
INSTITUTE
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Emerging arboviruses in Europe

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KEYNOTE LECTURE IN MEMORIAM OF JEAN-PIERRE THYS
SYMPOSIUM BVIKM/SBIMC 24/05/2022

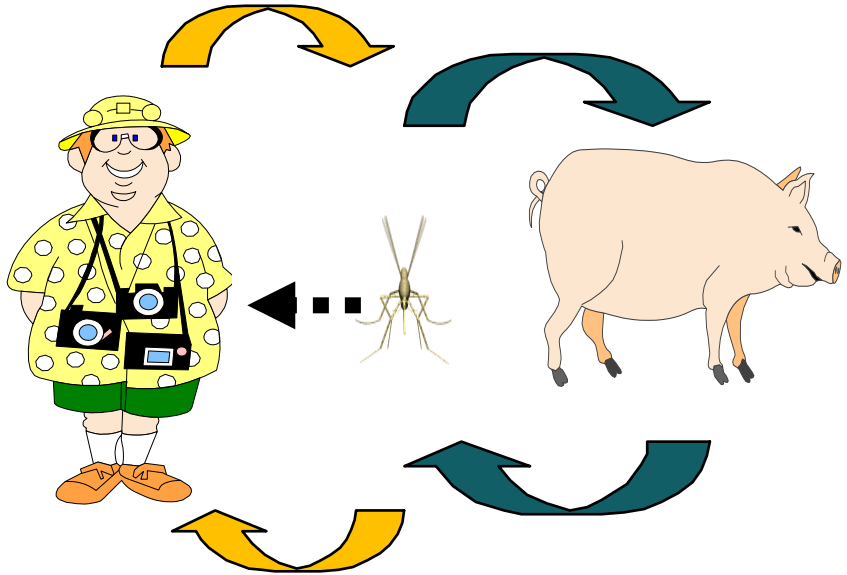
Tribute to Jean-Pierre Thys, pioneer in infectious disease specialty in Belgium

Arbovirus = « ARthropod-BOrne » viruses

- Majority of species
- Zoonotic disease
- Man = dead-end

"Viruses maintained in nature principally, or to an important extent, through biological transmission

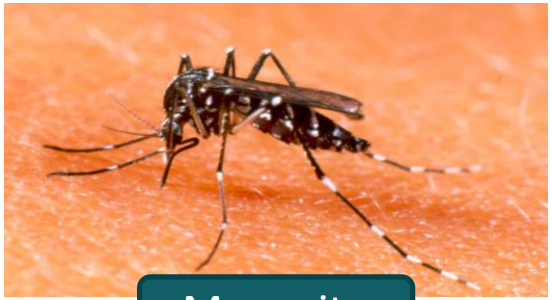
between susceptible vertebrate hosts by hematophagous arthropods or through trans-ovarian and possibly venereal transmission in arthropods."



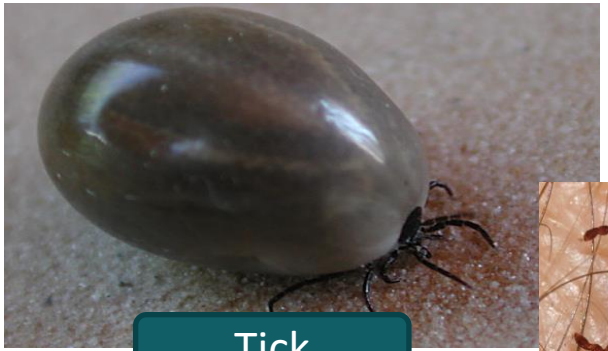
> 500 species, including 150 causing human disease

- Only few species
- Amplification in humans
- Epidemic potential

Arbovirus: 4 types of vectors



Mosquito



Tick

Sand fly

Midge

Arboviruses: 3 main families

- *Bunyaviridae*
- *Flaviviridae*
- *Togaviridae*

Summary of taxonomy and essential ecology of medically important travel-related arboviruses.

Family genus	Serogroup	Virus	Abr.	Vector	Host	Geographical distribution	Occur.[a]
Bunyaviridae							
Nairovirus	Crimean-Congo hemorrhagic fever	Crimean-Congo hemorrhagic fever virus	CCHFV	Tick	Domestic and wild animals, birds, small mammals	South-East and Eastern Europe, Africa, Asia	Sp and En
Orthobunyavirus	Bwamba	Bwamba virus	BWAV	Mosquito	Unknown	Sub-Saharan Africa	En
	Bunyamwera	Bunyamwera	BUNV	Mosquito	Possibly rodents	Sub-Saharan Africa	En
		Ilesha virus	ILEV	Mosquito	Unknown	Sub-Saharan Africa	En
		Ngari virus	NRIV	Mosquito	Unknown	Sub-Saharan Africa	En
	California encephalitis	La Cross virus	LCV	Mosquito	Small mammals	North America	En
		Guaroa virus	GROV	Mosquito	Unknown	Central and South America	En
		Tahyna virus	TAHV	Mosquito	Hares, rabbits, hedgehogs, small mammals	Europe, Asia, Africa	En
	Simbu	Oropouche virus	OROV	Midge	Humans, Sloths (maybe primates, birds)	Central and South America	En
	Ungrouped viruses	Tataguine virus	TATV	Mosquito	Unknown	Sub-Saharan Africa	En
Phlebovirus	Phlebovirus fever	Toscana virus	TOSV	Sandfly	Humans, bats	Southern Europe	En
		Sandfly fever other	SFV	Sandfly	Human, rodents	Southern Europe, Northern Africa, Asia	En
		Rift Valley fever virus	RVFV	Mosquito	Rodents, bats, cattle	Africa, Western Asia	En and Ep
Flaviviridea							
Flavivirus	Dengue virus	Dengue virus	DENV	Mosquito	Primates, humans	Asia, Africa, Americas	En and Ep
	Japanese encephalitis	Japanese encephalitis virus	JEV	Mosquito	Ardeid birds, pigs	South and South-East Asia, Oceania	En and Ep
		West Nile virus	WNV	Mosquito	Birds	North and South America, South and Eastern Europe, South-East Asia, Oceania	En and Ep
		St. Louis encephalitis virus	SLEV	Mosquito	Birds	Americas	En and Sp
		Murray Valley virus	MVEV	Mosquito	Ardeid birds	Oceania	En
	Mammalian tick-born virus group I	Kyasanur Forest disease virus	KFDV	Tick	Small mammals, humans	South-East and Western Asia	Ep
		Alkhurma hemorrhagic fever virus	AHFV	Tick	Small mammals	Western Asia	Ep
		Tick-borne encephalitis virus	TBEV	Tick	Small mammals, birds	Central, Northern and Eastern Europe, and Asia	En
	Ntaya virus	Ilheus virus	ILHV	Mosquito	Birds	Central and South America	En
	Yellow fever	Yellow fever virus	YFV	Mosquito	Primates, humans	Sub-Saharan Africa and South America	En and Ep
Reoviridae							
Coltivirus	Colorado tick fever	Colorado Tick fever virus	CTFV	Tick	Small mammals	North America	Sp
Seadornavirus	Banna	Banna virus	BANV	Mosquito	Unknown	Asia	En
Togaviridae							
Alphavirus	Barmah Forest	Barmah Forest virus	BFV	Mosquito	Wild birds, marsupials	Australia	Ep and Sp
	Eastern equine encephalitis	Eastern equine encephalitis virus	EEEV	Mosquito	Aquatic birds, small mammals, marsupials	Americas	Sp
	Semliki forest	Chikungunya virus	CHIKV	Mosquito	Primates, humans	Africa and Asia	En and Ep
		Mayaro virus	MAYV	Mosquito	Primates birds, humans	South America	En
		O'Nyong-nyong	ONNV	Mosquito	Primates, humans	Sub-Saharan Africa	En and Ep
		Ross River virus	RRV	Mosquito	Marsupials, mammals	Oceania	Ep
	Western equine encephalitis (sindbis like)	Sindbis virus	SINV	Mosquito	Birds	Northern Europe, Asia, Africa, Oceania	Ep
	Western equine encephalitis (recombinants)	Western equine encephalitis virus	WEEV	Mosquito	Birds, small mammals	Americas	Sp and Ep
	Venezuelan equine encephalitis	Venezuelan equine encephalitis virus	VEEV	Mosquito	Small mammals	Americas	En and Ep

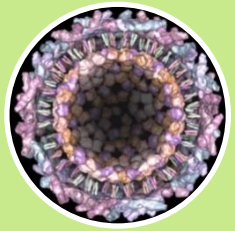
[a] Occurrence; En: endemic, Ep: epidemic, Sp: sporadic.

Cleton N. *J Clin Virol* 2012

Arboviruses: 3 main families

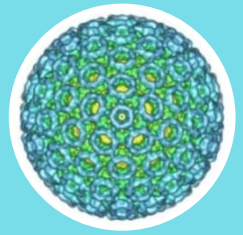
- ***Bunyaviridae***
  - **Genus Nairovirus:** Crimean-Congo hemorrhagic fever (CCHFV)
  - **Genus Phlebovirus:** Toscana virus (TOSV); Sandfly fever virus (SFV); Rift Valley fever virus (RVFV)
  - **Genus Orthobunyavirus (9)**
- ***Flaviviridae* (3 genera)**
  - **Genus flavivirus (9 serogroups)**
    - Dengue virus (DENV); Japanese encephalitis virus (JEV); West Nile virus (WNV); Yellow fever virus (YFV); Zika virus (ZIKV); Tick-borne encephalitis virus (TBEV)
- ***Togaviridae***
  - **Genus alphavirus (7 serogroups)**
    - Chikungunya virus (CHIKV); Eastern, Western, Venezuelan Equine Encephalitis viruses (EEEV, WEEV, VEEV); Sindbis virus (SINV); Ross River virus (RRV); Mayaro virus (MV),…

Arboviruses: 3 main families and main human pathogens



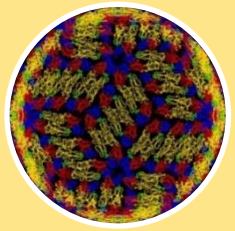
Togaviruses

- Chikungunya virus
- Eastern, Western and Venezuelan equine encephalitis viruses
- Ross river virus
- Mayaro virus



Bunyaviruses

- Crimean-Congo
- hemorrhagic fever virus
- Toscana virus; Sandfly fever virus
- Rift Valley fever virus



Flaviviruses

- Yellow fever virus
- Dengue virus
- Japanese encephalitis virus
- West Nile virus
- Zika virus
- Tickborne encephalitis virus

Arboviruses: 4 main clinical syndromes

Most infections are asymptomatic (> 90%)

Arthralgia and/or rash (AR)

DENV, CHIKV, ZIKV, RRV,…

Febrile disease (FD) + Neurological syndrome (NS)

JEV, TBEV, WNV, EEEV,

Hemorrhagic syndrome (HS)

