Oltre l'epidemia da SARS-CoV-2: l'impatto su vita e lavoro ed i patogeni da monitorare nel prossimo futuro

26 ottobre 2023 ore 9.30-14.00

L’incremento delle malattie trasmesse da vettore alle nostre latitudini

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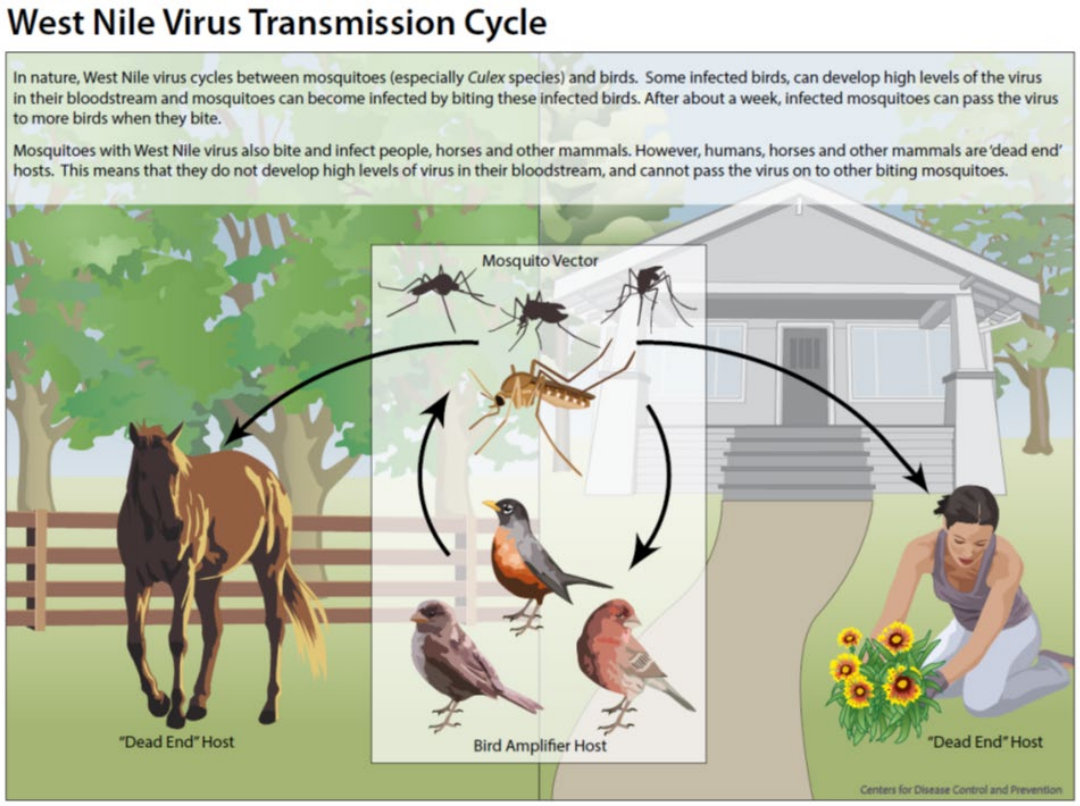
SOD Malattie Infettive e Tropicali
Azienda Ospedaliero Universitaria Careggi

West Nile Virus

- Flavivirus, *Vector-borne disease*
- Serbatoio: uccelli stanziali e migratori
- Vettore: zanzare ornitofile *Culex* spp.
- Altre vie di trasmissione: trapianti, trasfusioni, trasmissione verticale



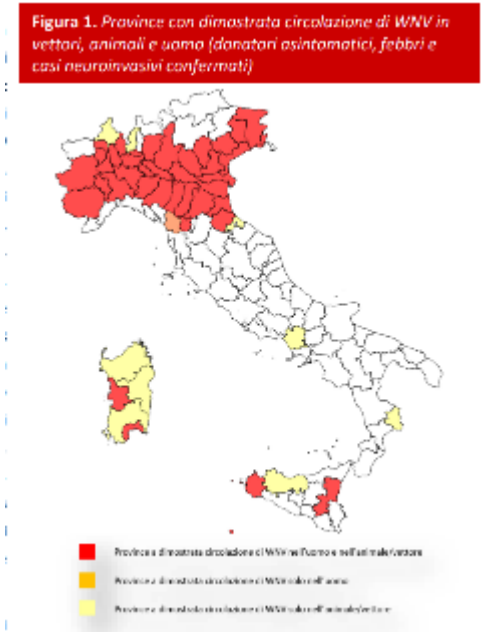
- Incubazione: 1-6 giorni
- Infezione asintomatica (80%)
- Sindrome similinfluenzale (20%): febbre, cefalea, astenia, malessere, mialgie e debolezza muscolare, disturbi gastrointestinali e rash maculare su tronco ed estremità
- Raramente epatite, pancreatite, orchite, miocardite, rabdomiolisi, corioretinite, aritmie
- Infezione neuroinvasiva (<1%): meningite/encefalite, sindrome di Guillain-Barré/radicolite, paralisi flaccida

West Nile Virus in Italy (2022)

- **588 confirmed cases**
  - 295 neuroinvasive disease (37 death, CFR 12.5%)
  - 89 blood donors (asymptomatic)
  - 194 West Nile fever
  - 10 minor symptoms

Distribution of neuroinvasive cases:

- Veneto 142
- Emilia-Romagna 69
- Piemonte 39
- Lombardia 26
- Sardegna 8
- Friuli Venezia Giulia 5
- Toscana 3
- Sicilia 3



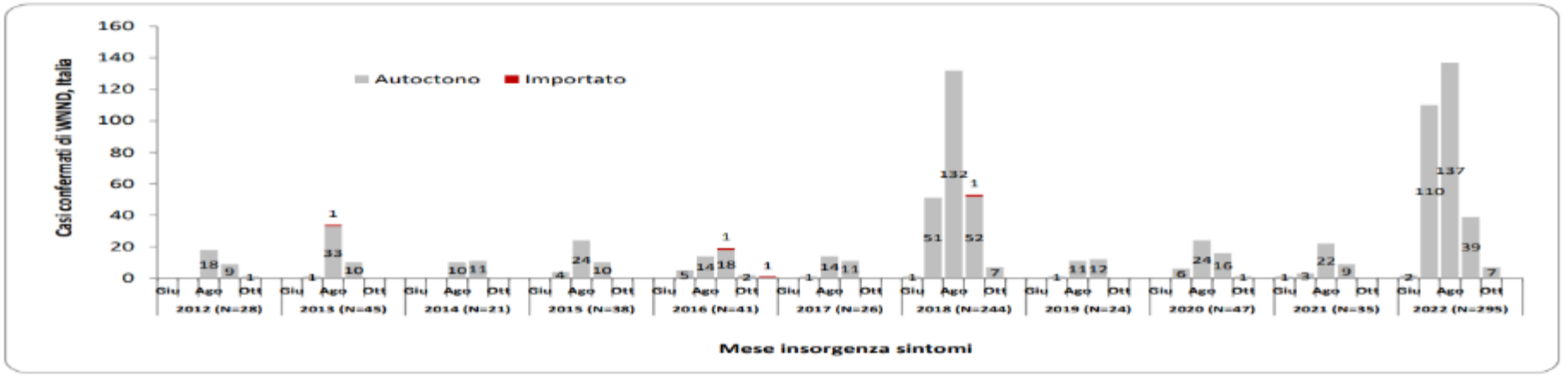


Figura 1. Andamento dei casi confermati di WNND per mese insorgenza sintomi. Italia: **2012 – 2022.**

West Nile Virus in Italy (2023)

