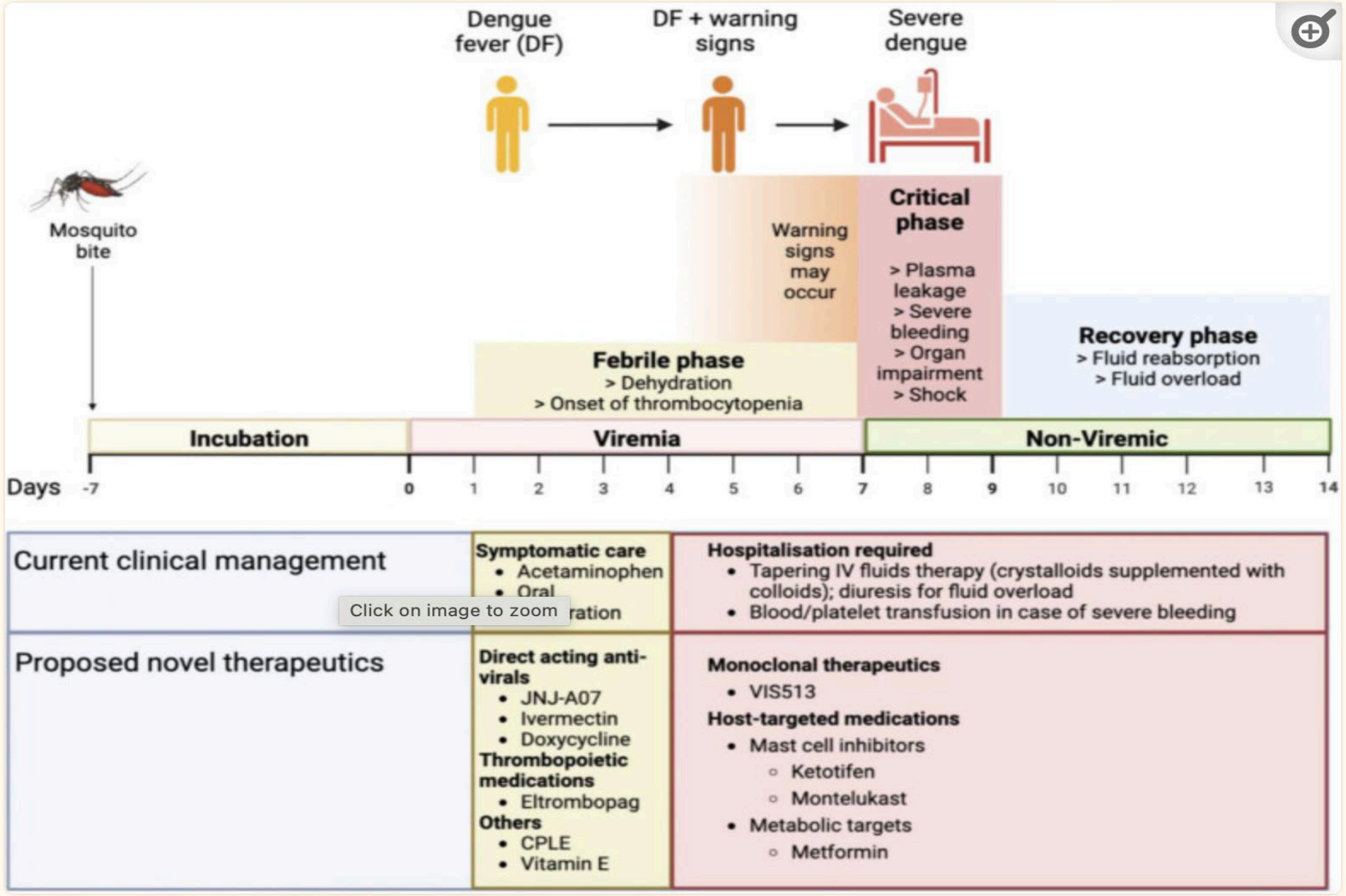
Teo A, Tan HD, Loy T, Chia PY, Chua CLL (2023) Correction: Understanding antibody-dependent enhancement in dengue: Are afucosylated IgG1s a concern?. PLOS Pathogens 19(10): e1011736.

Dengue: antibody-dependent enhancement (ADE)





The phenomenon, in which preexisting non-neutralizing antibodies lead to enhanced infection, is termed ADE. Beyond studies with patients suggesting this phenomenon in DENV infection, highlighting those described above with newborn infants and children



Palanichamy Kala M, St John AL, Rathore APS. Dengue: Update on Clinically Relevant Therapeutic Strategies and Vaccines.
Curr Treat Options Infect Dis. 2023;15(2):27-52. doi: 10.1007/s40506-023-00263-w. Epub 2023 Apr 18. PMID: 37124673; PMCID: PMC10111087.

