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Clincally important arboviruses

Dengue

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Case study: A traveller with rash, fever and headache

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Case history

- 51-year-old man
- Fever, myalgia and retroorbital pain since 1 day
- Returned from Southeast Asia 3 days ago (Thailand, Cambodia, Vietnam)
- No significant medical history
- No malaria prophylaxis taken

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Medical examination

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- Reduced overall state
- Elevated temperature of 39.4°C
- Rash

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Tourniquet test, also known as (Rumpel-Leede-) capillary-fragility test

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Laboratory results

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Parameter	Normal range	Day 1
Platelets, x10^6/µL	150-440	145 ↓
Haematocrit, %	38-52	42.7%
White blood cells, x10^3/µL	4.0-10.0	3.5 ↓
Lymphocytes, %	25-40%	7% ↓
Neutrophils, %	50-70%	77%
Atypical lymphocytes, %	0-2%	1%
Monocytes, %	2-8%	14%
C-reactive protein, mg/dL	≤5	23.4 ↑
Aspartate transaminase, U/L	≤50	65 ↑
Alanine aminotransferase, U/L	≤50	67 ↑
Gamma glutamyltransferase, U/L	≤60	22
Alkaline phosphatase, U/L	40-130	58

- Thrombocytopenia
- Leukopenia
- Elevated liver enzymes

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Microbiology results

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- Malaria: negative (blood smears, performed on 2 consecutive days)
- Blood cultures: negative
- Influenza PCR: negative

Untersuchung	Ergebnis	Einheit	Grenzwert
Cytomegalievirus (CMV)			
anti-CMV IgG (EIA)	1:7300	Titer	< 1:230
anti-CMV IgM (EIA)	negativ		
Bewertung: Serologisch kein Hinweis auf akute Infektion oder Reaktivierung durch Cytomegalievirus. Durchseuchungstiter.			
Epstein-Barr-Virus (EBV)			
anti-EBV IgG (EIA)	310	U/ml	< 25
anti-EBV IgM (EIA)	negativ		
Bewertung: Serologisch kein Hinweis auf akute Infektion oder Reaktivierung durch Epstein-Barr-Virus. Durchseuchungstiter.			
Hepatitis-E-Virus (HEV)			
anti-HEV IgG (EIA)	negativ	qualitativ	
anti-HEV IgM (EIA)	negativ	qualitativ	
Bewertung: Serologisch kein Hinweis auf akute oder früher abgelaufene Hepatitis E-Virusinfektion.			
HUMANES IMMUNDEFIZIENZ-VIRUS (HIV)			
anti-HIV 1/2 IgG/IgM + p24-Ag (CMIA)	negativ		

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Day of presentation

Untersuchung	Ergebnis	Einheit	Grenzwert
Denguevirus			
anti-Denguevirus IgG (EIA)	negativ	Units	9 - 11
anti-Denguevirus IgM (EIA)	positiv	Index	
Denguevirus NS1-Antigen (EIA)	positiv		
Bewertung: Serologisch V.a. akute oder kürzliche Denguevirus-Infektion.			
Bewertung: Positiver Nachweis von Denguevirus NS1-Antigen. Hinweis auf akute Infektion.			
Bewertung: Meldepflichtiger direkter Nachweis eines Krankheitserregers gemäss § 7 Infektionsschutzgesetz - IfSG! Eine Labormeldung an das zuständige Gesundheitsamt ist erfolgt. Meldepflichtiger indirekter Nachweis eines Krankheitserregers gemäss § 7 Infektionsschutzgesetz - IfSG! Eine Labormeldung an das zuständige Gesundheitsamt ist erfolgt.			