- **283 casi in Italia nell'uomo** dall'inizio di maggio 2023 al 28 settembre 2023
- 166 forma neuro-invasiva (32 Piemonte, 53 Lombardia, 18 Veneto, 1 Liguria, 52 EmiliaRomagna, 4 Puglia, 1 Sicilia, 3 Sardegna) 2 casi importati (1 Ungheria, 1 Francia)
- 63 casi identificati in donatori di sangue (13 Piemonte, 31 Lombardia, 3 Veneto, 1 Friuli-Venezia Giulia, 14 Emilia-Romagna) 1 caso importato (Germania),
- 54 casi di febbre (5 Piemonte, 14 Lombardia, 29 Veneto, 5 Emilia-Romagna, 1 Puglia).
- 17 decessi

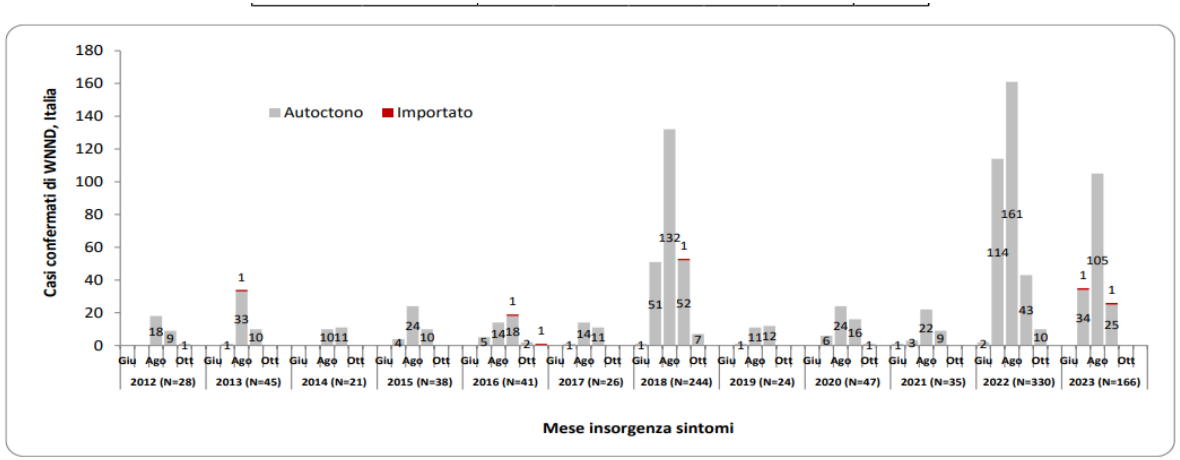


Figura 1. Andamento dei casi confermati di WNND per mese insorgenza sintomi. Italia: **2012 – 2023.**

Figura 1. *Province con dimostrata circolazione di WNV in vettori, animali e uomo (donatori asintomatici, febbri e casi neuroinvasivi confermati)*

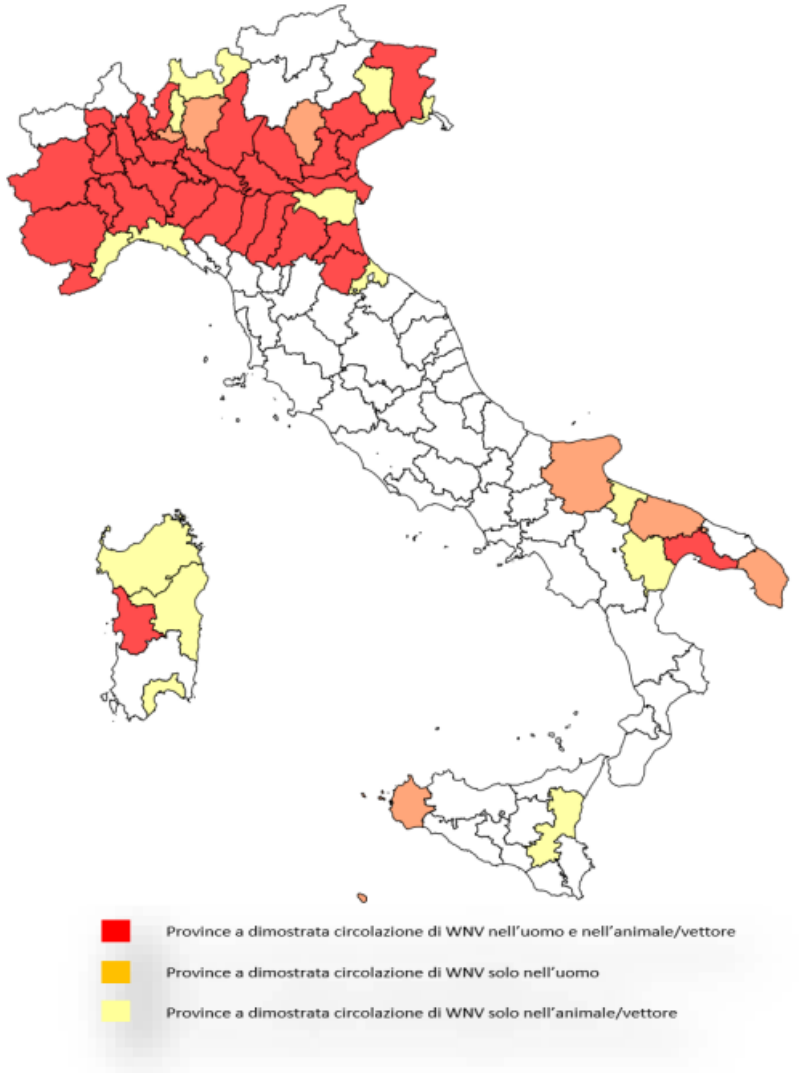


Tabella 2 Focolai e casi di WND negli equidi-**2023**

Figura 2 Distribuzione geografica dei casi di WND negli equidi-**2023**

Figura 7 Distribuzione geografica dei pool di zanzare risultate positive nei confronti del WNV - **2023**

Appartengono alle specie bersaglio:

- **Gazza (*Pica pica*)**
- **Cornacchia grigia (*Corvus corone cornix*)**
- **Ghiandaia (*Garrulus glandarius*)**

Figura 3 Distribuzione geografica degli uccelli bersaglio risultati positivi nei confronti del WNV - **2023**

Figura 5 Distribuzione geografica degli uccelli selvatici risultati positivi nei confronti del WNV - **2023**

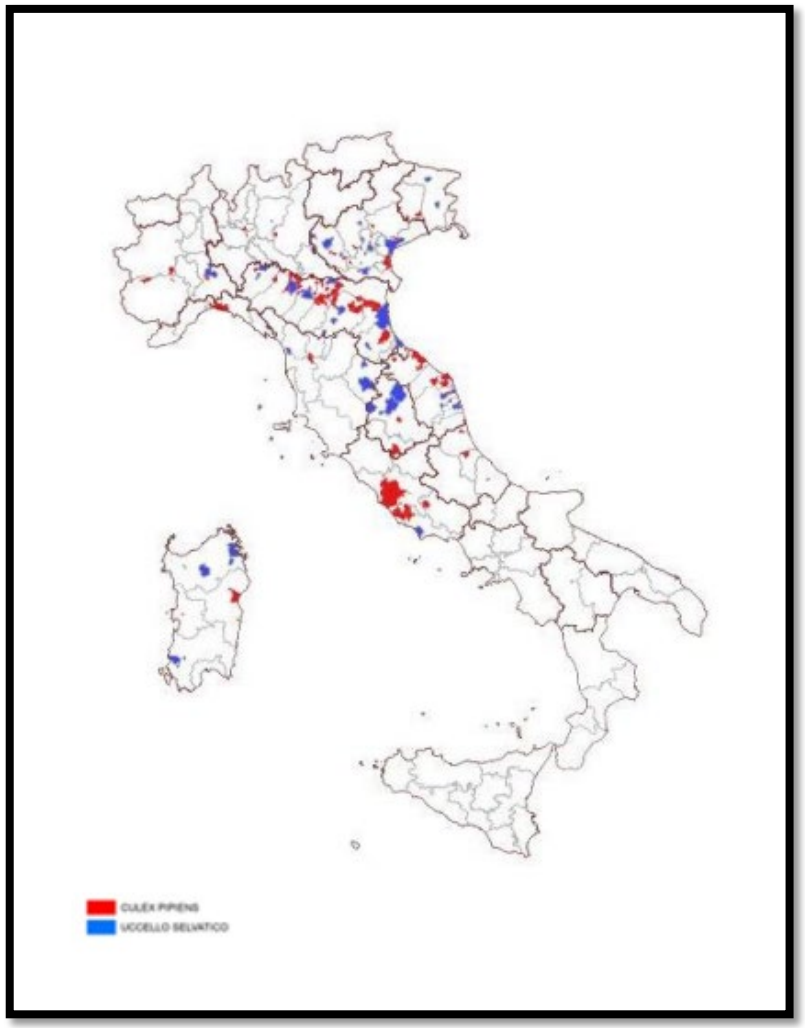
Usutu Virus (USUV)