DENV, YFV, RVFV, CCHV,…

Arboviruses: 2 major epidemiological scenarios

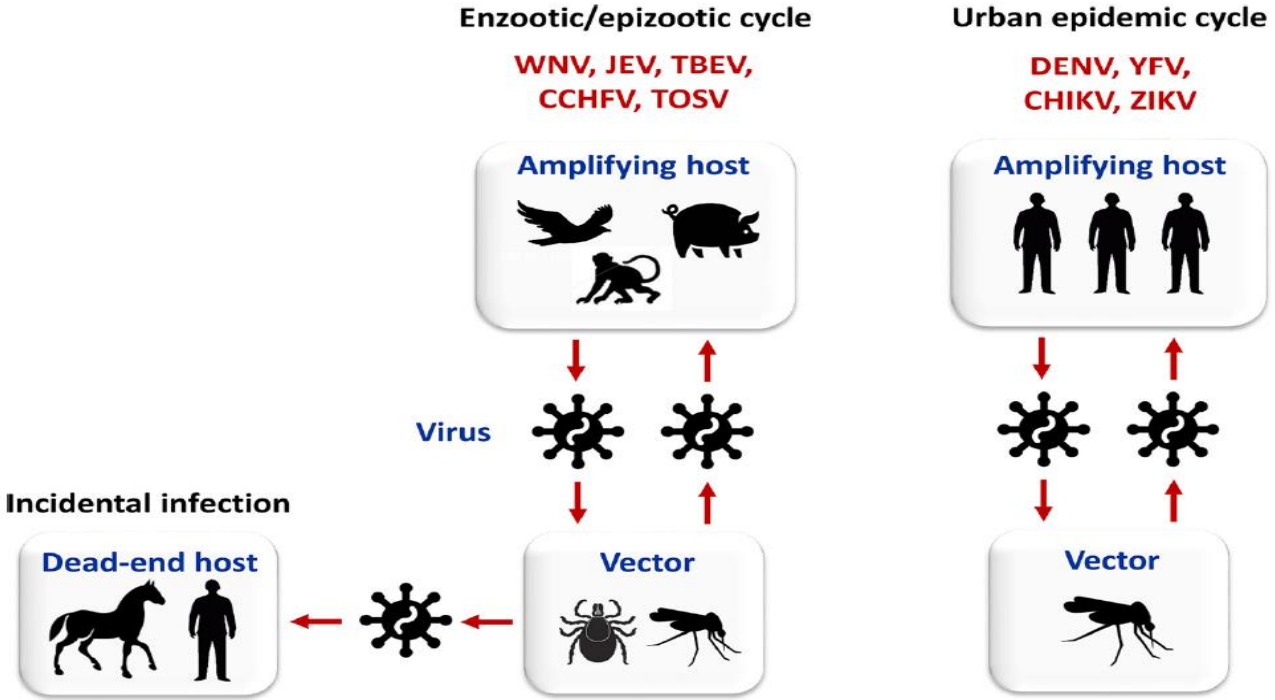
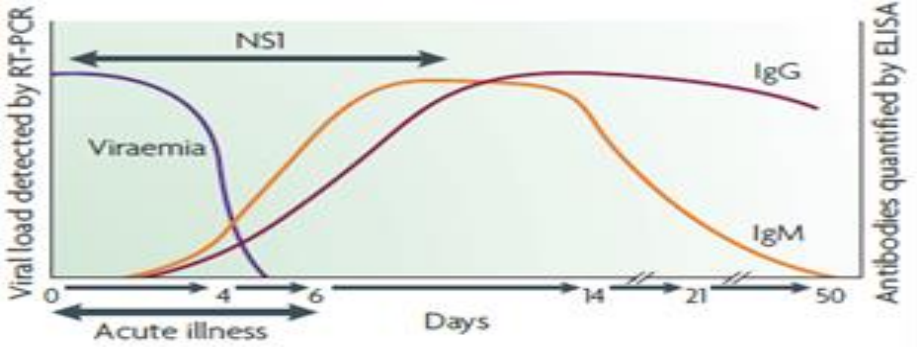
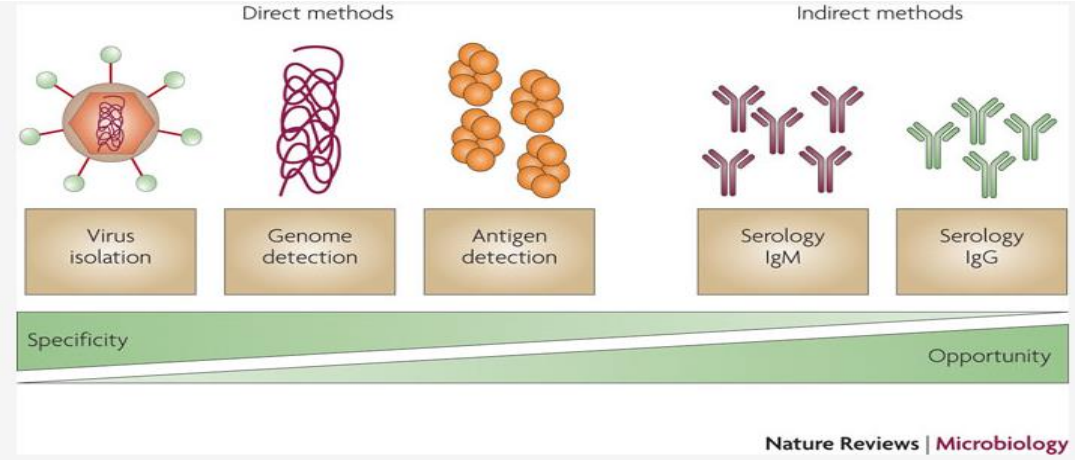


Fig. 1. Transmission cycles of arboviruses.

Arboviruses: diagnosis (in general)





Arboviruses: diagnosis (in general)

Combination of direct and indirect diagnostic tests:


Development of Zika Antigen Rapid Test

March 4, 2016 Uncategorized

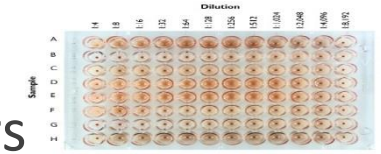
In order to further enhance the detection of Zika Virus, Biocan has commenced development of a new test, Zika Virus Antigen Rapid Test which will help in early detection of Zika Virus. The goal is to develop a Zika Antigen & Antibody Combo Rapid Test which will greatly enhance the overall detection scope of Zika Virus. Biocan is anticipating that the Zika Antigen Rapid Test will be ready for initial clinical trails by end of March 2016.

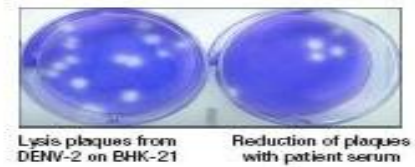
Direct:

- Antigen ----------> minutes
- RT-PCR ----------> hours
- viral culture ----------> days

Indirect:

- serology ----------> hours
- neutralization assays ----------> days

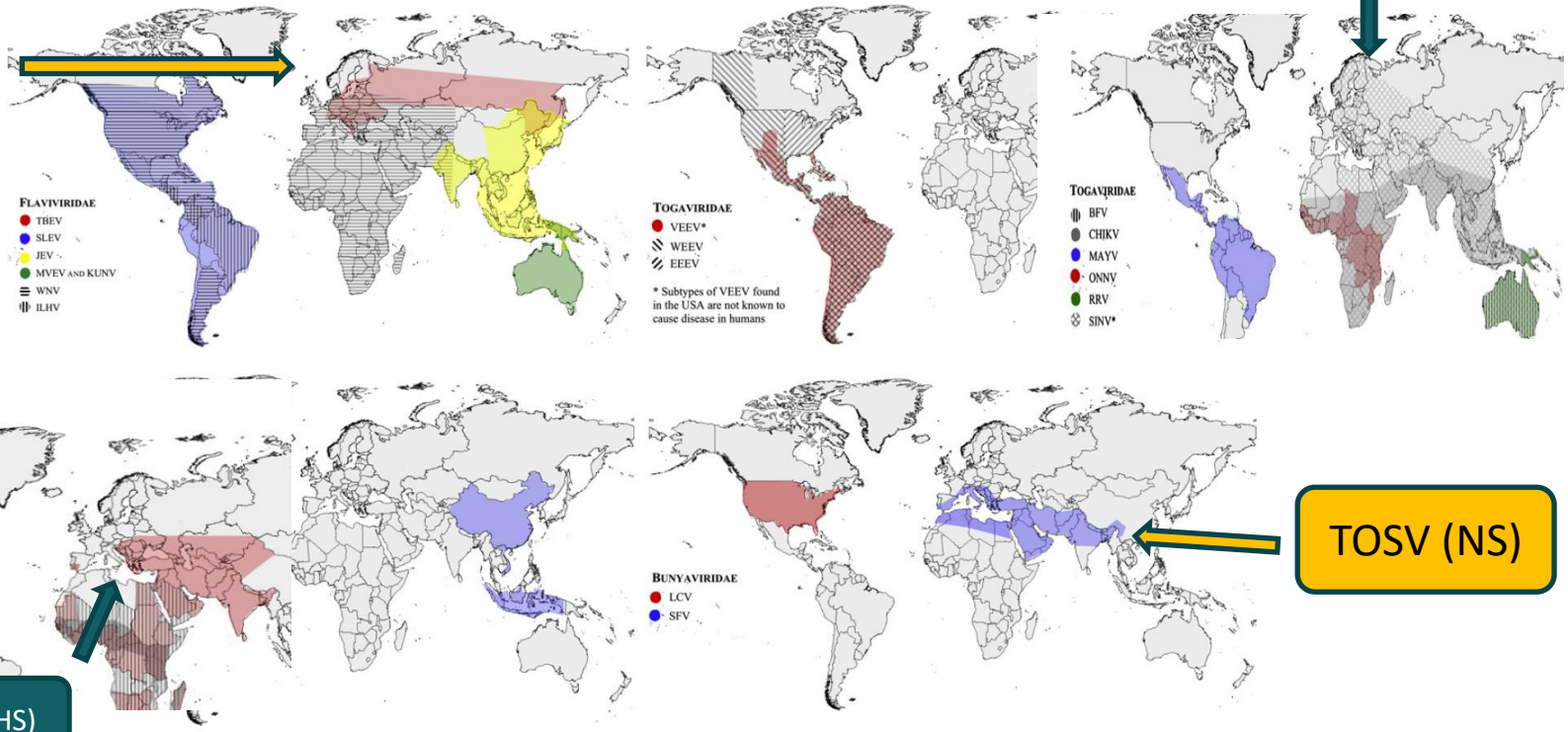




Arboviruses endemic in Europe (up to 2010)

SINV (AR)

TBEV (NS)