Dengue: la situazione in America del Sud

Nel 2023 «El Niño Southern Oscillation» (ENSO) ha influenzato il clima dell'America Meridionale

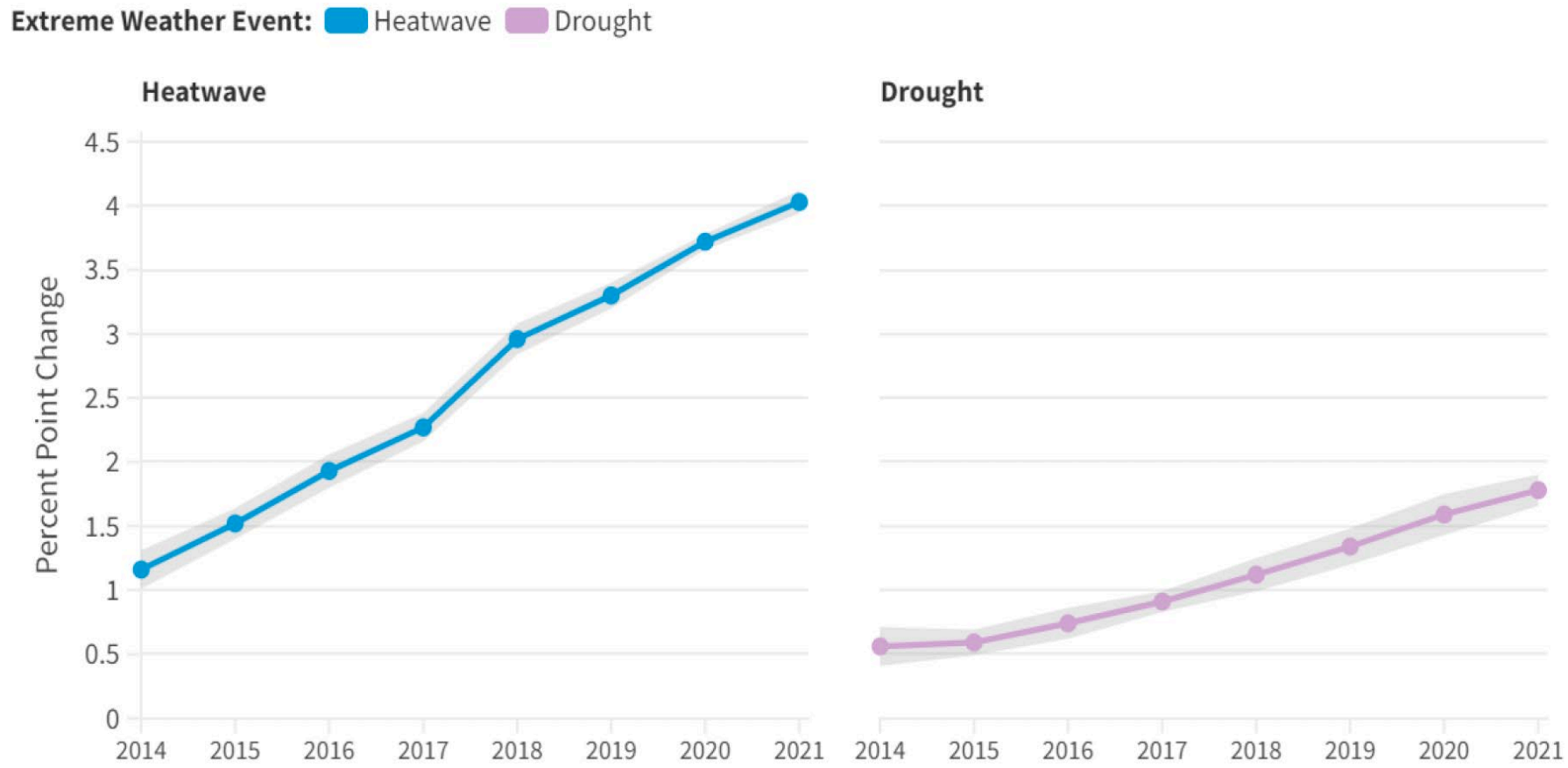
- La regione settentrionale del Brasile ha registrato meno precipitazioni del previsto e ha dovuto affrontare una siccità storica. Una parte della popolazione ha dovuto immagazzinare acqua aumentando i luoghi con acqua stagnante, potenziali siti di riproduzione delle zanzare.
- Allo stesso tempo, il sud è stato colpito da numerose inondazioni. L'intenso volume d'acqua ha causato un aumento dei luoghi di accumulo di acqua, che ha comportato anche un aumento dei siti di riproduzione.