- Isolated for the first time in South Africa in 1959
- First human case in Central African Republic in 1981
- Introduced in Tuscany in 1996 (archived tissue samples from birds)
- Main reservoir and amplifyng host: birds (highly viremic)
- Vector: infected mosquitos of *Culex* species
- Dead-end-host: horses and humans
- Several lineages (3 African and 5 European)

USUTU epidemiology - Italy

- Introduced in Tuscany in 1996 (archived tissue samples from birds)
- Prevalent lineages: Europe-1, 2, 3 and 4
- First two confirmed cases of neuroinvasive disease in humans in 2009
- Detected in native (mainly *Culex pipiens*) and invasive mosquito species (*Aedes albopictus and Ae. japonicus*)
- Between 2017 and 2021 detected in 5 regions (Emilia Romagna, Friuli Venezia Giulia, Latium, Lombardy, Veneto)
- 8 human cases in 2018, 1 in 2019 and 2020, 2 in 2021 and 2022
- Often misidentified with WNV (serological cross-reactions)
- Significant seroprevalence (blood donors and asymptomatic subjects)

Usutu virus in Italy (2022)



- 6 uman cases (3 Friuli-Venezia Giulia, 1 Piemonte, asymptomatic blood donors) (1 Emilia-Romagna, 1 Lombardia, fever)

- Detected in 145 mosquito pools and 145 birds in Abruzzo, Liguria, Emilia Romagna, Lombardy, Marche, Friuli Venezia Giulia, Umbria, Tuscany, Latium and Veneto.

Usutu virus in Italy (2023)

Sorveglianza integrata del WN e Usutu virus

7 **Sorveglianza USUTU virus**

Il **virus Usutu** è stato identificato in **65 pool di zanzare e 81 uccelli in Abruzzo, Emilia Romagna, Toscana, Veneto, Lombardia, Marche, Sardegna e Piemonte.**

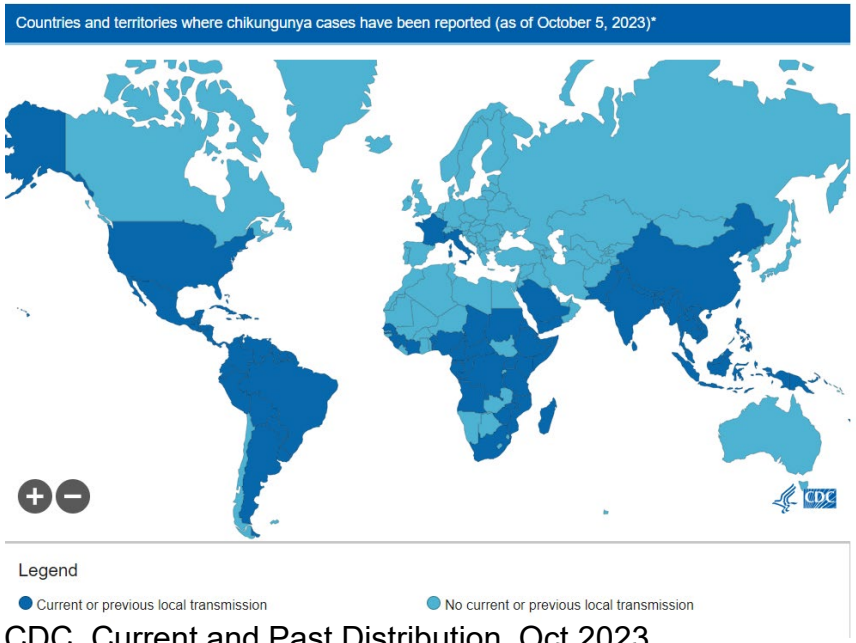
Figura 9 Distribuzione geografica dei pool di zanzare ed uccelli risultati positivi nei confronti dell'USUV - **2023**


Aedes
albopictus

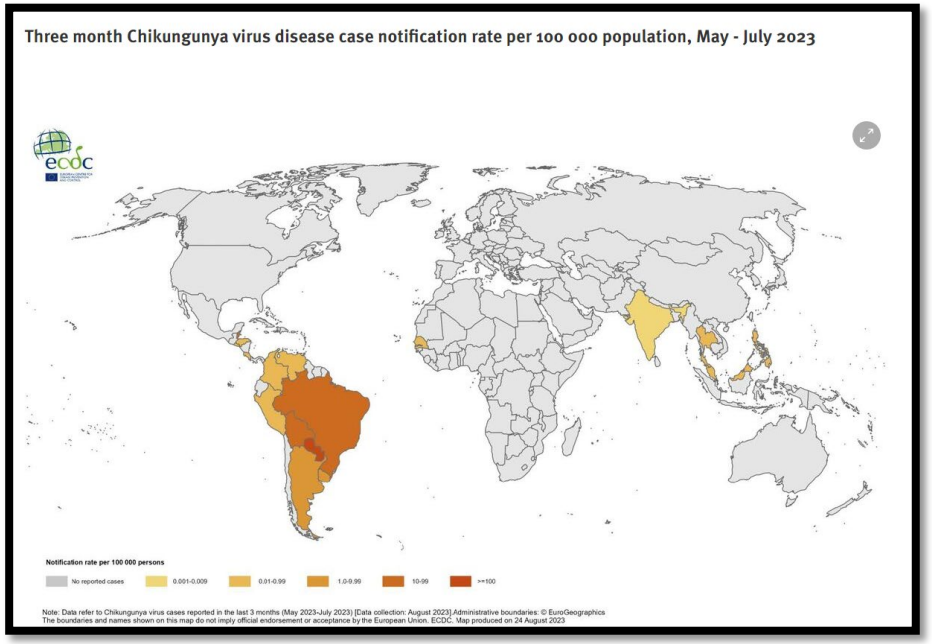

Aedes
aegypti

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



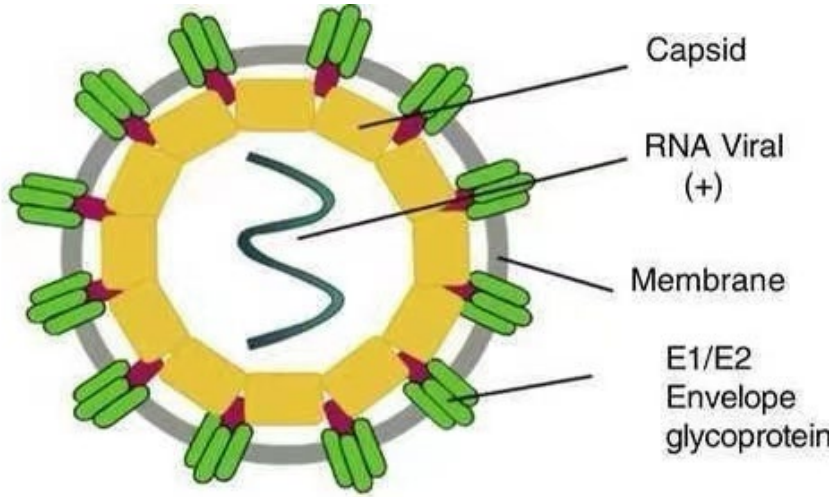
CDC. Current and Past Distribution, Oct 2023