1 weeks after initial presentation

Untersuchung	Ergebnis	Einheit	Grenzwert
Denguevirus			
anti-Denguevirus IgG (EIA)	63.20	Units	9 - 11
anti-Denguevirus IgM (EIA)	positiv	Index	

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Day of presentation

Untersuchung	Ergebnis	Einheit	Grenzwert
Denguevirus			
anti-Denguevirus IgG (EIA)	negativ	Units	9 - 11
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Bewertung: Serologisch V.a. akute oder kürzliche Denguevirus-Infektion.			
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1 weeks after initial presentation

In Germany: Notifiable disease!

Untersuchung	Ergebnis	Einheit	Grenzwert
Denguevirus			
anti-Denguevirus IgG (EIA)	63.20	Units	9 - 11
anti-Denguevirus IgM (EIA)	positiv	Index	

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Further course of disease...

- No hospitalization due to only mild disease presentation
- Patient was sent home
- Paracetamol was advised for antipyretics/analgetics
- Control of RR, platelets, hematocrit
- Follow-up visit 1 week after initial presentation

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Dengue fever

Epidemiological risk factors, clinical presentation, differential diagnosis and treatment

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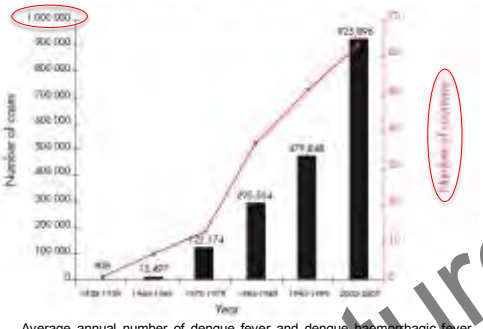
Dengue fever – a truly emerging infectious disease



Average annual number of dengue fever and dengue haemorrhagic fever cases reported by WHO, and of countries reporting dengue.

Source: Dengue guidelines for diagnosis, treatment, prevention and control. WHO, TDR 2009.

WHO fact sheet N°117, updated May 2015:

- **390 million dengue infections/year (95% credible interval 284–528 million)**
- **Clinically manifest (any disease severity): 96 million dengue infections/year (67–136 million)**

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Where is dengue present?

Current estimate of people/countries at risk for dengue:

- 3900 million people
- 128 countries

Source: Brady OJ et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis. 2012

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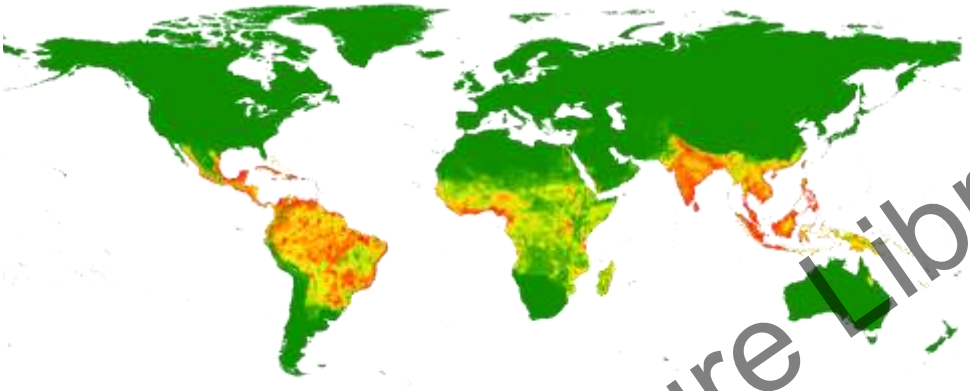

Estimated number of apparent infections:

Latin America: ~13.3 million Africa: ~15.7 million Asia: ~66.8 million

Source: Bhatt et al., Nature 2013

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Dengue virus

- Familiy *Flaviviridae*, genus *Flavivirus*
- Arthropod-borne (Arbovirus)
- Main vectors: *Ae. aegypti, Ae. albopictus*
- 4 serotypes: DENV-1, DENV-2, DENV-3, DENV-4
- Cross-protection low between serotypes
- Circulation of different serotypes in the same region („hyperendemicity“)
- Causative agent of dengue fever