Dengue: Climate change

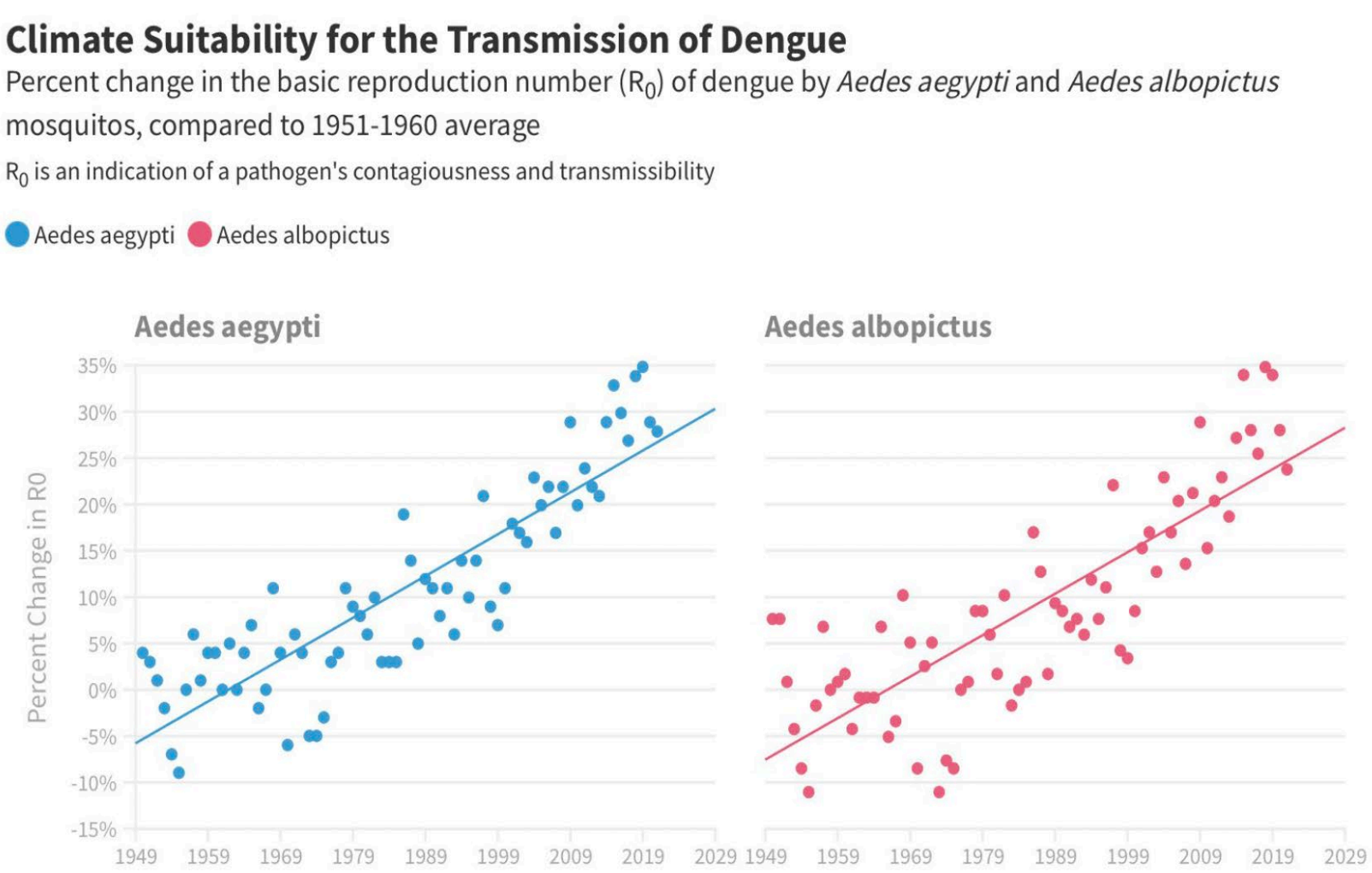
LANCET COUNTDOWN: TRACKING PROGRESS ON HEALTH AND CLIMATE CHANGE

Impact of Extreme Weather on Food Insecurity

Change in the share of the population reporting moderate or severe food insecurity due to change in heatwave days and drought months ocurring during the growth season of four major crops (maize, rice, sorghum, and wheat) , compared to 1981-2010