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

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- 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 increase 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

2007

Chikungunya: From Indian Ocean to Romagna

Estimated **<u>254 locally acquired infections (1 death)</u>**

Courtesy Dr Rezza

Chikungunya in Italia per la 2° volta

Ministero della Salute

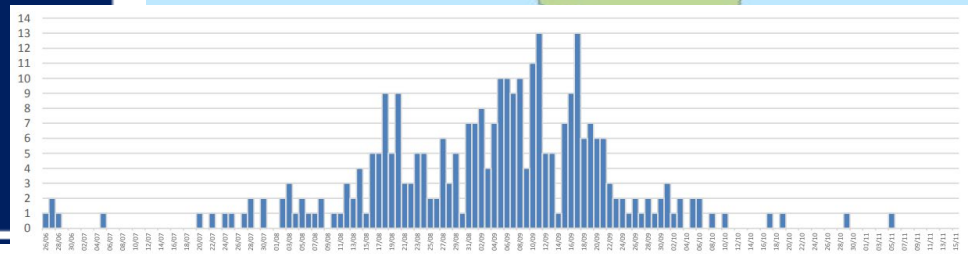
ISTITUTO SUPERIORE DI SANITÀ

Primo caso esordito 26/06/17

Primo caso diagnosticato 15/09/17

Ultimo caso esordito 05/11/17

ECSA strain ; Non ha mutazione E1-A226V
100% homology with two strains from Pakistan and India from 2016



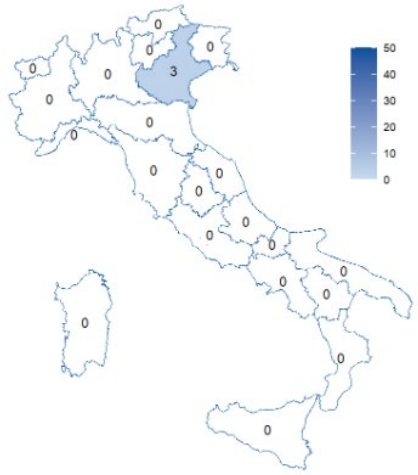
http://www.salute.gov.it/portale/temi/documenti/chikungunya/bollettino_chikungunya_ULTIMO.pdf

Chikungunya

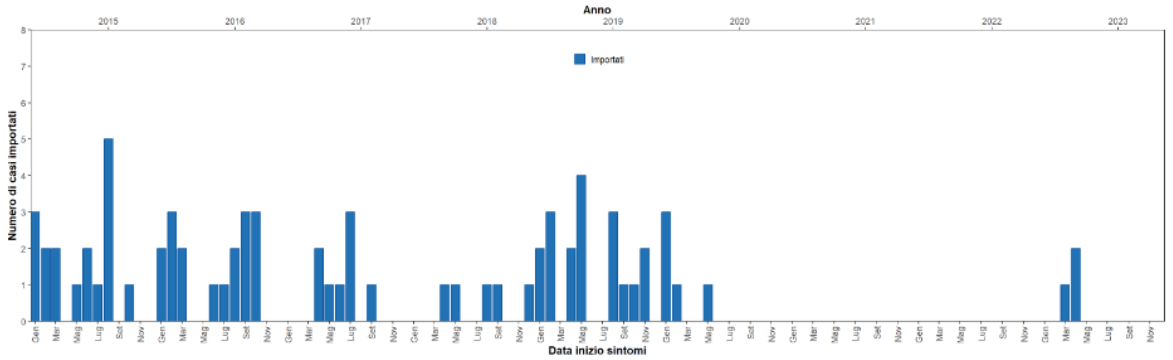
3	66.67% | 33.33%	41 anni	0	0 casi | 3 casi
Casi*	Maschi | Femmine*	Età mediana*	Decessi*	Autoctoni | Importati*

*Dati provvisori dal 1° gennaio all'11 settembre 2023

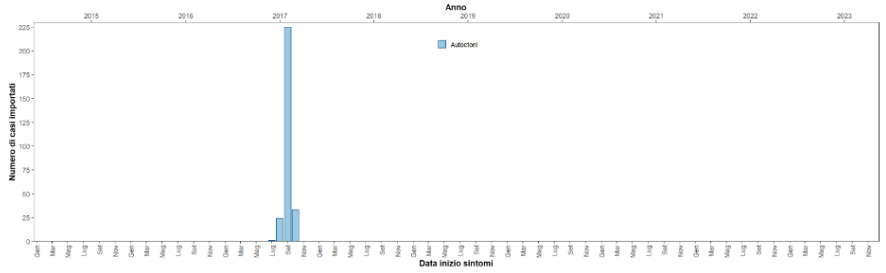
Casi per Regione*



Casi importati confermati di Chikungunya dal 2015 al 2023*



Epidemia di casi autoctoni del 2017

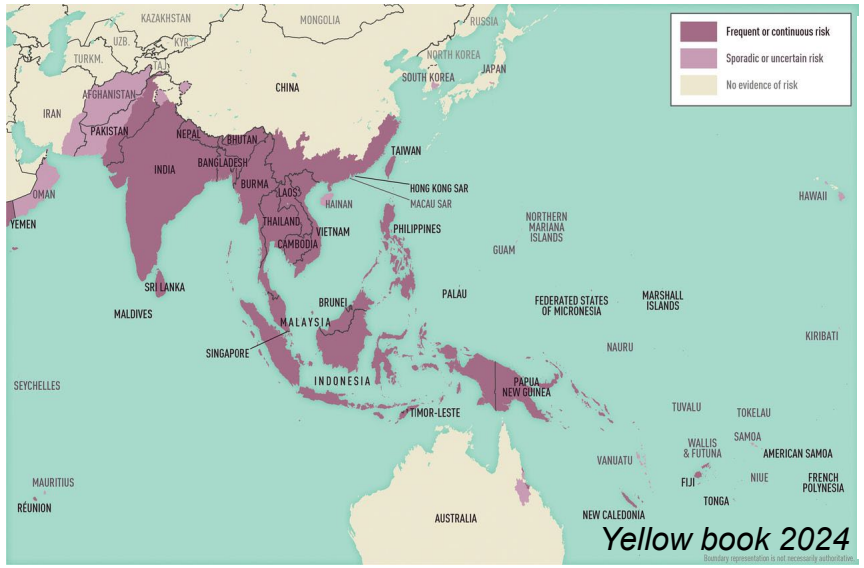


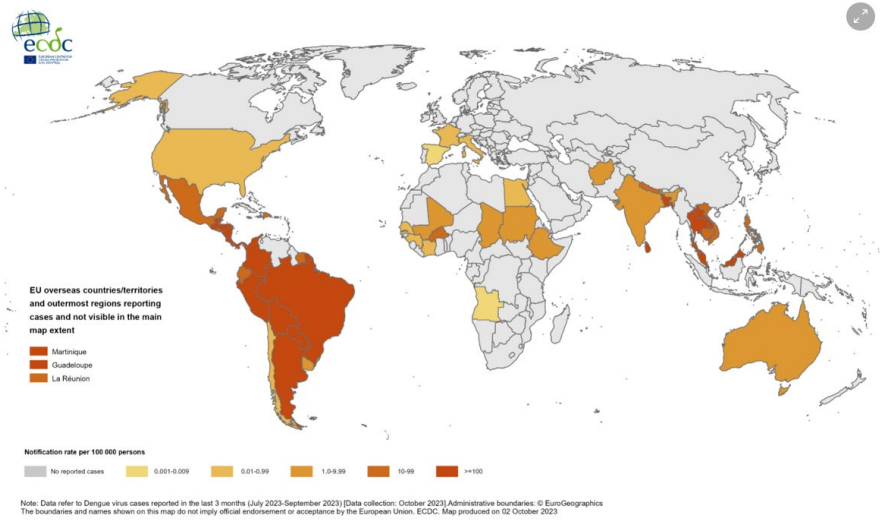
Per citare: Del Manso M, Di Maggio E, Perego G, Petrone D, Mateo-Urdiales A, Caporali MG, Bella A, Venturi G, Di Luca M, Giannitelli S, Ferraro F, Pezzotti P, Riccardo F; Arbovirosi in Italia - 2023