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Dengue fever

- Incubation time 4-10 (max. 14) days
- Wide spectrum of illness
- Most infections are asymptomatic or subclinical
- Secondary infection with a different dengue serotype from the original infecting virus: Risk for severe disease
- Primarily in patients living in hyperendemic areas
- Travellers: low risk for severe disease
- Individual risk factors: age, ethnicity and chronic disease

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Dengue fever - symptoms

- Gastrointestinal symptoms (nausea, vomiting, diarrhea), 50%
- High fever, 90%
- Headache, pain behin the eyes, joint pain, bone pain, 60-80%
- Rash an mild bledding, 50%
- Respiratory symptoms (cough, sore throat, and nasal congestion), 30%

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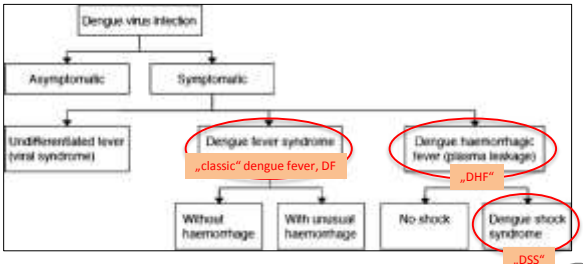
Dengue classification 1997



The 1997 WHO classification of dengue virus infection

- spectrum of disease instead of distinct phases
- overlap between DHF and DSS

➔ complicated clinical care

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Dengue classification 2009

➔ More sensitive in capturing severe cases

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Dengue fever – course of disease

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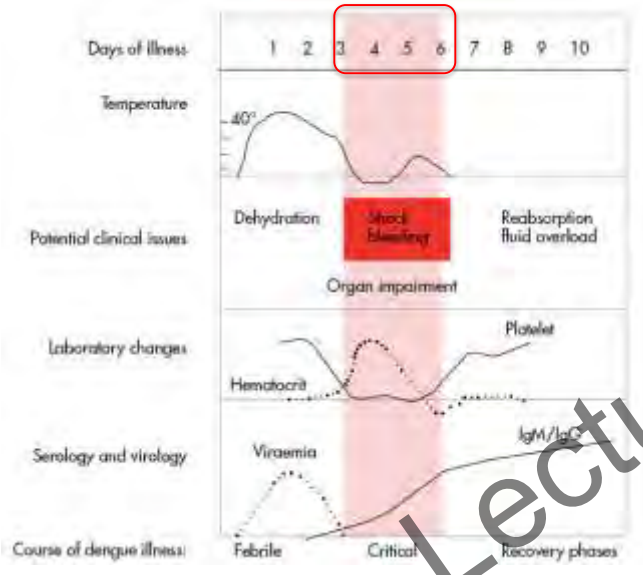
Slides kindly provided by Prof. T. Junghanss



Critical period!

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Differential diagnosis of dengue fever

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Febrile phase of dengue	
Flu-like symptoms	Influenza, measles, Chikungunya, infectious mononucleosis, HIV seroconversion illness
Illness with a rash	Rubella, measles, scarlet fever, meningococcal infection, Chikungunya, Zika, drug reactions
Diarrhea	Rotavirus, Norovirus, other enteric infections, e.g. bacterial
Illnesses with neurological manifestations	Meningo/encephalitis, febrile seizures, other arboviruses (e.g. WNV, TBEV, Toscana)

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Differential diagnosis of severe dengue

Critical phase of dengue infection	
Infectious	Acute gastroenteritis, malaria, leptospiroses, typhoid, typhus, viral hepatitis, acute HIV seroconversion illness, bacterial sepsis, septic shock
Malignancies	Acute leucemia and other malignancies
Other clinical pictures	Acute abdomen (e.g. appendicitis, cholecystitis) Diabetic ketoacidosis Lactic acidosis Leukopenia and thrombocytopenia (± bleeding) Platelet disorders Renal failure Respiratory distress Systemic Lupus Erythematosus