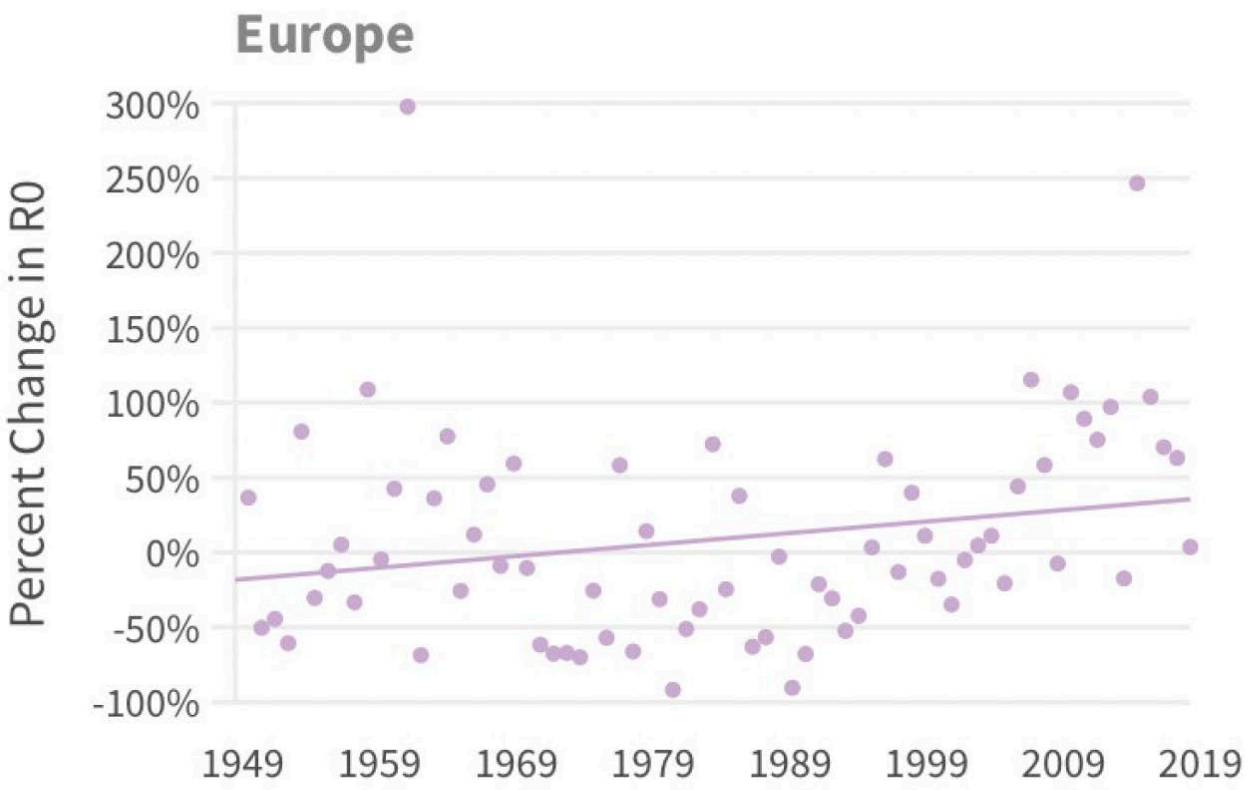


Dengue: proiezioni R_0

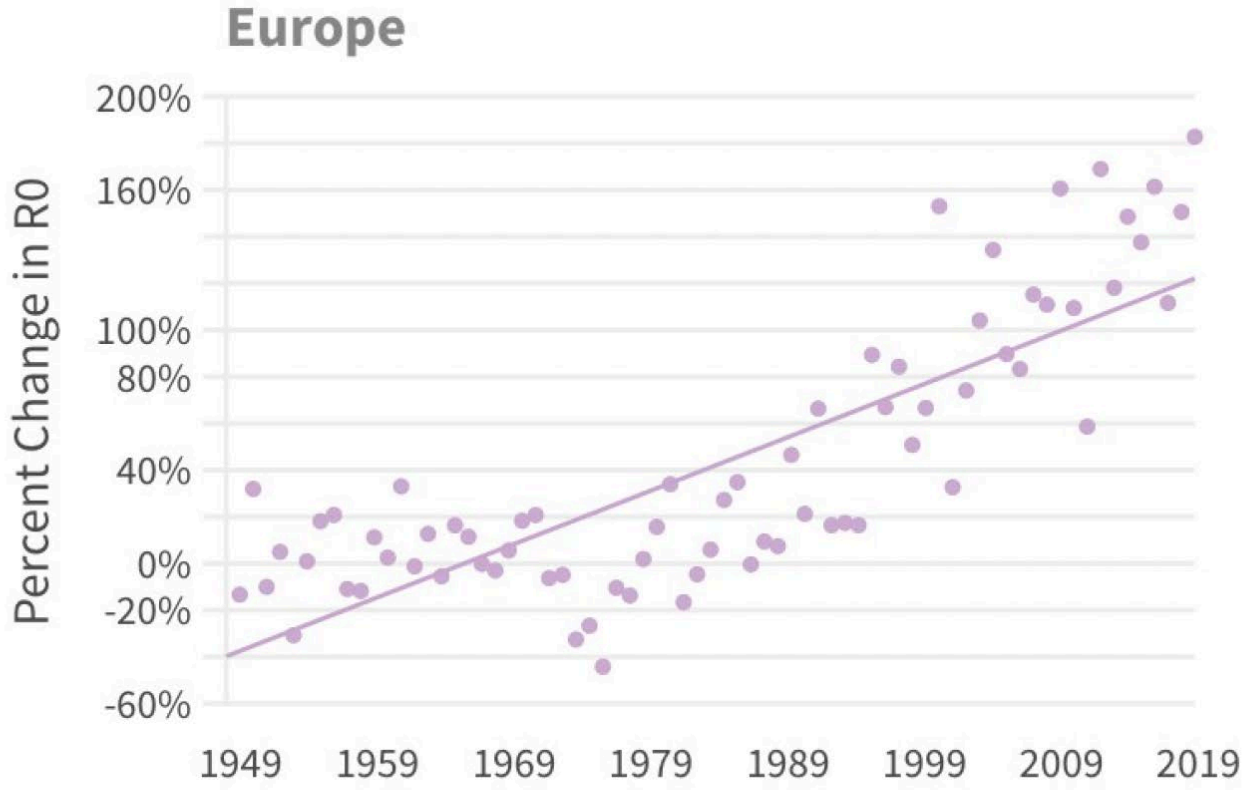


R_0 "numero di riproduzione di base": rappresenta il numero medio di infezioni secondarie prodotte da ciascun individuo infetto in una popolazione completamente suscettibile (mai venuta a contatto con il nuovo patogeno emergente)