Data di ultimo aggiornamento: 26 settembre 2023

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

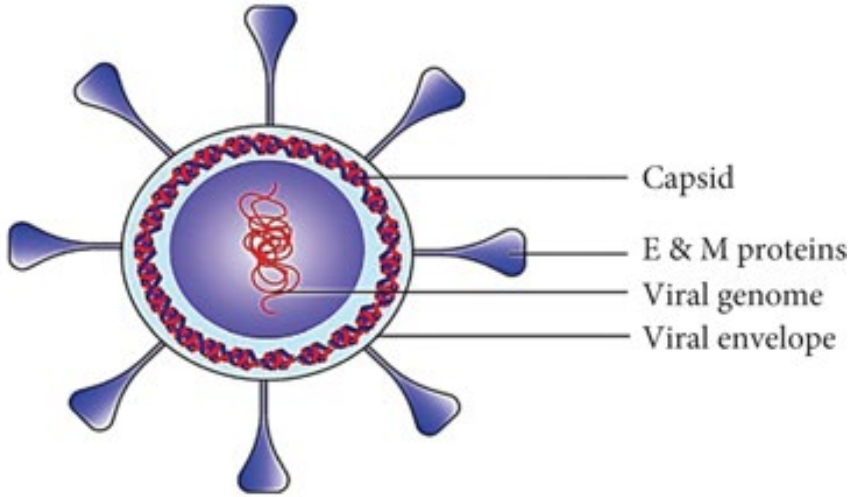


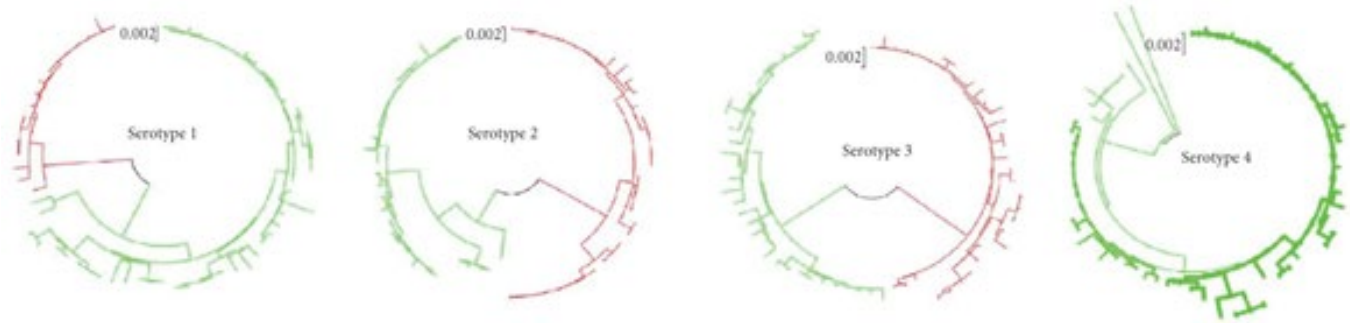


ECDC. Dengue Worldwide. https://www.ecdc.europa.eu/en/dengue-monthly. October 2023

Dengue- Virological aspects

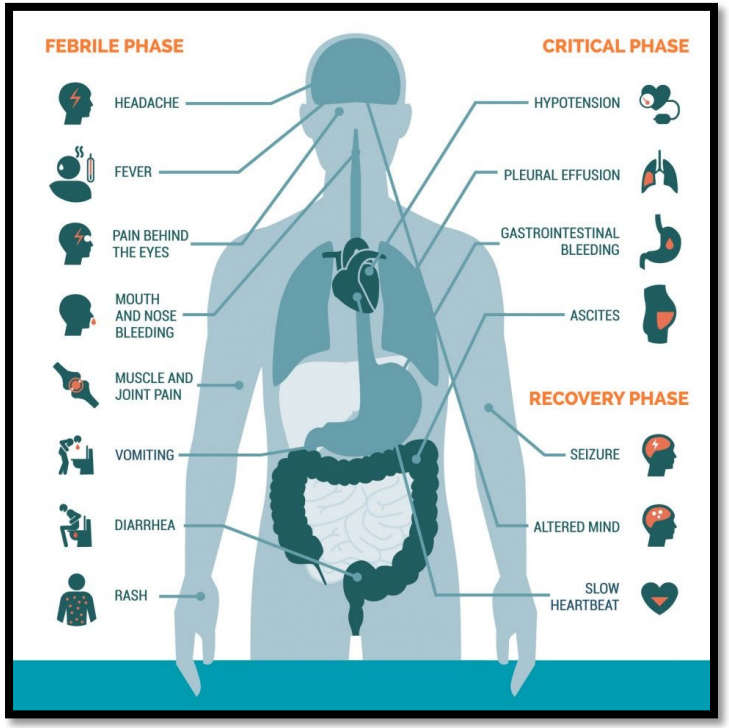
- Family Flaviviridae
- Genus *Flavivirus*
- 4 serotypes (DENV 1, 2, 3, 4)
- Transmission:
  - Vectorial *(Aedes* spp)
  - Mother-to-child
  - Transplant/transfusion
  - Needle injury
  - Sexual





Dengue- clinical features

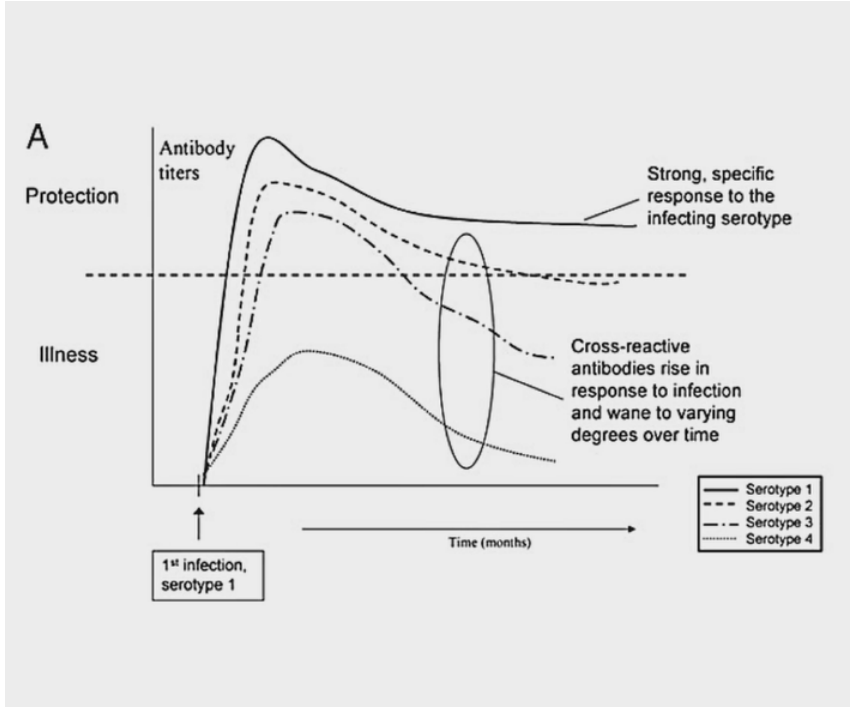
- Symptomatic infection 20%
- Febrile diseases with possibile complications:
  - Shock
  - Bleeding
  - Severe organ involvement (liver, CNS, hearth)
  - Severe perinatal infection
- Erythematous rash, leukopenia (neutropenia), thrombocytopenia, incresed transaminases, normal CRP
- Severe cases: 0.16%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