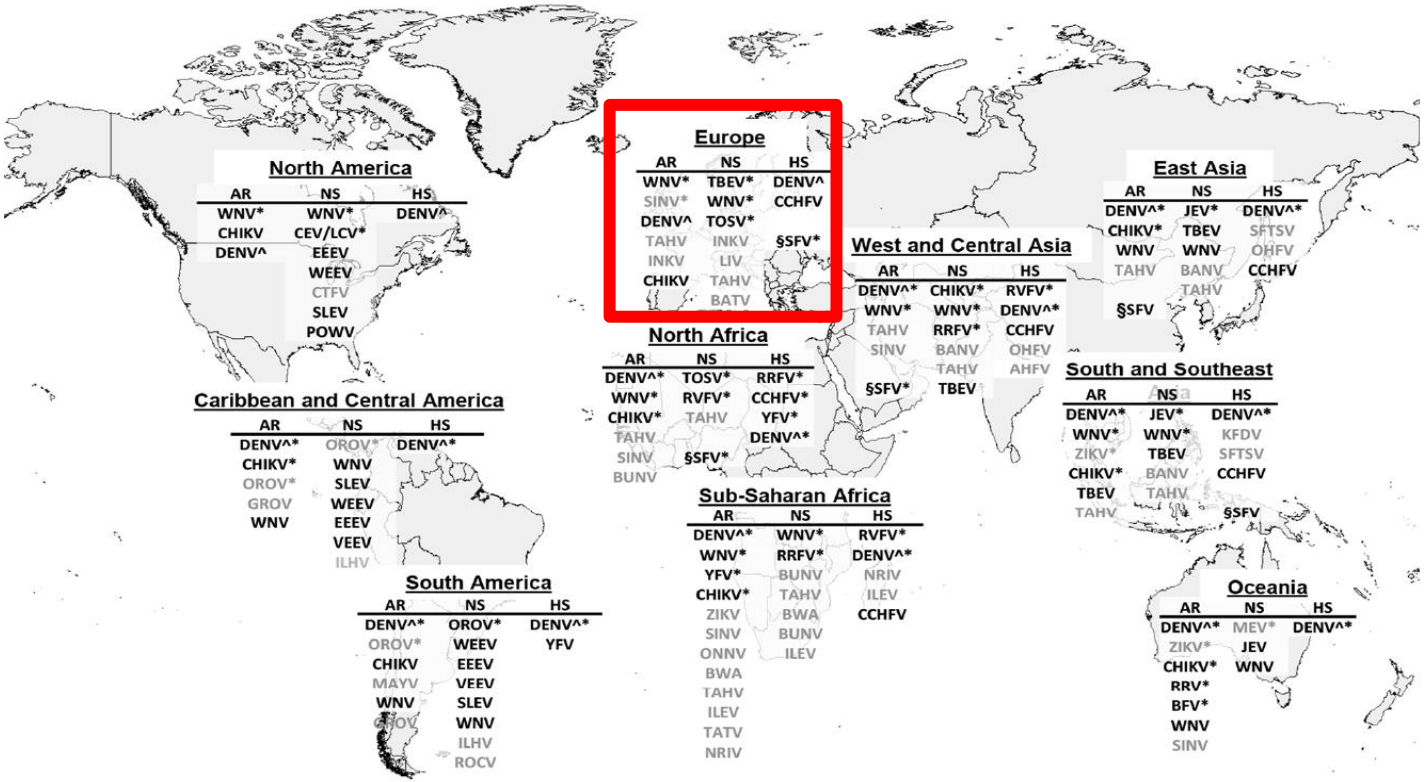


TOSV (NS)

CCHFV (HS)

Map 1. Neuroinvasive arboviruses. General geographical overview of medically important arboviruses that cause NS based on Tables 1 and 2.

Arboviruses with transmission in Europe (2022)



Cleton N. *PLoS NTD* 2015

Arboviruses in Europe (2022)

- **Endemic in Europe**
  - **Tick-borne**
    - **Tick-borne encephalitis (TBEV)**
    - Crimean-Congo hemorrhagic fever (CCHFV)
  - **Sandfly-borne**
    - **Toscana fever (TOSV)**
  - **Mosquito-borne**
    - **West Nile disease (WNV)**
    - Sindbis virus (SINV)
- **In establishment ?**
  - **Dengue (DENV)**
  - **Chikungunya (CHIKV)**
- **Only in travelers**
  - ZIKV, JEV, YFV,…

Difficult clinical distinction between presenting syndromes

Mix of travel-related and autochthonous cases with geographical overlapping

Tick-borne encephalitis (TBE), transmission

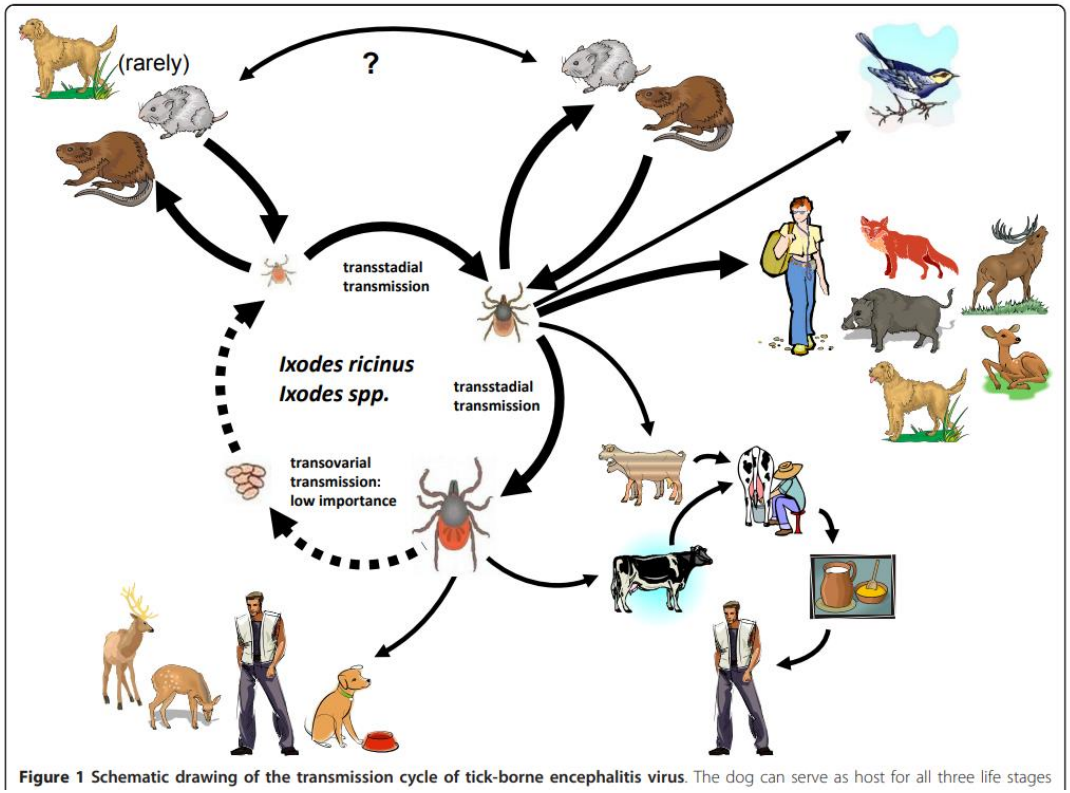
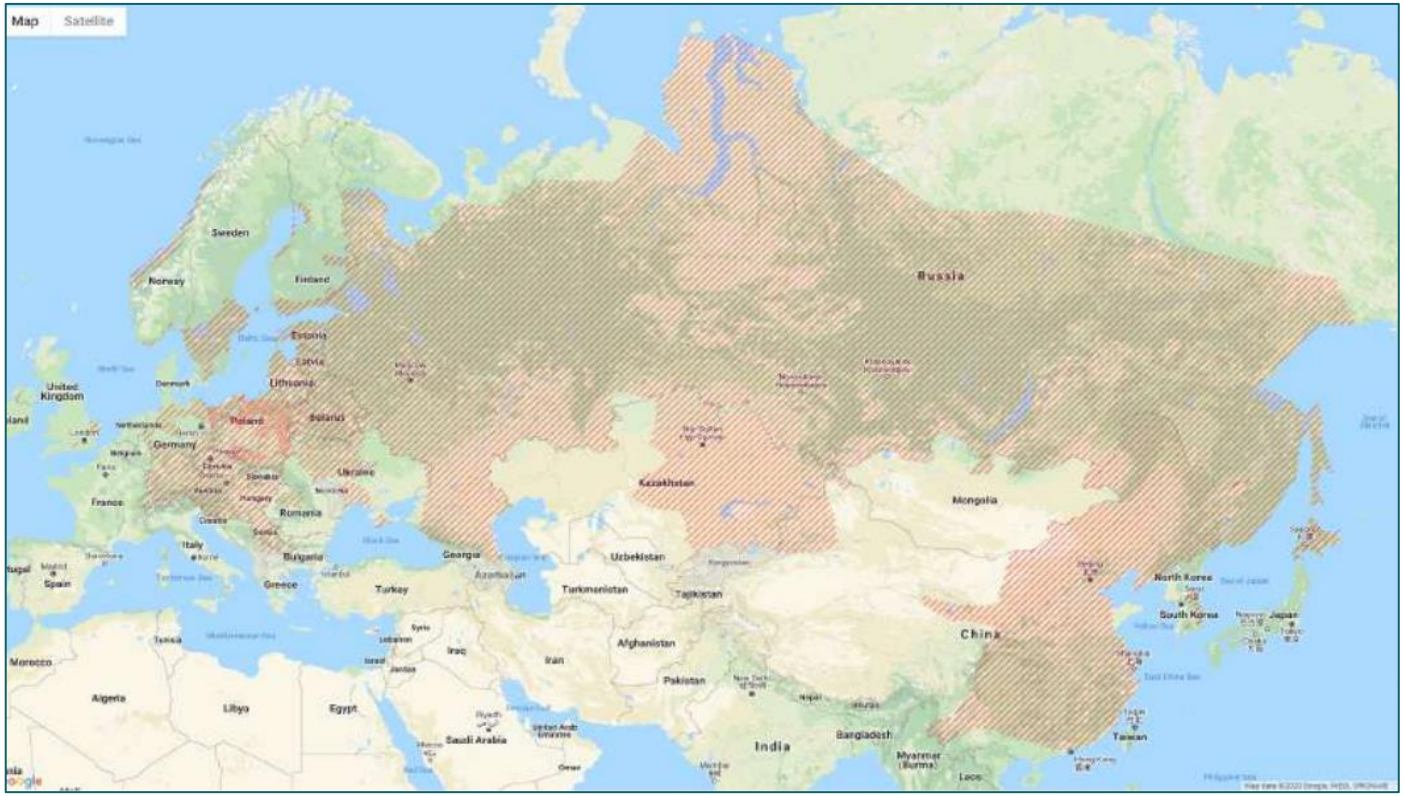


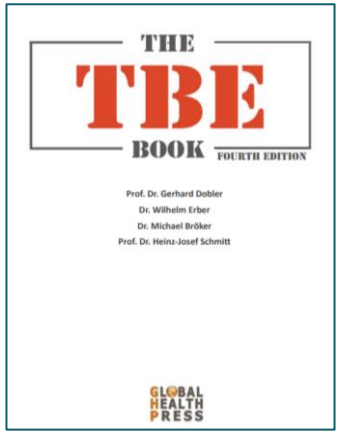
Figure 1 Schematic drawing of the transmission cycle of tick-borne encephalitis virus. The dog can serve as host for all three life stages

Ixodes tick

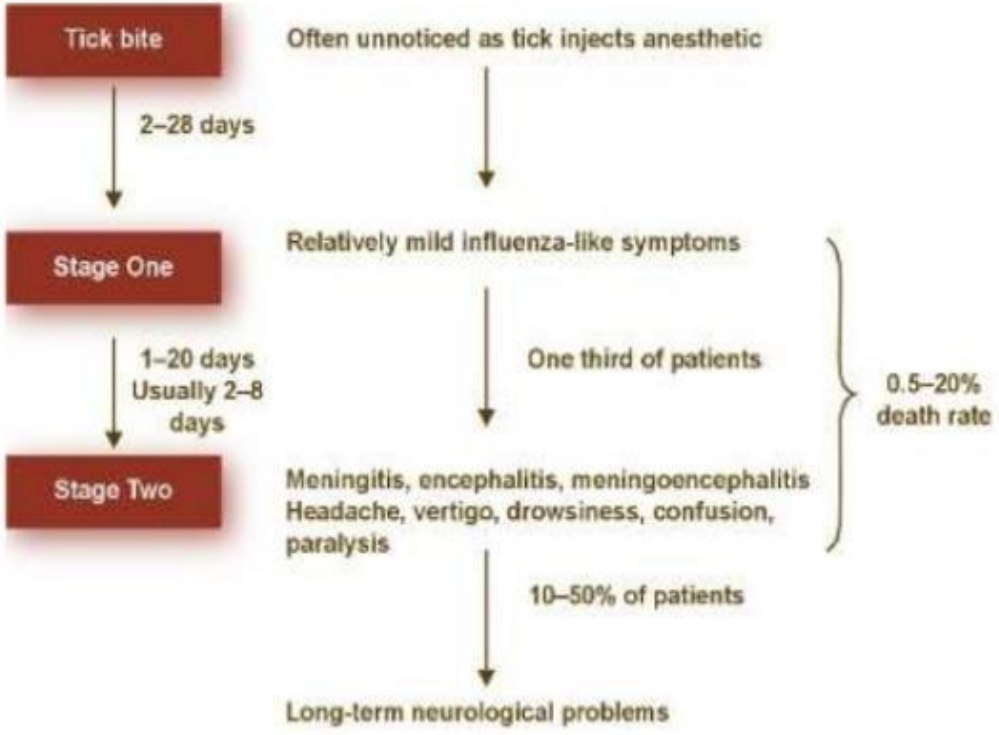
Figure 1: Unengorged *Ixodes ricinus* ticks in different developmental stages
From top, anticlockwise, one adult female, two larvae, and one nymph.