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Differential diagnosis of dengue to other, severe travel-acquired diseases

	Typhus abdominalis	*Malaria tropica*	! *Dengue*
Distribution	Worldwide, especially in coutnries with low hygiene	Africa, Sub-Sahara, Middle and South America, Asia	Asia, Middle- and South America (Africa)
Incubation period	3-60 days	12 months	1- 14 days
Symptoms	Fever, Headache, Myalgia	Fever, Headache, Myalgia	Fever, Headache, Myalgia Sudden onset
Clinical signs	Fever, hepatosplenomegaly	Fever, splenomegaly	Fever, rash

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Laboratory findings

- Leukopenia (common in both adults and children)
- Thrombocytopenia (<100,000 cells/mm^3)
- Serum aspartate transaminase, AST (modest: 2 -5 x upper limit of normal)
- AST: occasionally marked elevations (5 -15 x the upper limit of normal)

Source: UpToDate, 2016 27

Dengue – Diagnostic methods

- Detection of viral RNA (PCR) (Determination of serotype/genotype)
- Detection of NS-1 antigen (ELISA)
- Virus isolation in cell culture
- Detection of IgM and IgG (IF, ELISA)

  ! Pitfalls in serology: Cross-reactivity within Flaviviruses (e.g. Vaccination against Yellow fever, Japanese encephalitis, Tic-borne encephalitis)

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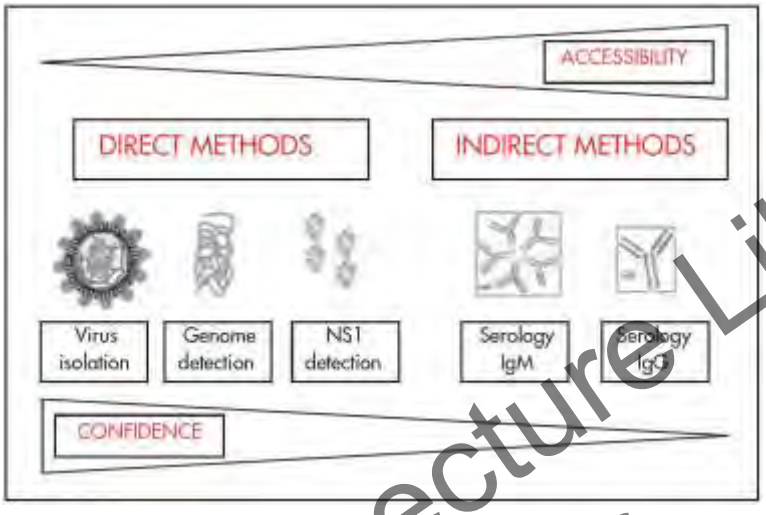

Source: Dengue guidelines for diagnosis, treatment, prevention and control WHO, TDR 2009.

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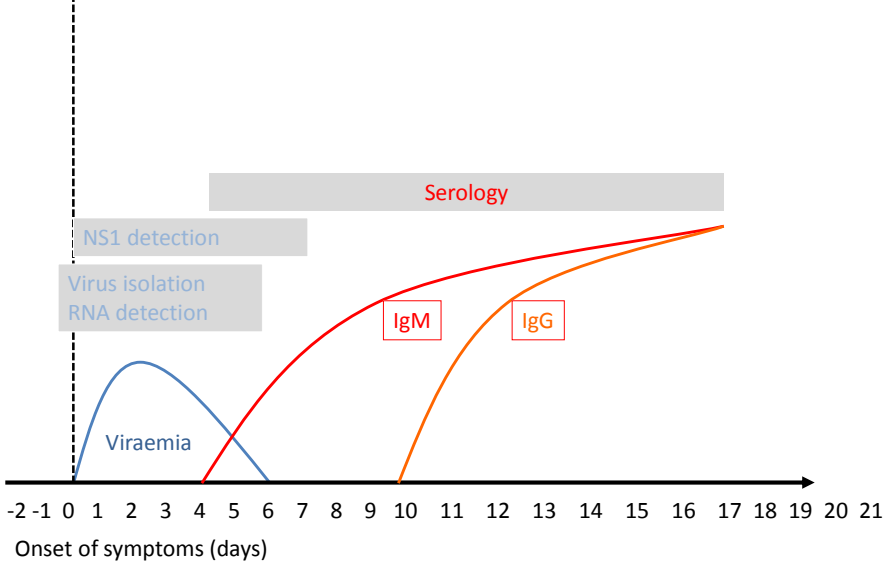
Dengue – time line and diagnostics