Dengue: proiezioni R_0 in Europa



Aedes aegypti

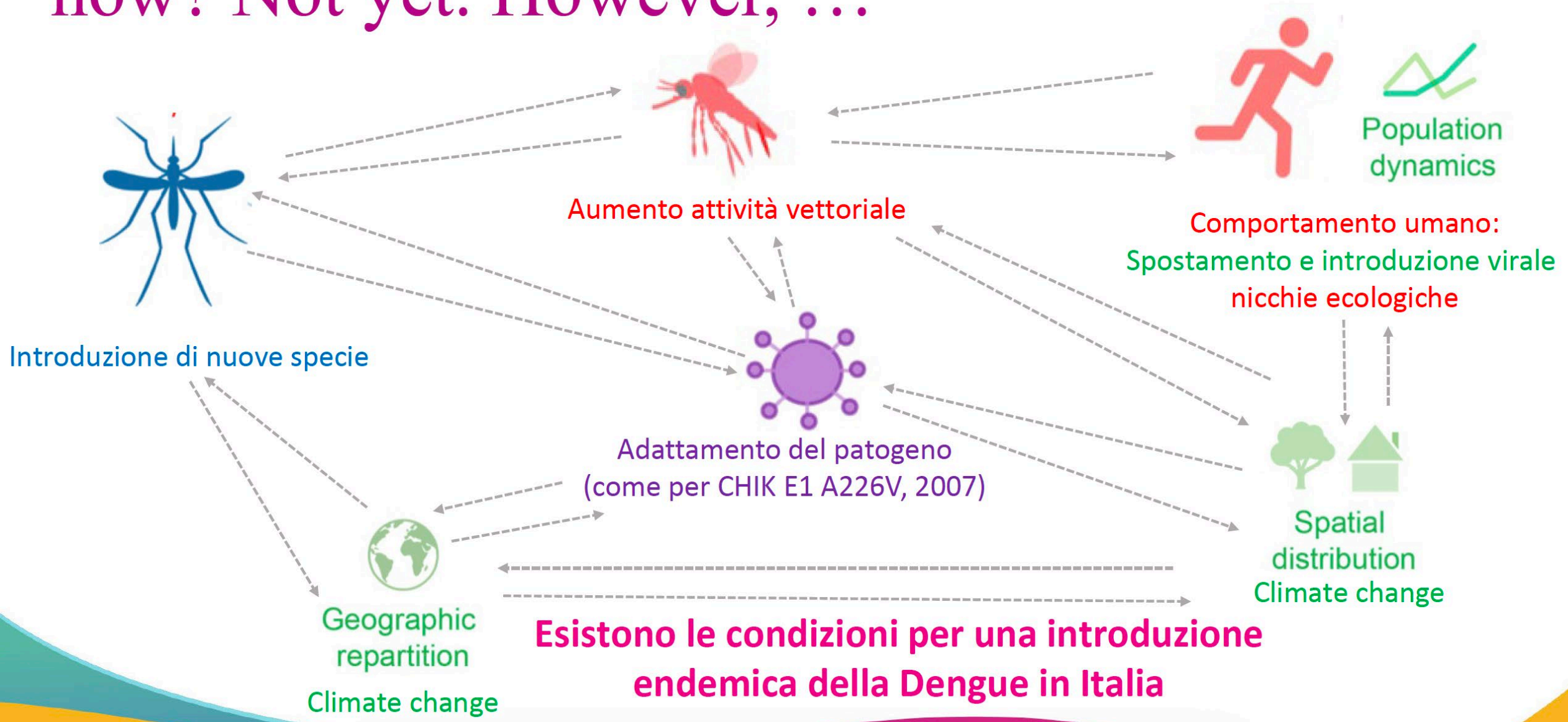


Aedes albopictus

Dengue: should we consider it an endemic disease now? Not yet. However, …

- Vettore presente in Italia: *Ae. albopictus*
- Cambiamenti climatici (aumento temperatura, modifica precipitazioni piovose) con ampliamento delle nicchie ecologiche per *Ae. Albopictus*, incremento R0 per Dengue e possibile introduzione di *Aedes aegypti*
- Fenomeni di introduzione di Dengue sempre più frequente (viaggi e mobilità della popolazione)
- Casi asintomatici e paucisintomatici che ostacolano rapida identificazione e notifica dei casi per tracciamento e interventi di disinfestazione con adulticidi e larvicidi
- Possibile ruolo svolto da reservoirs animali