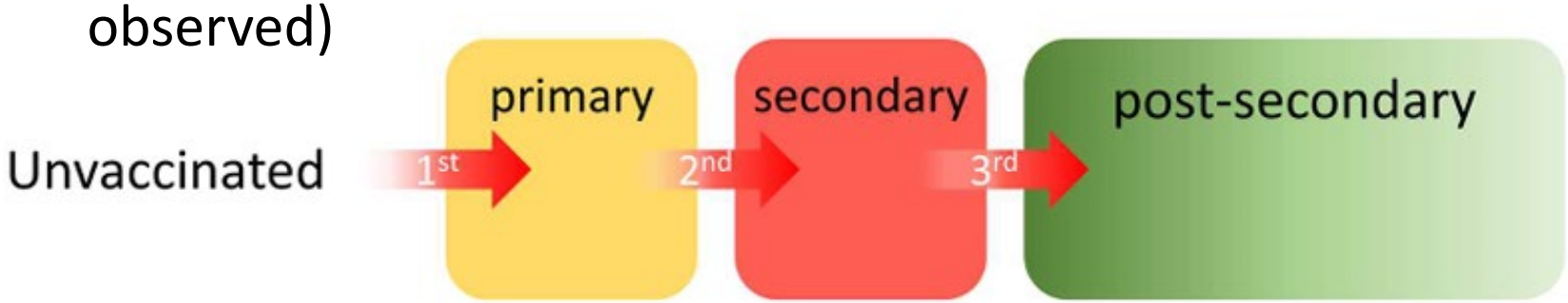


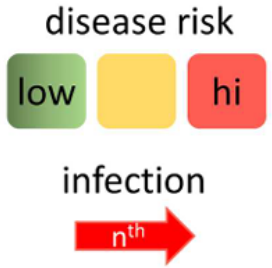
PAHO. Epidemiological Update for Dengue, Chikungunya and Zika in 2022. Updated: Jun 25 2023 1:00AM

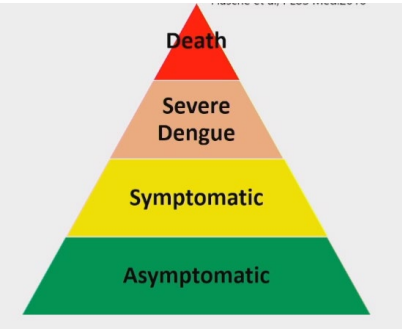
Dengue- Immunological aspects

- **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

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 ✉

Journal of Travel Medicine, taab074, https://doi.org/10.1093/jtm/taab074

Published: 12 May 2021 **Article history** ▾

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

JTM Journal of Travel Medicine

International Society of Travel Medicine
Promoting healthy travel worldwide
Established 1991

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

Ralph Huits, MD, DTMH, PhD[1,*] and Eli Schwartz, MD, DTMH, FISTM[2,3]

[1]Department of Clinical Sciences, Institute of Tropical Medicine, Nationalestraat 155, B-20000 Antwerp, Belgium, [2]The Center for Travel and Tropical Medicine, Sheba Medical Center, Ramat Gan, 52621, Israel and [3]Sackler School of Medicine, Tel Aviv University, Tel Aviv, 69978, Israel

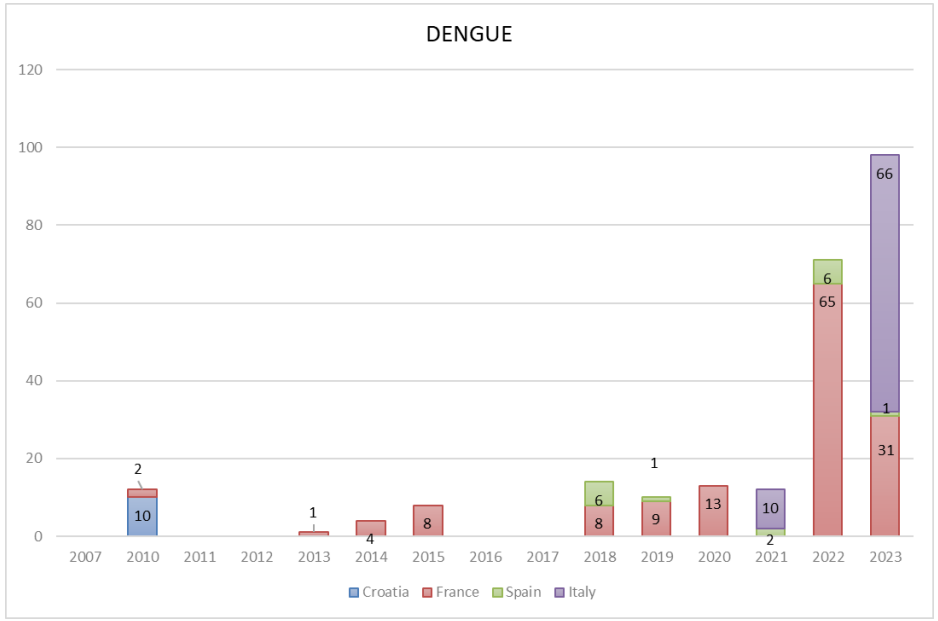
*To whom correspondence should be addressed. Email: rhuits@itg.be

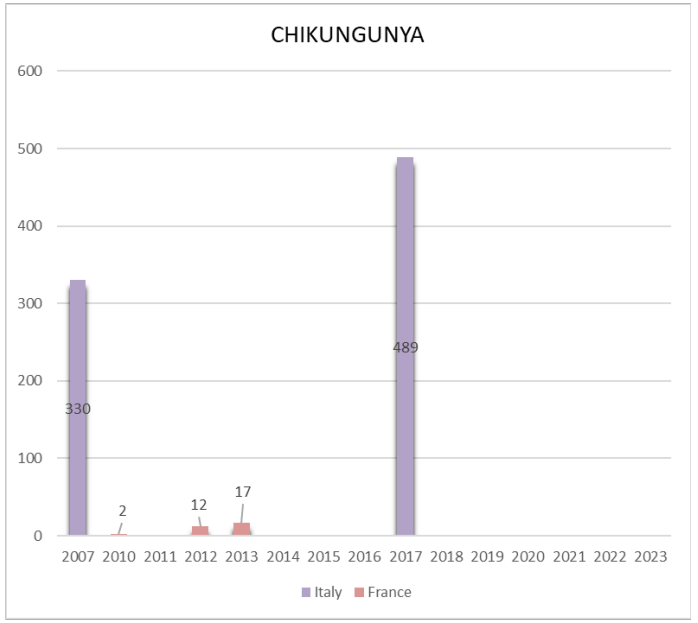
Submitted 10 December 2020; Revised 28 January 2021; Editorial Decision 2 February 2021; Accepted 4 February 2021

→ 9 fatalities in travelers
8 female
7 with primary infection

Dengue & Chikungunya locally acquired cases in Europe

- **1096** locally acquired cases in Mediterranean Europe
- **Italy**: 819 Chikungunya and 76 Dengue cases (82% 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 24/10/2023

Source: https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/chikungunya-virus-disease/surveillance-threats-and Consulted on 24/10/2023