Dengue – Therapy I

- No specific antiviral treatment available
- Early recognition of severe dengue (warning signs!)
- Many cases: Outpatient management possible

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Dengue – Therapy II

- ***Management of fever***: Fluid intake, acetaminophen (No aspirin or nonsteroidal antiinflammatory agents!)
- ***Management of bleeding***: Blood transfusion, platelet transfusion
- ***Management of plasma leakage***: i.v. fluids
- ***Treatment of shock*****:** i.v. fluids according to WHO treatment protocols

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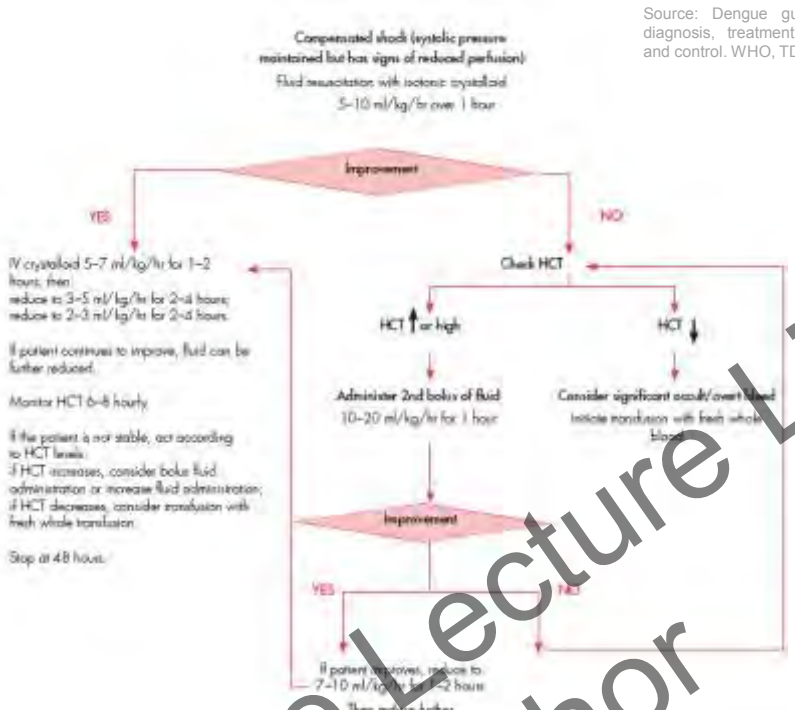

Source: Dengue guidelines for diagnosis, treatment, prevention and control. WHO, TDR 2009.

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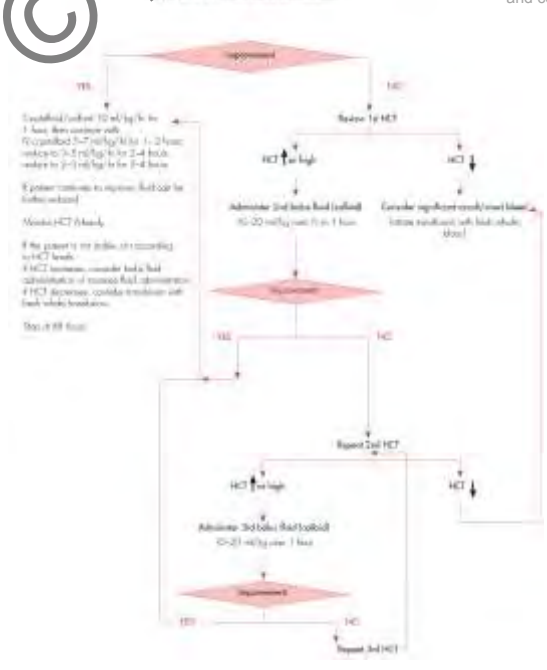