Dengue: should we consider it an endemic disease now? Not yet. However, …



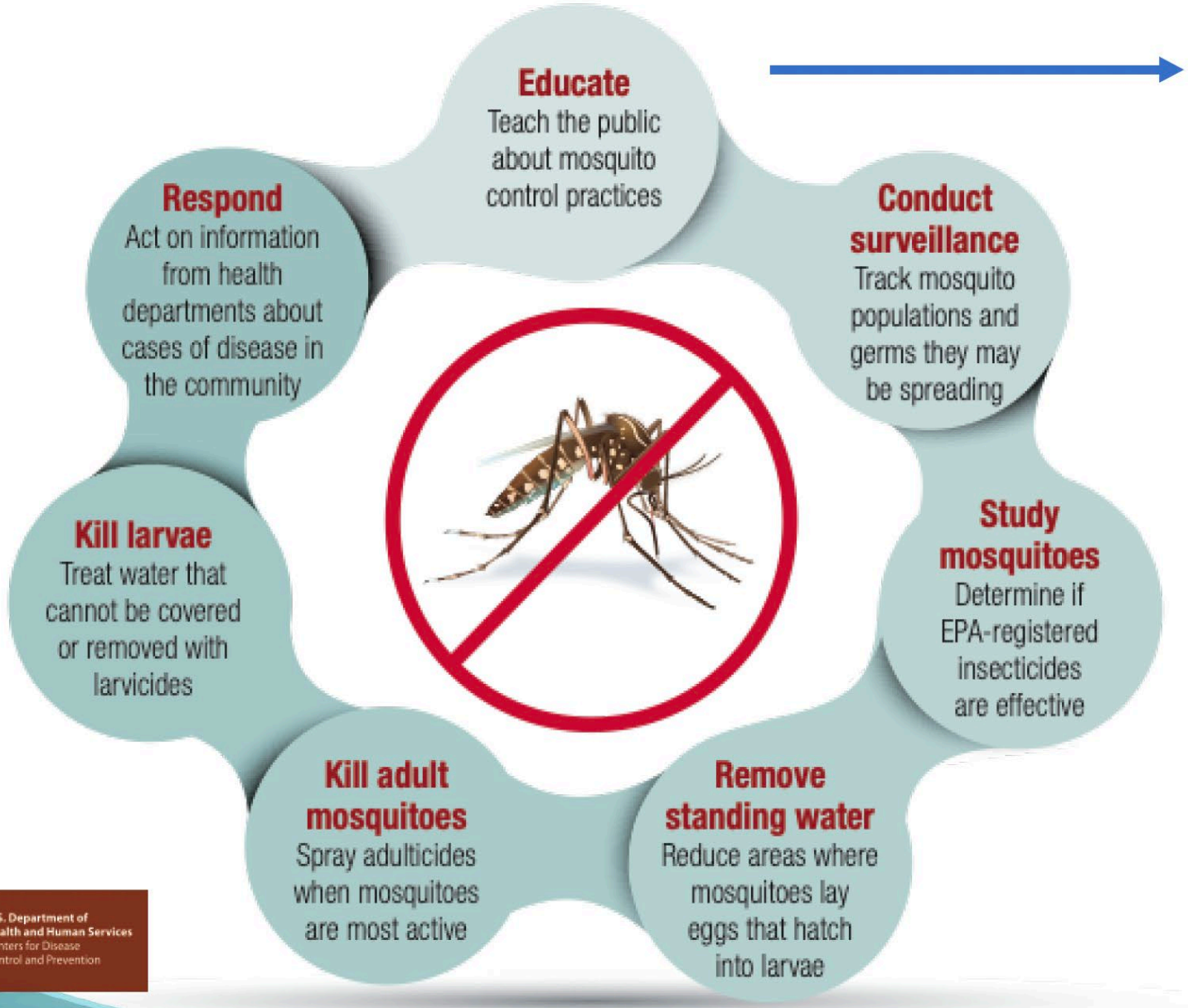
Dengue: controllo del vettore

- Tutte le attività di controllo dei vettori hanno un beneficio limitato se la popolazione generale non è incoraggiata a limitare i siti di riproduzione delle zanzare ed evitare contatti uomo-vettori.
- Le strategie preventive dovrebbero rafforzare la comunicazione al pubblico in generale e agli operatori sanitari.
- Necessario un forte coinvolgimento sia degli enti pubblici che privati nelle azioni contemporanee volte a controllare le popolazioni di vettori.
- Un approccio **One Health** è fondamentale per prevenire l'emergenza e la diffusione della dengue nelle aree temperate

Dengue: strategie di prevenzione

- Per impedire la diffusione di Dengue nelle aree temperate, è necessario attuare tempestivamente diverse misure di sanità pubblica:
  - È fondamentale notificare tempestivamente i casi
  - Stratificare il rischio ed effettuare interventi dando priorità alle popolazioni a maggio rischio
  - Mettere in atto un sistema di sorveglianza proattivo poiché una diagnosi ritardata può favorire una circolazione virale incontrollata

Dengue: controllo del vettore



outdoor

indoor

Dengue: vaccini

- Indicazione della vaccinazione nei viaggiatori e nei soggetti ad alto rischio per esposizione professionale