Tick-borne encephalitis (TBE), global distribution





Tick-borne encephalitis, clinical



Zajkowska. *Emerg Infect Dis* 2013

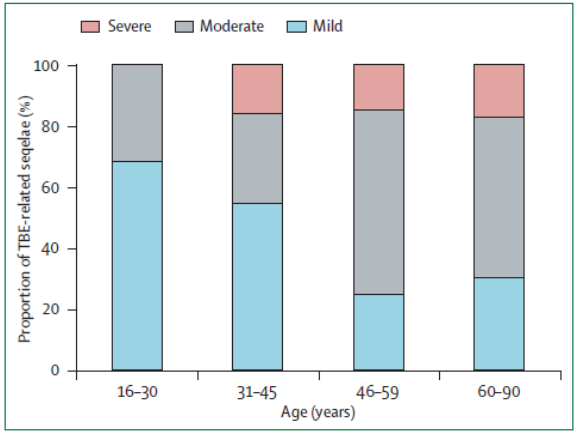
A Bender et al. J Neurol Neurosurg Psychiatry 2005;76:135-137

Tick-borne encephalitis, clinical (neurological complications)

	Duniewicz et al[68]	Falisevac et al[69]	Radsel-Medvescek et al[70]	Krech et al[71]	Jezyna et al[72]	Kaiser[36]	Grygorczuk et al[73]	Mickiene et al[38]	Wahlberg et al[74]
Number of patients	589	1218	315	234	215	656	152	133	301
Headache	67%	..	100%	74%	100%		84%	95·5%	81·7%
Altered consciousness	..	..	13·7%	29%	35·5%	31%	24%	18·8%	12%
Sensory impairment	..	..	..	9%	..	2·9%	2%	..	..
Seizures	0·3%	..	..	2%	3·3%	1·7%	..	..	..
Ataxia	30%	..	..	..	..	18%	24%	26·3%	0·3%
Hemiparesis	..	0·3%	..	..	..		1·9%	2·6%	0·3%
Tremor	75%	..	78%	..	31·6%	4·3%	7%	21·8%	..
Dysphasia	..	..	..	..	..	2·5%	0·7%	3·8%	..
Spinal nerve paralysis	12·8%	2·7%	6·3%	10%	8·8%	15%	7·2%	3·8%	4·3%
Cranial nerve paralysis	..	..	3·5%	..	..	11%	3·3%	5·3%	..

..= data not given.

Table 2: **Summary of neurological symptoms in the acute stage of tick-borne encephalitis in studies including a minimum of 100 patients**



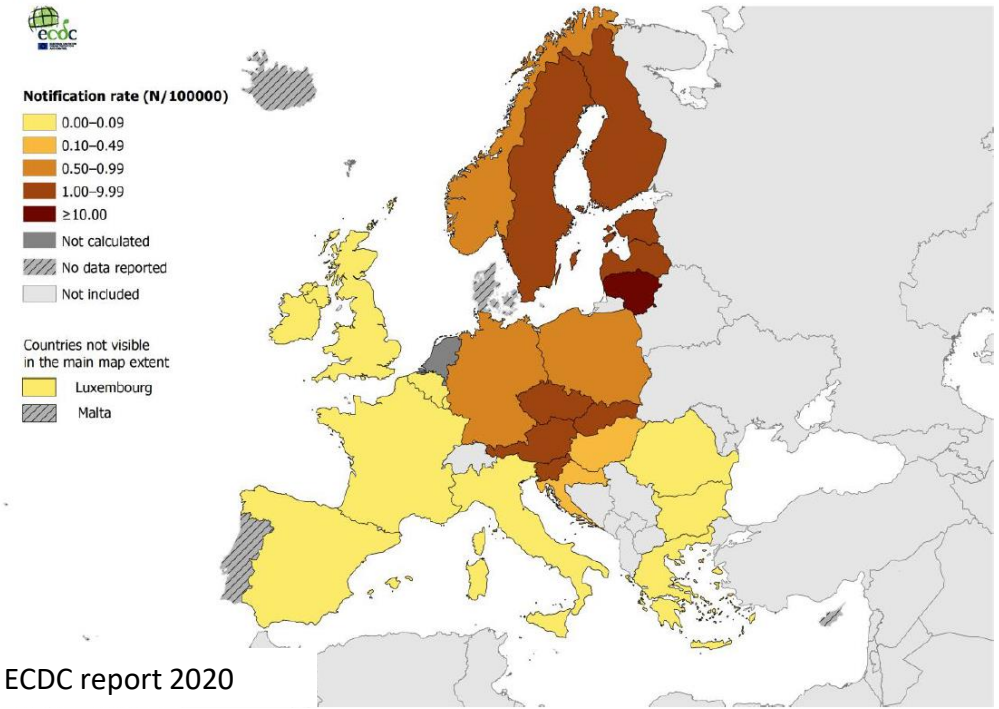
Lindquist L. *Lancet* 2008

Tick-borne encephalitis, diagnosis & management

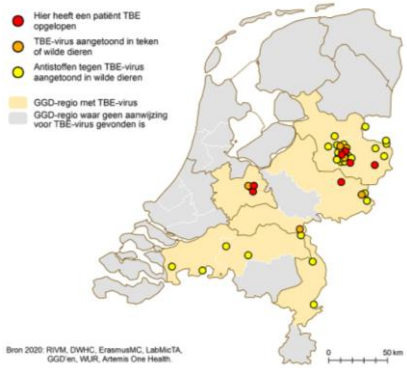
- Virus isolation, PCR, VNT
- Serology: cross reaction with flavivirus vaccine or infection
- Supportive care (10% ICU); no specific antivirals; steroids likely deleterious
- Safe vaccine available
- Protection against ticks

Distribution of TBE in Europe

Figure 1. Distribution of confirmed tick-borne encephalitis cases per 100 000 population by country, EU/EEA, 2019



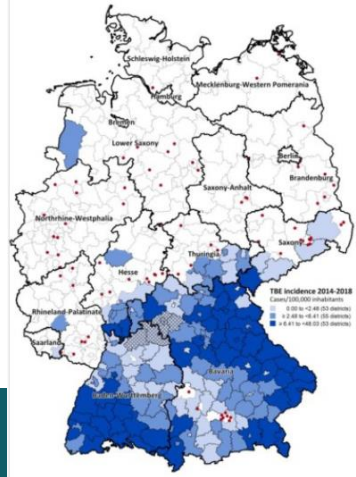
ECDC report 2020



TBE in Rhone-Alpes-Provence, France

Home › Publications › HPS Weekly Report › 2020 › Issue 25 › TBE in Rho...

23 June 2020



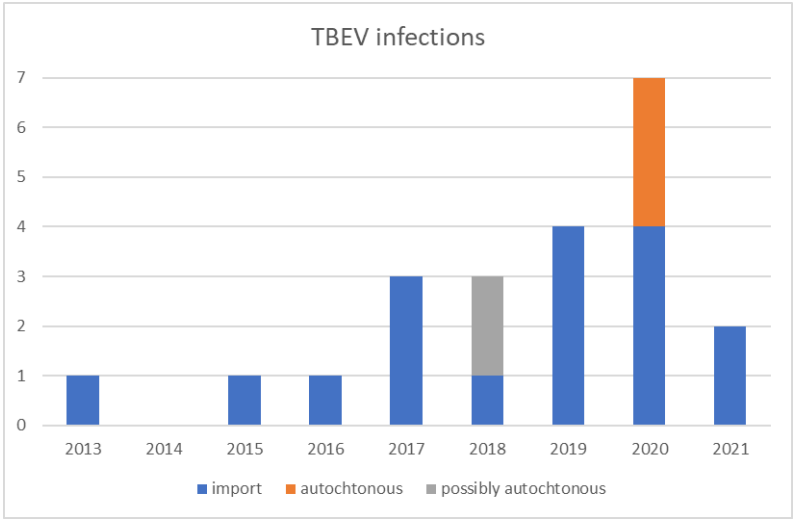
TBE in Belgium

Autochthonous Cases of Tick-Borne Encephalitis, Belgium, 2020

Anke Stoefs, Leo Heyndrickx, Jonathan De Winter, Evelien Coeckelbergh, Barbara Willekens, Alicia Alonso-Jiménez, Anne-Marie Tuttino, Yvette Geerts, Kevin K. Ariën, Marjan Van Esbroeck

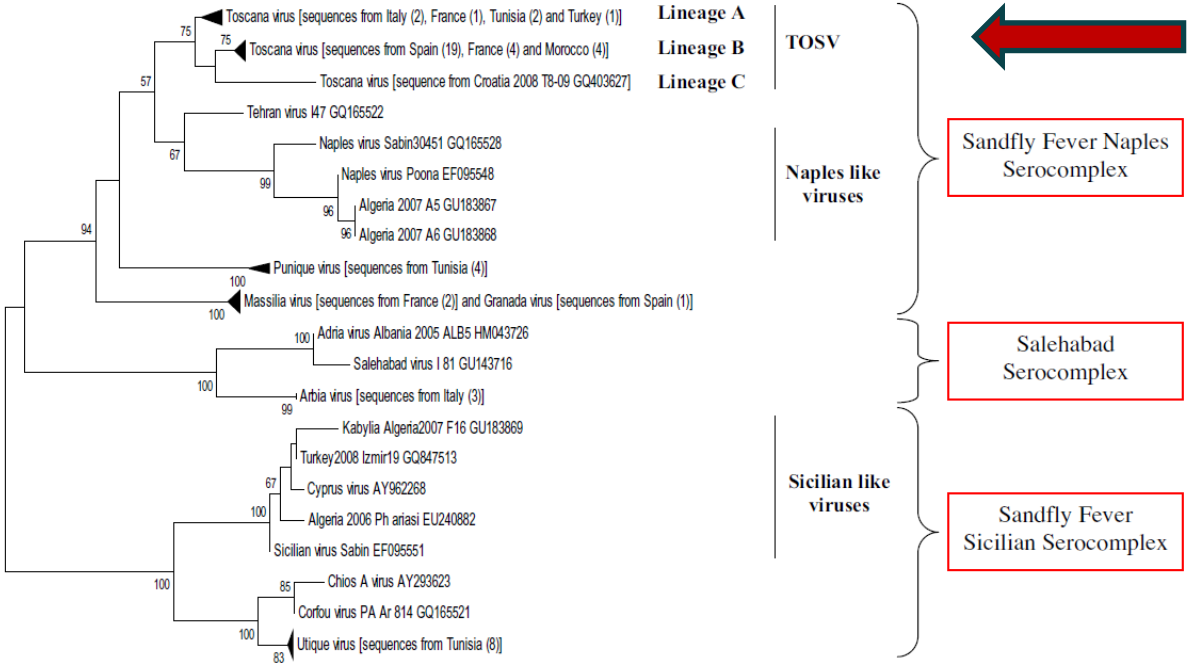
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 27, No. 8, August 2021

Figure. Geographic distribution of autochthonous human cases of tick-borne encephalitis, Belgium and the Netherlands (adapted from National Institute of Public Health and Environment [*10*]). Grey shading indicates communities in Belgium in which antibodies against tick-borne encephalitis virus have been detected in animals (adapted from S. Roelandt [*2*]).