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

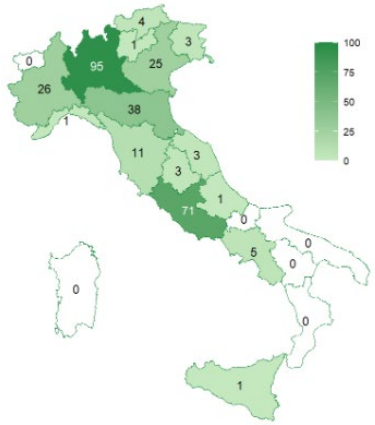
Dengue

Arbovirosi in Italia 2023 | Dengue | Zika Virus | Chikungunya | TBE | Toscana Virus

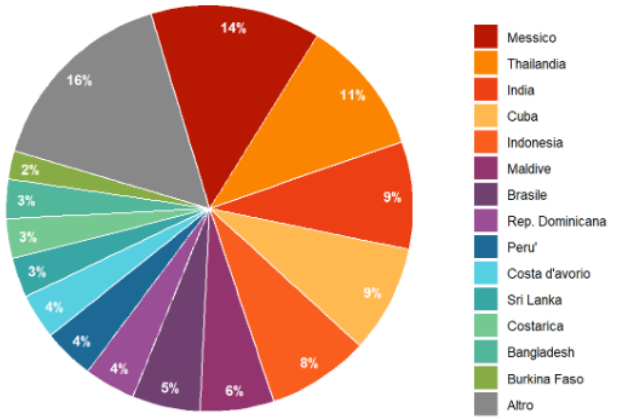
288	54.51% | 45.49%	37 anni	0	66 casi | 222 casi
Casi*	Maschi | Femmine*	Età mediana*	Decessi*	Autoctoni** | Importati*

*Dati provvisori dal 1° gennaio al 23 ottobre 2023
**Verosimile trasmissione autoctona, in corso di accertamento

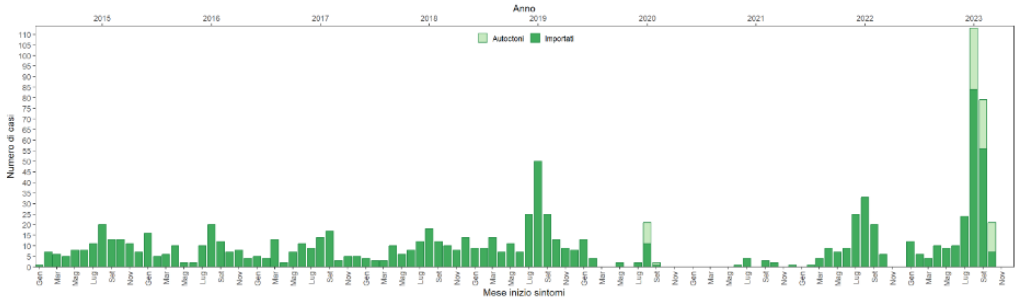
Casi per Regione*

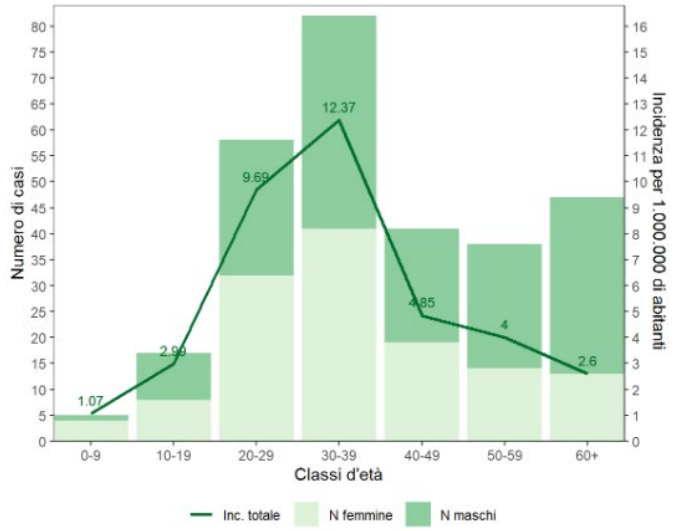


Luogo di probabile esposizione dei casi importati*



Casi confermati di Dengue dal 2015 al 2023*





Per citare: 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: 24 ottobre 2023

RAPID COMMUNICATION

First autochthonous dengue outbreak in Italy, August 2020

Luca Lazzarini[1], Luisa Barzon[2,3,4], Felice Foglia[5], Vinicio Manfrin[6], Monia Pacenti[3], Giacomina Pavan[6], Mario Rassu[6], Gioia Capelli[2,7], Fabrizio Montarsi[2,7], Simone Martini[2,8], Francesca Zanella[2,9], Maria Teresa Padovan[5], Francesca Russo[2,9], Federico Gobbi[2,10]

In August 2020, during the coronavirus disease (COVID-19) pandemic, five locally acquired cases of dengue virus type 1 were detected in a family cluster in Vicenza Province, North-East Italy where Aedes albopictus mosquitoes are endemic. The primary case was an importation from West Sumatra, Indonesia. This is the first outbreak of autochthonous dengue reported in Italy. During the COVID-19 pandemic, screening of febrile travelers from endemic countries is crucial in areas where competent vectors are present.

Journal of Travel Medicine
International Society of Travel Medicine
Promoting healthy travel worldwide
Journal of Travel Medicine, 2021, 1–9
Advance Access Publication Date: 18 August 2021
Original Article

Original Article

Autochthonous dengue outbreak in Italy 2020: clinical, virological and entomological findings

Luisa Barzon, MD[1,2,3,*], Federico Gobbi, MD[1,4], Gioia Capelli, PhD[1,5], Fabrizio Montarsi, PhD[1,5], Simone Martini, DSc[1,6], Silvia Riccetti, PhD[2], Alessandro Sinigaglia, PhD[2], Monia Pacenti, PhD[3], Giacomina Pavan, MD[7], Mario Rassu, MD[7], Maria Teresa Padovan, MD[8], Vinicio Manfrin, MD[9], Francesca Zanella, MD[1,10], Francesca Russo, MD[1,10], Felice Foglia, MD[8], and Luca Lazzarini, MD[9]

Montecchio Maggiore (Vicenza, Agosto 2020): **12 casi (uno importato e 11 autoctoni)**

24/10/2023 - Casi di Dengue in Italia: i dati aggiornati

- Sono 66 i casi confermati di Dengue trasmessi localmente in Italia e notificati al 23 ottobre 2023. Questi casi sono riferiti a quattro episodi di trasmissione non collegati tra loro in provincia di Lodi (36 casi confermati), in provincia di Latina (2 casi) e in provincia di Roma (27 casi con esposizioni in diverse parti della città metropolitana di Roma e 1 caso ad Anzio, per cui sono in corso indagini per verificare eventuali collegamenti epidemiologici). Tutti i casi, di cui è noto l'esito, sono guariti o in via di miglioramento.