- **Controindicati** nelle donne in gravidanza o in allattamento e nei soggetti immunocomrpomessi, o in trattamento con terapie immunosoppressive, salvo adeguato intervallo di wash-out (viremie vaccinali sintomatiche)

Dengue: vaccini

- Qdenga (febbraio 2023):
  - **Vivo attenuato**
  - Prodotto in cellule Vero mediante tecnologia del DNA ricombinante. Geni di proteine di superficie sierotipo-specifiche (DENV-1, -2, -3, -4) ingegnerizzati nella struttura della dengue di tipo 2.
  - 2 iniezioni a distanza di 3 mesi
  - Adulti <4anni (non disponibili dati per adulti >60aa)

- Dengvaxia (luglio 2019)
  - **Vivo attenuato**
  - Prodotto in cellule Vero come virus della febbre gialla/dengue chimerico, sierotipo-1, -2, -3, -4
  - 3 iniezioni a intervalli di 6 mesi
  - Adulti, giovani e bambini (di età compresa tra 6 e 45 anni) che hanno avuto una precedente infezione dal virus dengue accertata mediante un test (ADE!)

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Live, Attenuated, Tetravalent Butantan–Dengue Vaccine in Children and Adults

E.G. Kallás, M.A.T. Cintra, J.A. Moreira, E.G. Patiño, P.E. Braga, J.C.V. Tenório, V. Infante, R. Palacios, M.V.G. de Lacerda, D.B. Pereira, A.J. da Fonseca, R.Q. Gurgel, I.C.-B. Coelho, C.J.F. Fontes, E.T.A. Marques, G.A.S. Romero, M.M. Teixeira, A.M. Siqueira, A.M.P. Barral, V.S. Boaventura, F. Ramos, E. Elias Júnior, J. Cassio de Moraes, D.T. Covas, J. Kalil, A.R. Precioso, S.S. Whitehead, A. Esteves-Jaramillo, T. Shekar, J.-J. Lee, J. Macey, S.G. Kelner, B.-A.G. Coller, F.C. Boulos, and M.L. Nogueira