Courtesy Dr M. Van Esbroeck, CLKB, ITM

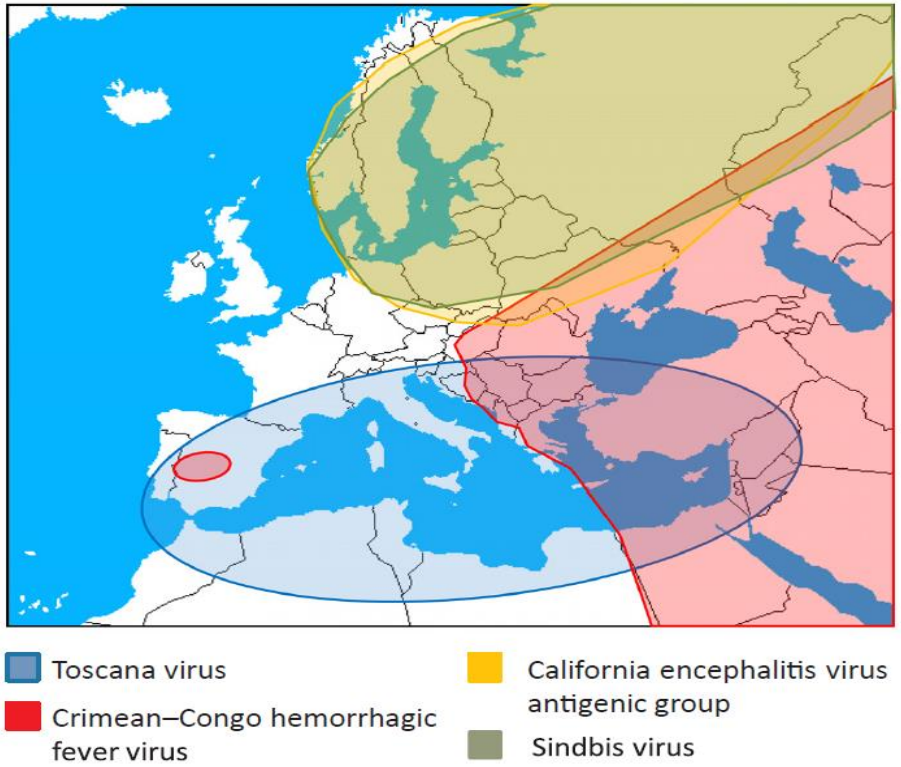
Toscana virus and other sandfly-borne phleboviruses



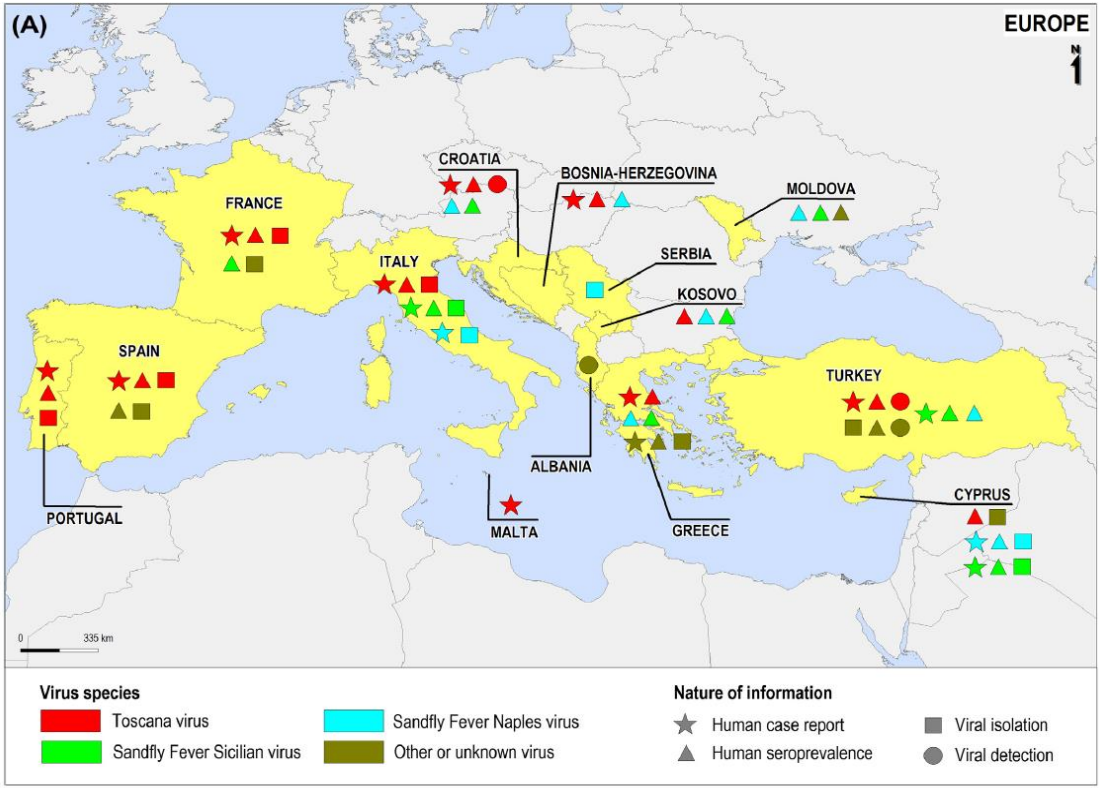
Phlebotomus

Fig. 2. Female *Phlebotomus papatasi* sandflies taking a blood meal from a mouse tail (Courtesy Filiz Gunay, University of Hacettepe).

Toscana virus, global distribution



Toscana virus & other sandfly-borne phleboviruses, clinical

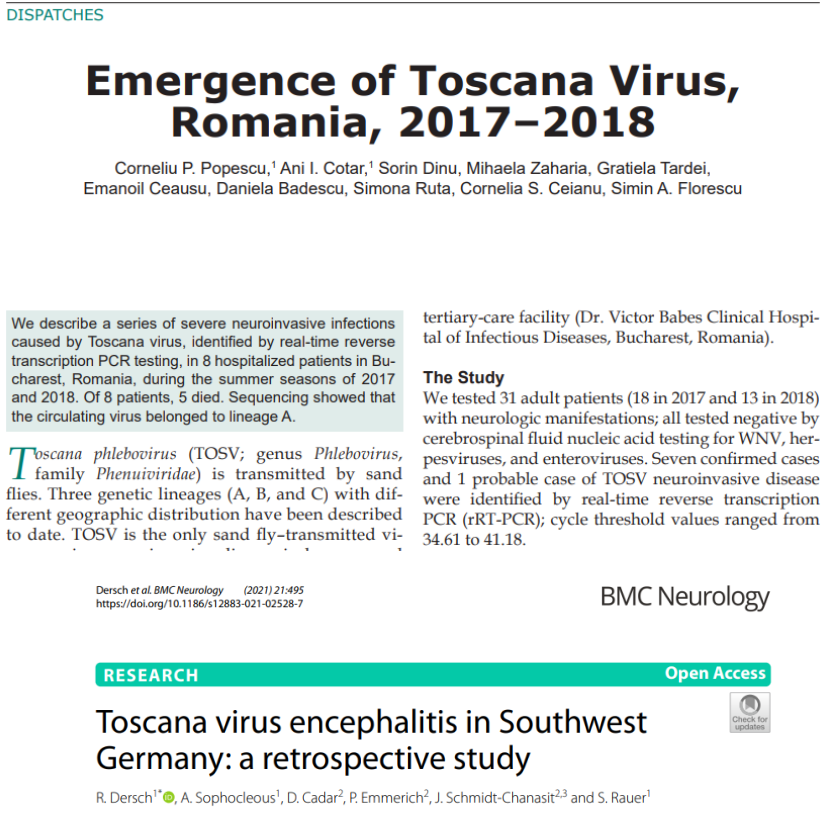


Toscana virus:
(aseptic) meningitis, encephalitis,

Other sandfly viruses:
short febrile illness (“papataci fever” or “three-day fever”)

Toscana virus disease, diagnosis & management

- Virus isolation, PCR
- Serology (little cross-reaction)
- Supportive care
- No specific treatment nor vaccine



DISPATCHES

Emergence of Toscana Virus, Romania, 2017–2018

Corneliu P. Popescu,[1] Ani I. Cotar,[1] Sorin Dinu, Mihaela Zaharia, Gratiela Tardei, Emanoil Ceausu, Daniela Badescu, Simona Ruta, Cornelia S. Ceianu, Simin A. Florescu

We describe a series of severe neuroinvasive infections caused by Toscana virus, identified by real-time reverse transcription PCR testing, in 8 hospitalized patients in Bucharest, Romania, during the summer seasons of 2017 and 2018. Of 8 patients, 5 died. Sequencing showed that the circulating virus belonged to lineage A.

Toscana phlebovirus (TOSV; genus *Phlebovirus*, family *Phenuiviridae*) is transmitted by sand flies. Three genetic lineages (A, B, and C) with different geographic distribution have been described to date. TOSV is the only sand fly–transmitted vi-

tertiary-care facility (Dr. Victor Babes Clinical Hospital of Infectious Diseases, Bucharest, Romania).

The Study

We tested 31 adult patients (18 in 2017 and 13 in 2018) with neurologic manifestations; all tested negative by cerebrospinal fluid nucleic acid testing for WNV, herpesviruses, and enteroviruses. Seven confirmed cases and 1 probable case of TOSV neuroinvasive disease were identified by real-time reverse transcription PCR (rRT-PCR); cycle threshold values ranged from 34.61 to 41.18.