Source: Dengue guidelines for diagnosis, treatment, prevention and control. WHO, TDR 2009.

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Dengue – a risk for Europe?

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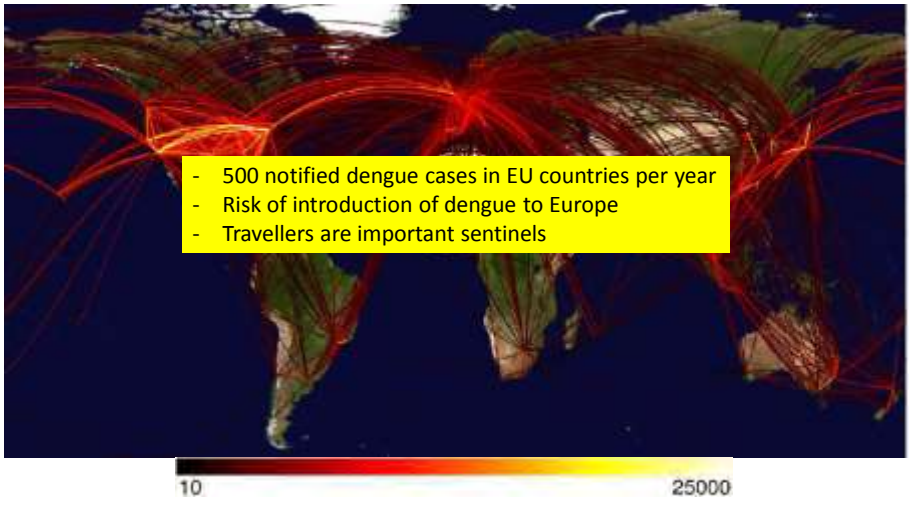

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Source: Hufnagel et al., PNAS 2004

Autochtonous dengue outbreaks in Europe

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- 1927-1928: Greece
- 2010: Southern France
- 2010: Croatia
- 2012/2013: Madeira

➔ Concern amongst public health officials about a potential resurgence and spread of dengue in Europe

Sources:
Reiter, Yellow fever and dengue: a threat to Europe? Eurosurveillance 2010 15(10):19509.
La Ruche et al. First two autochthonous dengue virus infections in metropolitan France, September 2010. Euro Surveill. 2010
Schmidt-Chanasit J, et al. Dengue virus infection in a traveller returning from Croatia to Germany. Euro Surveill. 2010

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Climatic suitability for dengue vectors in Europe

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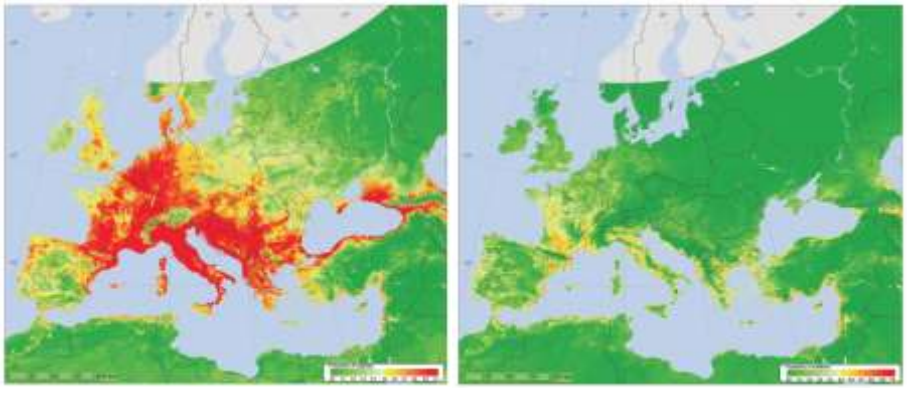
Ae. albopictus | *Ae. aegypti*