Previous exposure to DENV, by serotype — no. (%)‡			
DENV-1	4295 (41.9)	2666 (44.6)	6961 (42.9)
DENV-2	4487 (43.7)	2766 (46.3)	7253 (44.7)
DENV-3	3801 (37.1)	2365 (39.6)	6166 (38.0)
DENV-4	4538 (44.2)	2791 (46.7)	7329 (45.1)
Unknown or missing data§	395 (3.9)	235 (3.9)	630 (3.9)

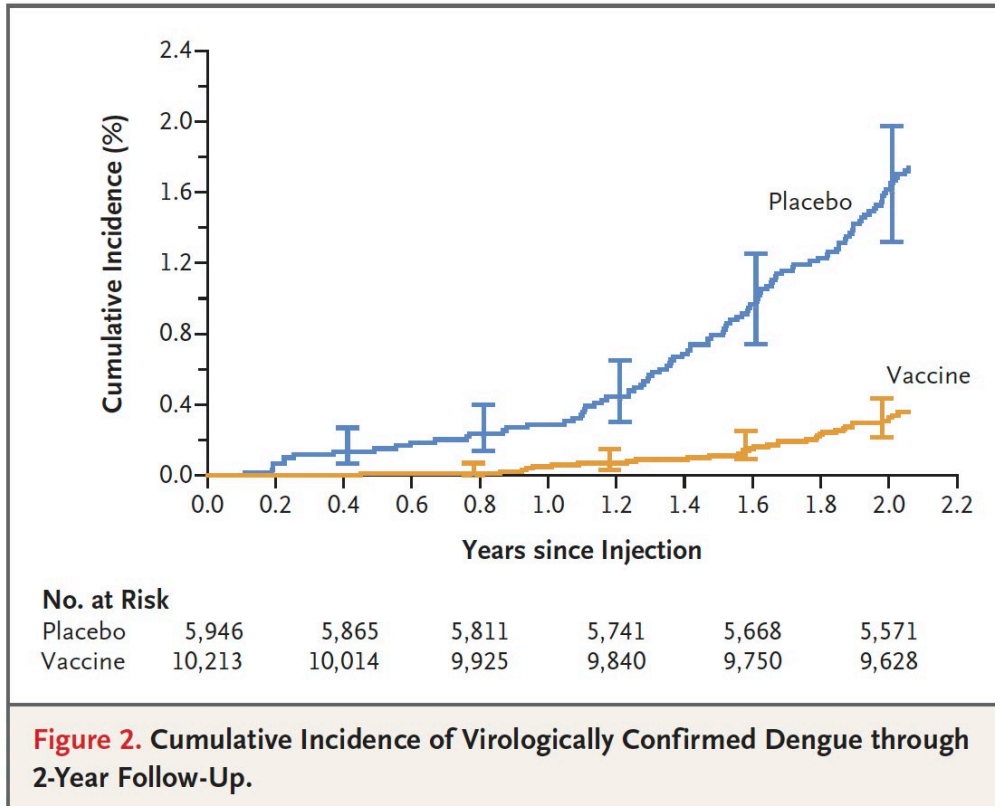

Figure 2. Cumulative Incidence of Virologically Confirmed Dengue through 2-Year Follow-Up.

In this phase 3 trial, a single administration of Butantan-DV was shown to have a favorable safety profile and be efficacious in preventing symptomatic, virologically confirmed dengue caused by DENV-1 and DENV-2, irrespective of previous dengue exposure, throughout a 2-year follow-up. These data support the continued development of Butantan-DV for the prevention of dengue disease in adults and children.

Dengue Vaccination

Pronounced (den-GEE)

Print

Sanofi-Pasteur will stop manufacturing its dengue vaccine for children. The manufacturer is discontinuing the vaccine citing a lack of demand in the global market to continue production of this vaccine. CDC, in collaboration with the Puerto Rico Department of Health, will continue alerting health professionals about the discontinuation of Dengvaxia and the use of this vaccine as recommended by the Advisory Committee on Immunization Practices (ACIP). Dengvaxia is safe and effective when administered as recommended. There are two other dengue vaccines either approved or in late stages of development. However, they are not currently available in the United States. People can continue to protect themselves and their families from dengue by preventing mosquito bites and controlling mosquitoes in and around their homes.

Conclusioni

- **Prevenzione (patologia che inesorabilmente aumenterà)**
- **Non abbiamo ancora una terapia antivirale**
- **Lo standard of care rimane la terapia di supporto (idratazione)**
- **Approccio combinato utilizzando vaccini e terapie.**