Dersch *et al. BMC Neurology* (2021) 21:495
https://doi.org/10.1186/s12883-021-02528-7

BMC Neurology

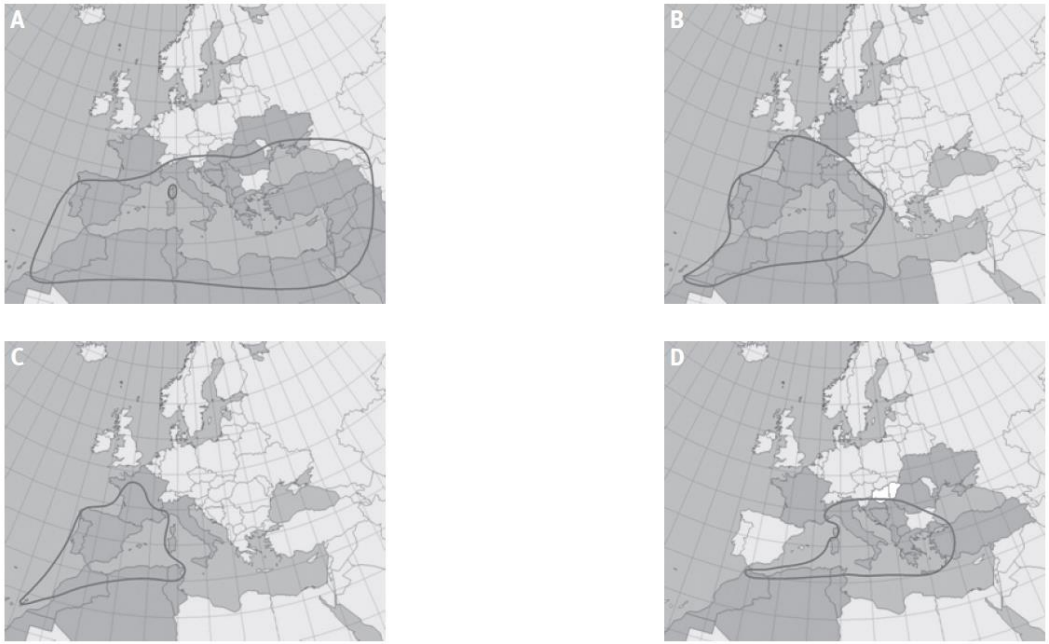
RESEARCH Open Access

Toscana virus encephalitis in Southwest Germany: a retrospective study

R. Dersch[1*], A. Sophocleous[1], D. Cadar[2], P. Emmerich[2], J. Schmidt-Chanasit[2,3] and S. Rauer[1]

Map of vector suitability for Toscana virus in Europe

Distribution of main vectors in the European Union and neighbouring countries around the Mediterranean Sea up to 2009



From left to right and from top to bottom: (a) *Phlebotomus papatasi*, (b) *P. perniciosus*, (c) *P. ariasi*, and (d) *P. perfiliewi s. st.*

Depaquit J. *Euro Surveill* 2010

West Nile virus, transmission

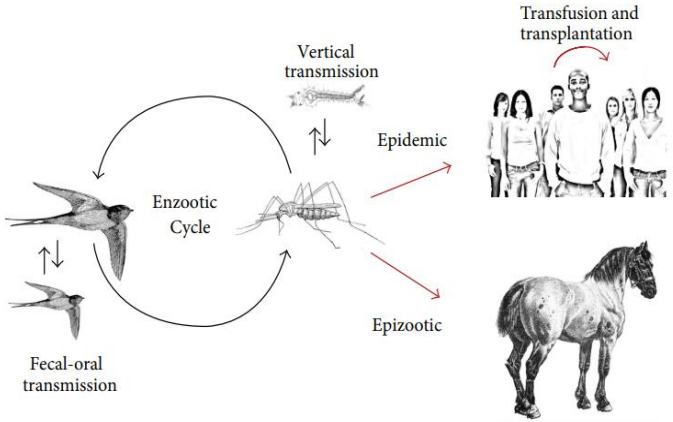


FIGURE 4: WNV transmission cycle: enzootic amplification of WNV by birds and mosquitoes supplemented by bird-to-bird transmission and transmission between cofeeding mosquitoes. Vertical transmission by mosquitoes provides the mechanism of virus overwintering. Humans and horses are counted as incidental dead-end hosts. Human-to-human transmission may come through blood transfusion, organ transplantation, and breast feeding and in utero.

Culex mosquito

West Nile virus, global distribution

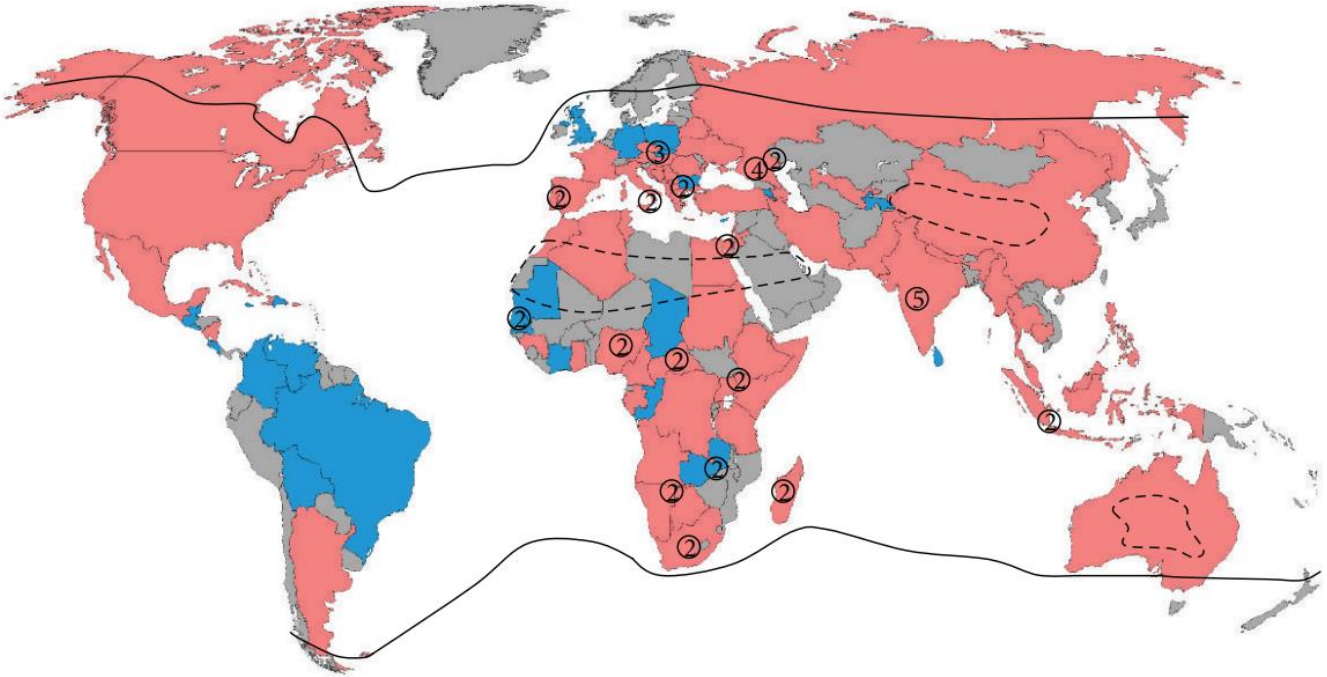
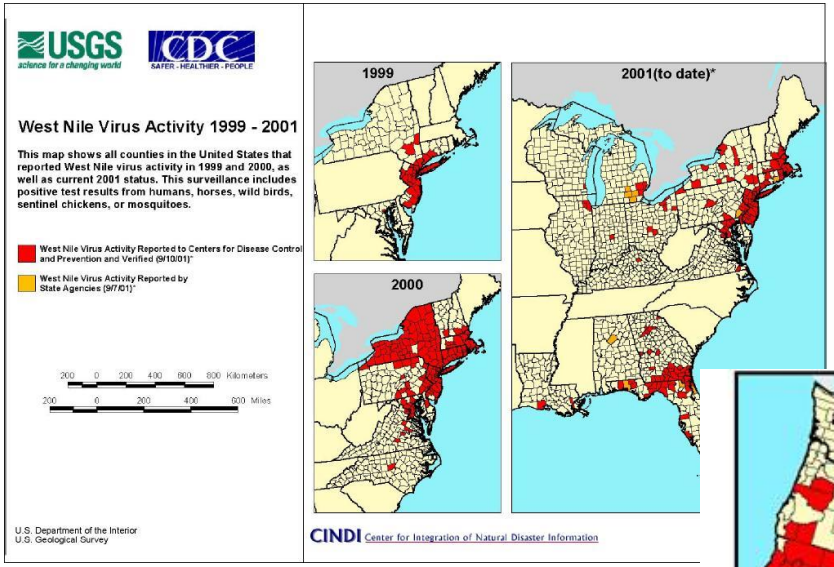
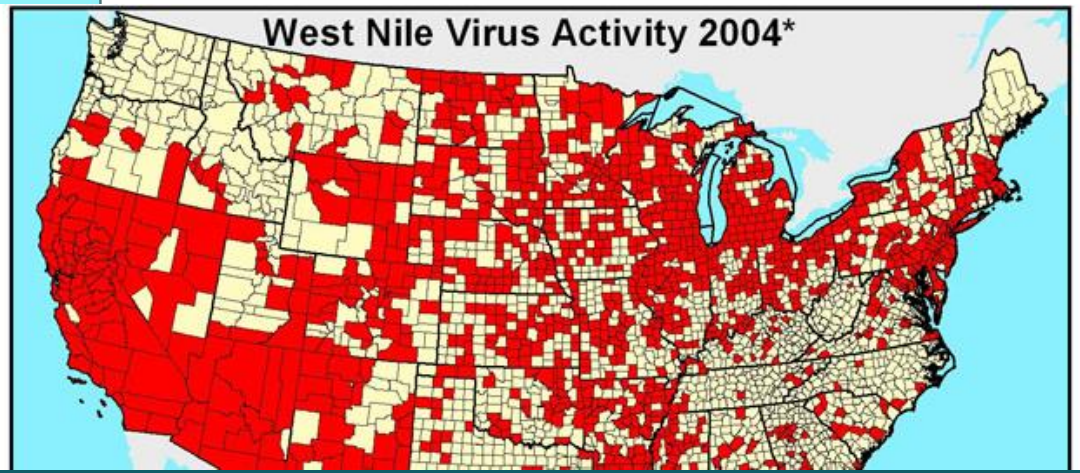


FIGURE 1: Global distribution of WNV by country: Red—human cases or human seropositivity; Blue—nonhuman/mosquito cases

West Nile virus, 2000 epidemic in USA

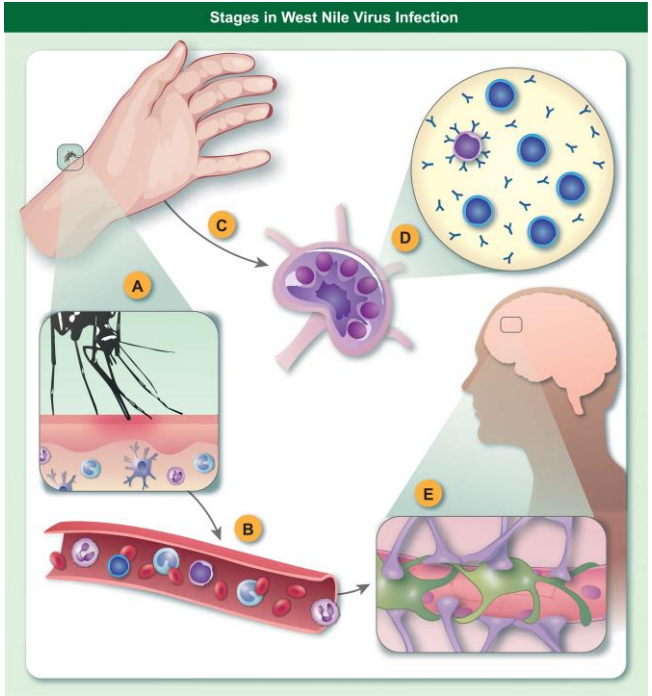




West Nile virus disease, clinical

- Incubation 5-15 days, sometimes shorter
- About 30% of infections are symptomatic
  - Flu-like symptoms; non-specific malaise
  - (Non-itchy) rash (50%)