➔ *Ae. albopictus* is a less efficient vector than *Ae. aegypti*

European Centre for Disease Prevention and Control. The climatic suitability for dengue transmission in continental Europe. Stockholm: ECDC; 2012.

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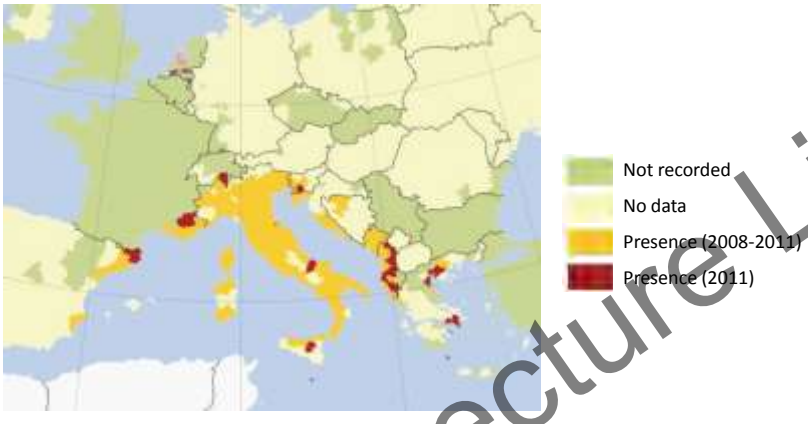
Presence of *Ae. albopictus* in Europe



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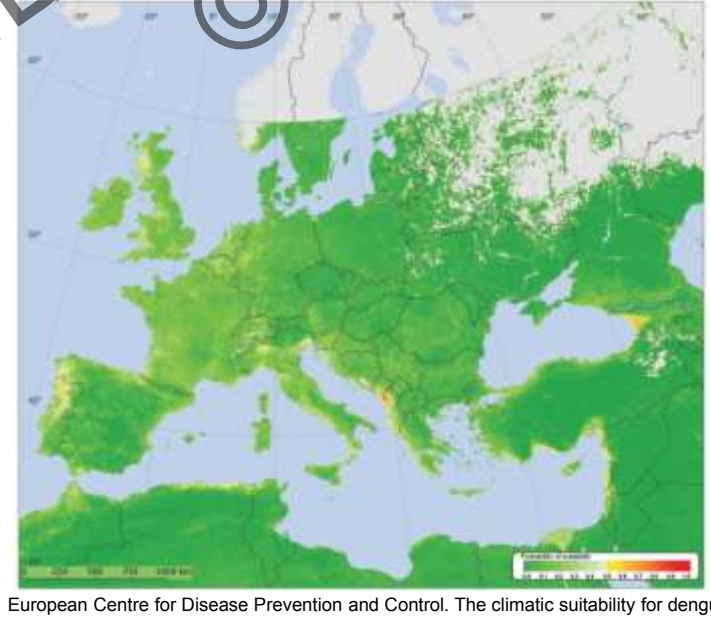
Climatic suitability for dengue transmission in Europe



European Centre for Disease Prevention and Control. The climatic suitability for dengue transmission in continental Europe. Stockholm: ECDC; 2012.

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Dengue in Europe

- Central and Mediterranean Europe is potentially climatically suitable for *Ae. albopictus*
- Mediterranean areas of Spain, France and Italy as well as south-eastern Europe: potentially suitable for *Ae. aegypti*
- Monitoring of vectors important

➔ **Current risk for dengue transmission low**

➔ **Dengue should be considered!**

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Thank you for your attention!

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