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Temperature and transmission of chikungunya, dengue, and Zika viruses: A systematic review of experimental studies on *Aedes aegypti* and *Aedes albopictus*

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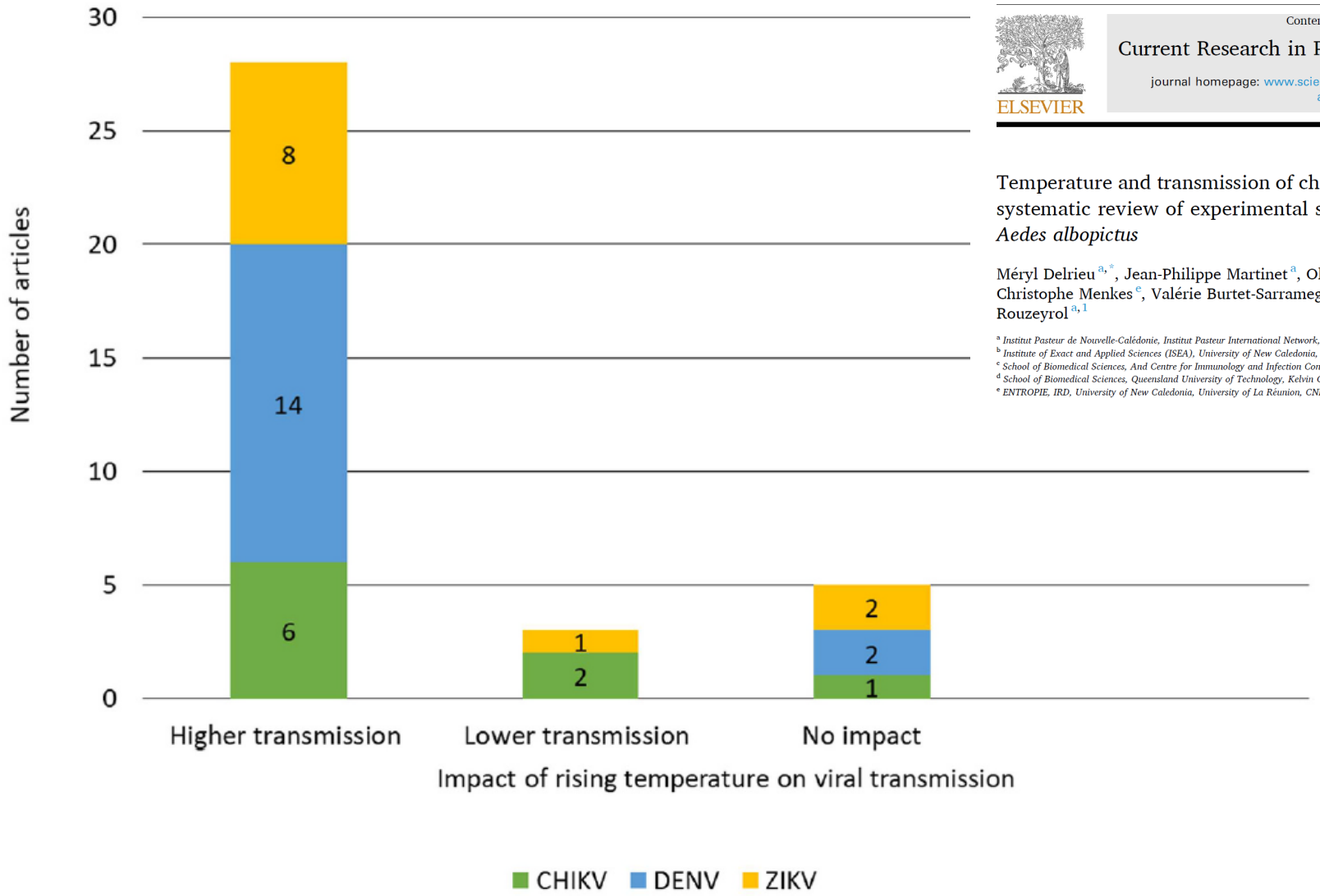

Fig. 3. Distribution of included articles according to the reported observed impact of increased temperature on transmission (higher, lower, no impact) of arboviruses by mosquito vectors. The number of studies in each category is given. *Note*: The numbers of included articles do not sum up to 34 because some studies relate to more than one category.

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comment

Climate change: an enduring challenge for vector-borne disease prevention and control

Climate change is already affecting vector-borne disease transmission and spread, and its impacts are likely to worsen. In the face of ongoing climate change, we must intensify efforts to prevent and control vector-borne diseases

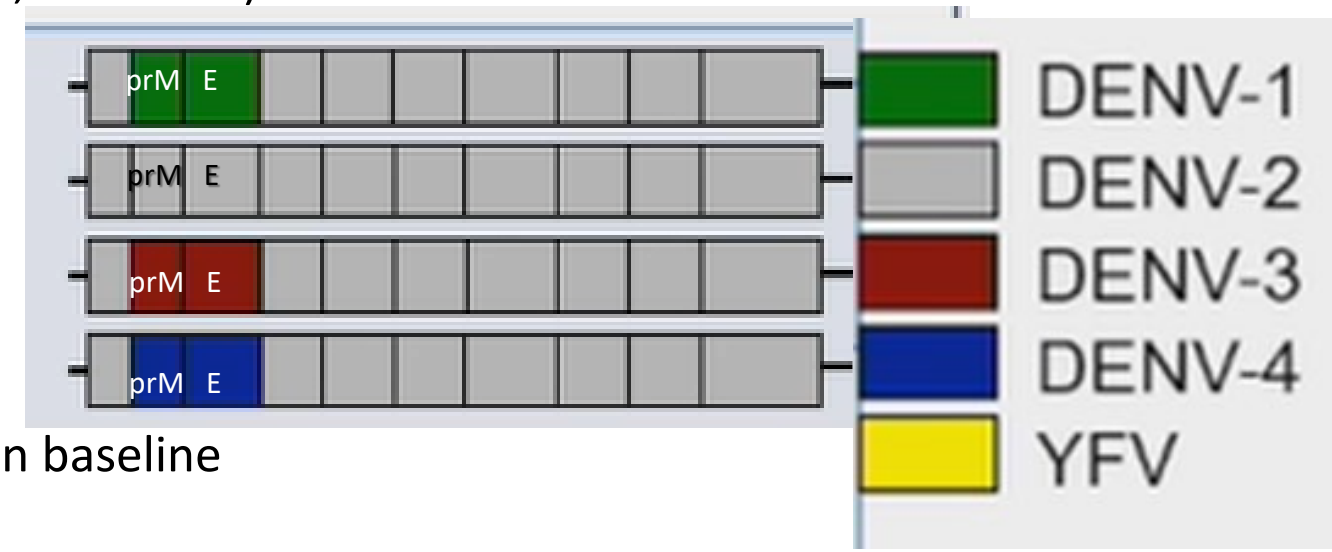
Joacim Rocklöv and Robert Dubrow

Table 2 | Non-climate drivers of the transmission and spread of vector-borne diseases

Globalization and environment	
Driver	Effect
Deforestation, mining and dams	Change vector and non-human host habitats
Ecosystem degradation/change	Changes vector and non-human host habitats
International travel and trade	Spreads pathogen and vector
Urbanization	Provides an ideal habitat for *A. aegypti*
Population displacement	Spreads pathogen to new locations or puts immunologically susceptible populations in contact with the vector and pathogen
Sociodemographic factors	
Driver	Effect
Population demographic composition	Children, the elderly and pregnant women may have elevated vulnerability
Level of economic development	Quality of housing (including presence of air conditioning) affects exposure to vectors
Baseline incidence of disease	Vulnerability to climate change may be highest at the margins of current endemic areas
Population health status	Low level of population health increases vulnerability
Humanitarian crises	War and famine confer high vulnerability
Public health systems	
Driver	Effect
Surveillance	Passive and active surveillance inform prevention and control efforts
Early warning systems	Preemptive vector control and other public health responses occur before impending outbreaks
Vector control	Vector control measures reduce vector abundance
Quality of healthcare system	Access to and quality of healthcare can affect size of infected human population, as well as case fatality rate and prevalence and severity of disabilities
Research	Research on vector control, disease treatment, vaccine development, pathogen and vector evolution, and how to best coordinate prevention and control efforts across sectors, can lead to progress in control of vector-borne diseases
Vector and pathogen characteristics	
Driver	Effect
Insecticide resistance	Vector proliferation
Vector evolution	Potential for greater vectorial capacity
Pathogen drug resistance	Increased pool of infected humans
Pathogen evolution	Potential for higher pathogen transmissibility or virulence

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)- 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.

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