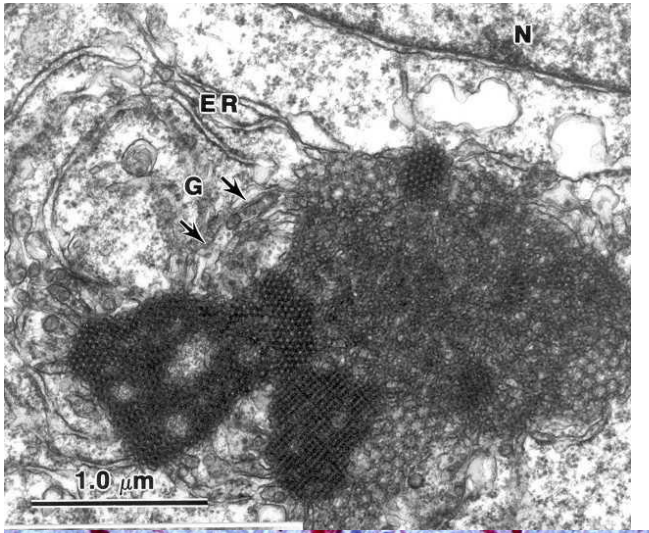
- 1%: West Nile neuroinvasive disease (WNND)
  - Encephalitis, meningitis, acute flaccid paralysis
  - 10% fatality rate; frequent sequelae

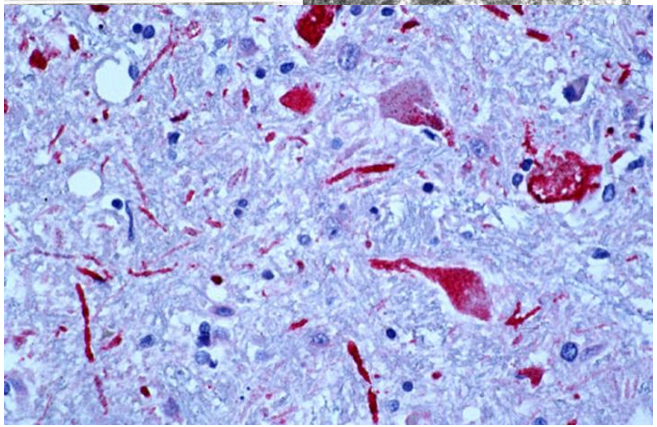


WNND incidence increases 1.5-fold for each decade of life.

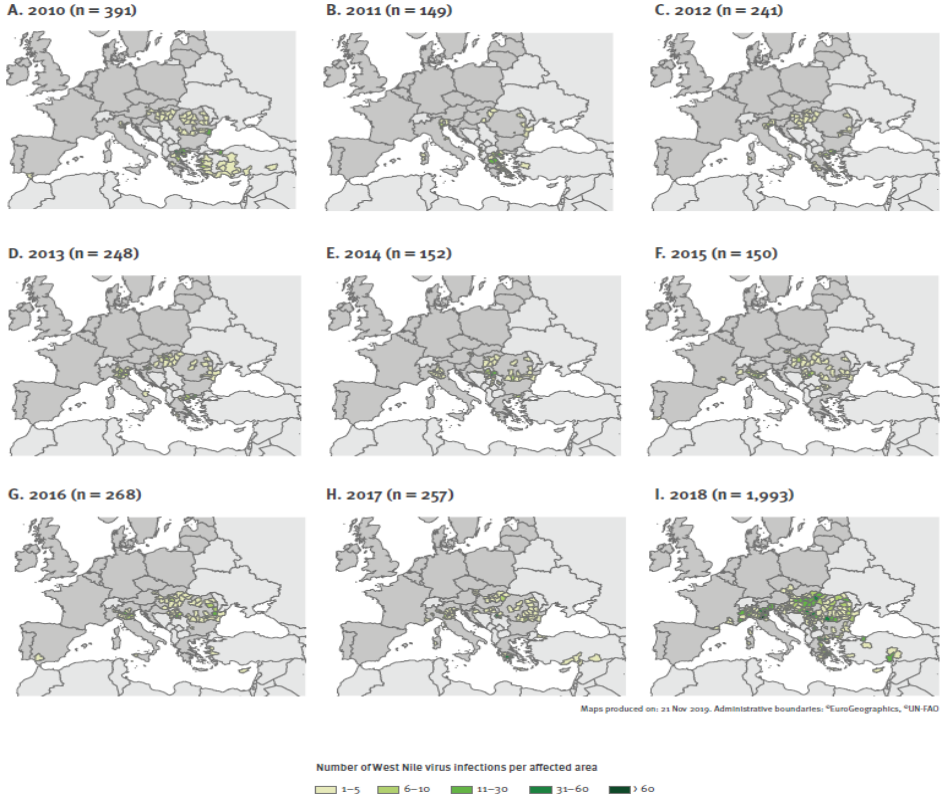
West Nile virus disease, diagnosis

- Antibody detection/ cross-reactivity!
- RT-PCR serum, urine, red blood cells
  - Duration of viremia 1-2 d
  - Longer window of detection in urine / RBCs
- CSF: RT-PCR, IgM
- Immunohistochemistry





West Nile virus disease in Europe



Yound JJ. *Euro Surveill* 2021

West Nile virus disease imported to Belgium

Epidemiol. Infect., Page 1 of 10. © Cambridge University Press 2014
doi:10.1017/S0950268814000685

Chikungunya virus and West Nile virus infections imported into Belgium, 2007–2012

Table 1. *Laboratory results of confirmed imported WNV infections at diagnosis*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Country	Florida, USA	Senegal/Guinea	DRC	Greece	Sudan
Year (month)	2007 (Sept.)	2008 (Aug.)	2012 (Mar.)	2012 (Aug.)	2012 (Dec.)
Sample type	Serum	Serum	CSF	Serum	Serum
Time after onset	5 days	?	?	1 week	3 weeks
Neuroinvasive case	Yes	No	Yes	Yes	No
ELISA IgM (ratio)	Positive (10·3)	Positive (6·00)	n.t.	Positive (25)	Positive (2·61)
ELISA IgG (ratio)	Negative	Positive (3·31)	n.t.	Negative	Positive (4·75)
SMNT (titre)	n.t.	Positive (1:640)	n.t.	n.t.	Positive (1:40)
IgG avidity index	n.t.	High	n.t.	n.t.	Intermediate
Polymerase chain reaction	n.t.	Negative	Positive	Positive	n.t.
ECDC case definition	Probable	Confirmed	Confirmed	Confirmed	Confirmed
Reference	Present study	Present study	Antoine-Moussiaux (unpublished data)	[3]	Present study

West Nile Virus Infection in Belgian Traveler Returning from Greece

To the Editor: West Nile virus (WNV) is an arthropod-borne virus that is transmitted to humans by mosquitos, primarily of the genus *Culex*. Most human infections are asymptomatic. Clinical symptoms occur in ≈20% of case-patients and include

case of WNV encephalitis imported by a traveler returning from Greece. A 73-year-old Belgian woman, who had a medical history of lymphoma, traveled to Kavala city (Macedonia, Greece). On August 14, 2012, she sought treatment at the Kavala General Hospital with a 6-day history of fever, headache, malaise, nausea, confusion, decline of consciousness, and neck stiffness. Results of laboratory testing on admission demonstrated an increased leukocyte count (9,670/μL;

Belgium. IgM and IgG against WNV were detected in both samples by ELISA (Focus Diagnostics) (Table). Immunofluorescence assays on serum revealed IgM against WNV only and IgG against West Nile, dengue, yellow fever, and Japanese encephalitis viruses, with the strongest reaction against WNV (Flavivirus Mosaic 1; Euroimmun, Lübeck, Germany). Real-time RT-PCR (adapted from [5]) on the serum demonstrated a weak positive signal. Repeated RNA extraction and

Table. Laboratory results confirming WNV infection of 73-year-old woman, Greece, 2012*†

Sample	Date	RT-PCR (C_t value)	WNV ELISA IgM (ratio)	WNV ELISA IgG (ratio)	Flavi IFAT IgM	Flavi IFAT IgG
Serum	Aug 15	Positive (45.47)	Positive (25)	Negative	ND	ND
CSF	Sep 3	ND	Positive (5.16)	Positive (2.21)	ND	ND
Serum	Sep 6	Positive (42.87)‡	Positive (4.76)	Positive (2.63)	WNV positive	WNV positive§

*WNV, West Nile virus; RT-PCR, reverse transcription PCR; Ct, cycle threshold; Flavi, flavivirus; IFAT, indirect fluorescent antibody technique; ND, not done; CSF, cerebrospinal fluid.
†The ELISA is positive if ratio >1.1 for IgM and >1.5 for IgG. The cutoff value for IFAT is 1/10 for both IgG and IgM.
‡Sequencing revealed a 116-bp sequence perfectly matched to the WNV amplicon and is highly suggestive for WNV lineage 2 on the basis of the presence of 2 specific nucleotides.
§Strongest signal for WNV, weak signal for other flaviviruses (Japanese encephalitis virus, dengue viruses 1–4, yellow fever virus).

EMERGING INFECTIOUS DISEASES®
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EID Journal > Volume 24 > Number 12—December 2018 > Main Article

Volume 24, Number 12—December 2018

Research Letter

Use of Next-Generation Sequencing for Diagnosis of West Nile Virus Infection in Patient Returning to Belgium from Hungary

Elke Wollants[1], David Smolders[1], Reinout Naesens, Peggy Bruynseels, Katrien Lagrou, Jelle Matthijnssens, and Marc Van Ranst
Author affiliations: KU Leuven Rega Institute, Rega Institute, Leuven, Belgium (E. Wollants, J. Matthijnssens, M. Van Ranst); ZNA Hospital Middelheim, Antwerp, Belgium (D. Smolders, R. Naesens, P. Bruynseels); University Hospital Leuven, Leuven, Belgium (K. Lagrou, M. Van Ranst)

Sindbis virus, clinical

Sindbis	Fever, rash, arthralgia/arthritis, paraesthesias	Europe, Africa, Australia, Asia, Philippines
Ockelbo	Fever, rash, arthralgia/arthritis, chronic arthralgia, paraesthesias,	Sweden, Norway
Pogosta	Fever, rash, arthralgia/arthritis, chronic arthritis,	Finland
Karelian fever	Fever, rash, arthralgia	Russia

Oligoarthritis > 90%
Skin rash > 90%

Chronicity > 50%

Laine M. *J Intern Med* 2004

Crimean-Congo hemorrhagic fever, transmission

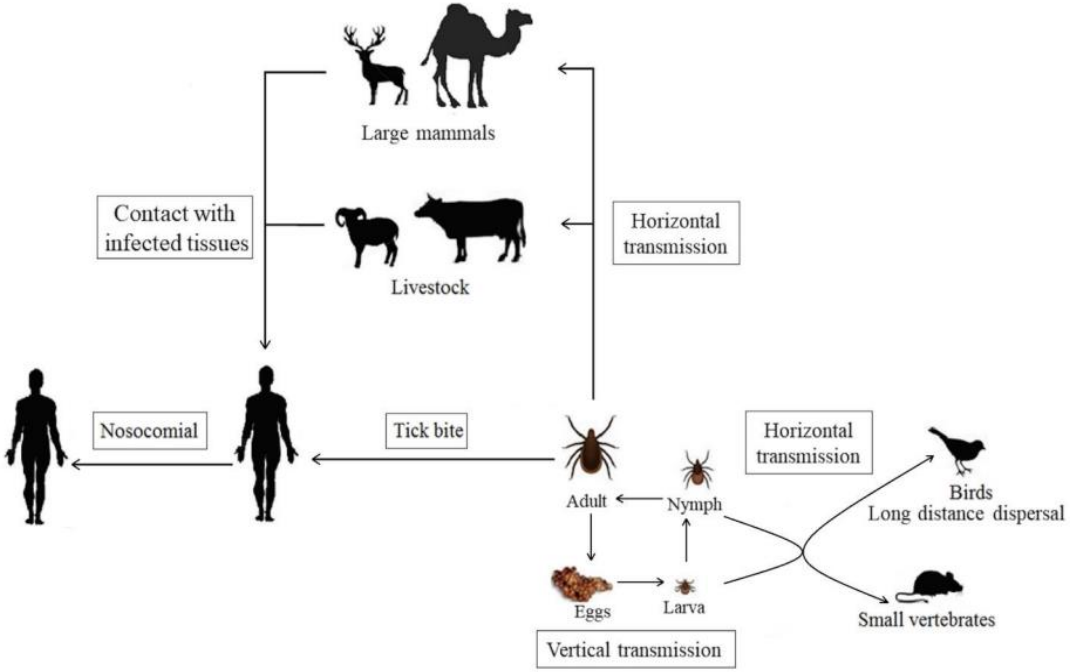
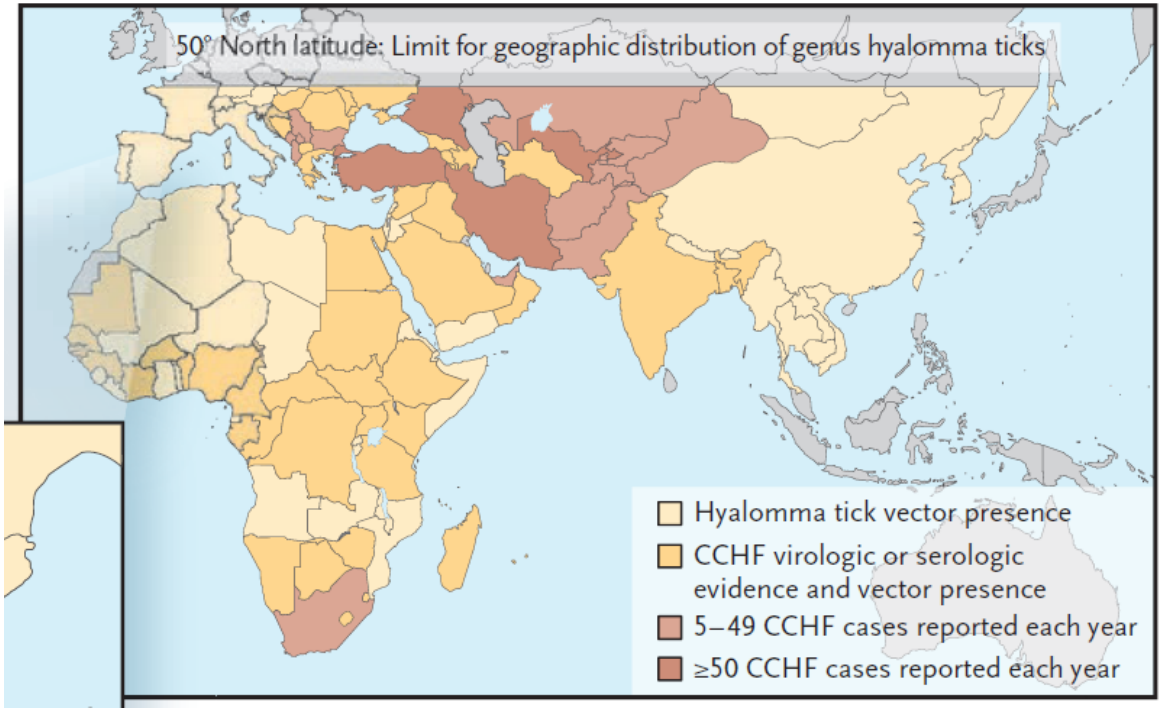


Figure 2. The transmission cycle of CCHFV. The boxes show transmission routes.

Hyalomma tick

NICD South Africa/R. Swanepoel

Crimean-Congo hemorrhagic fever, global distribution



Crimean-Congo hemorrhagic fever, clinical

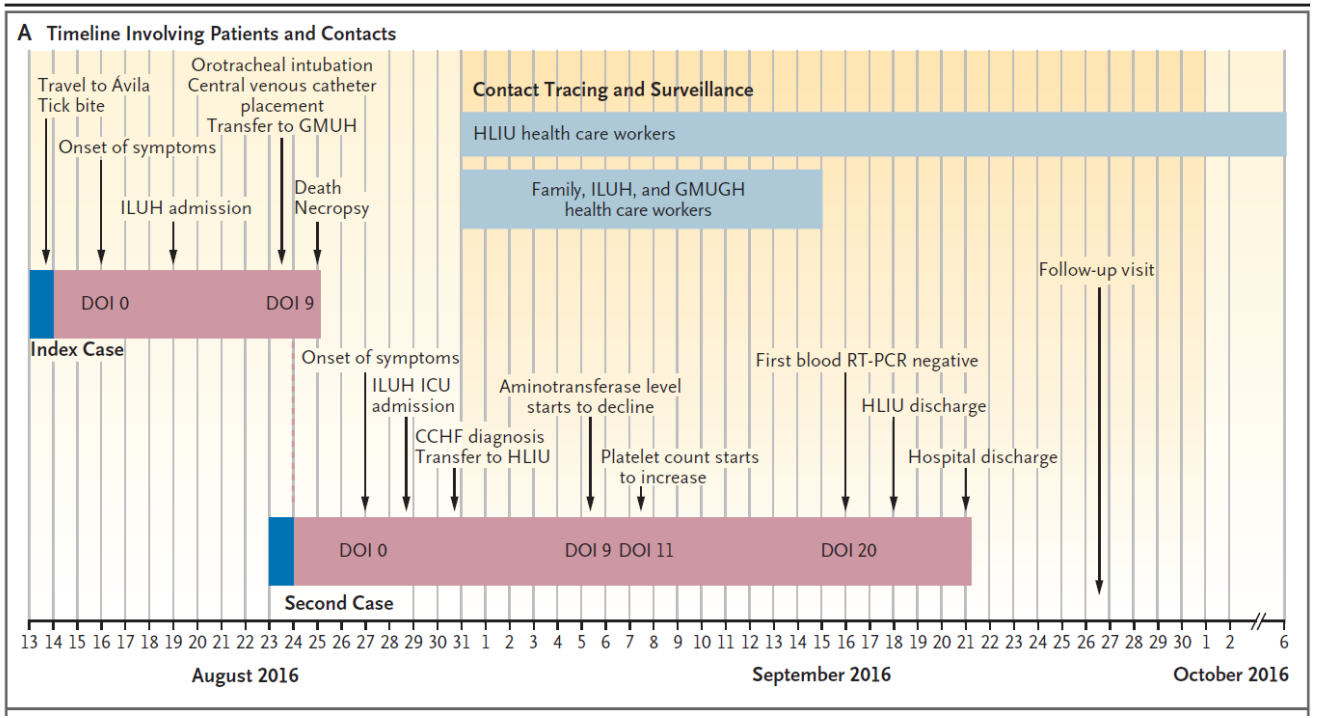
- Incubation period
  - ±3 d after tick bite,
  - ±6d after blood / tissue contact (max 13d);
  - 90% infections subclinical
- Sudden onset fever, flu-like illness, confusion, lethargy,
- Severe hepatitis, bleeding, hepatorenal and pulmonary failure, no meningitis
- Case fatality rate 15% if symptomatic, death in 2nd week of illness

Crimean-Congo hemorrhagic fever, clinical

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

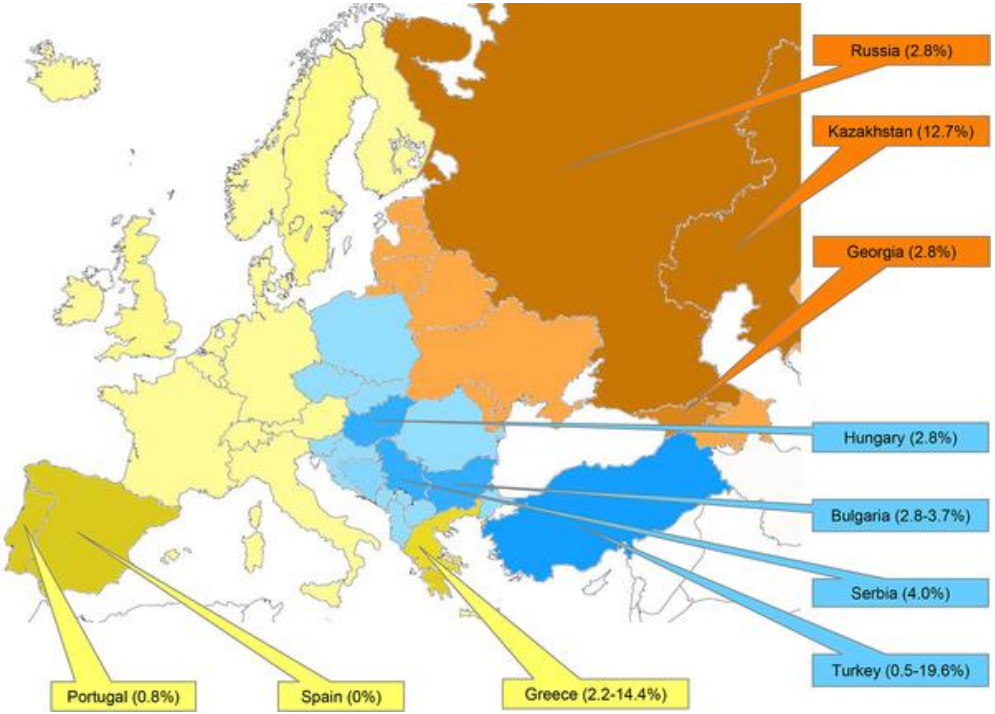
Autochthonous Crimean–Congo Hemorrhagic Fever in Spain



Crimean-Congo hemorrhagic fever, diagnosis/management

- Virus isolation, PCR, ELISA, Ag-test
- Patient isolation, barrier nursing (nosocomial: airborne possible)
- Treatment : ribavirin + supportive
- No safe vaccine available
- Gloves/protective clothing when handling animal tissues in endemic areas

Distribution of CCHFV in Europe



Seroprevalence surveys in humans

Key facts

- For 2016, two countries reported a total of six cases of Crimean-Congo haemorrhagic fever (CCHF).
- For the first time, Spain reported two confirmed autochthonous cases.
- Bulgaria reported the remaining four cases (CCHF is endemic in the Balkan region).

Key facts

- For 2017, Bulgaria reported two confirmed cases of Crimean-Congo haemorrhagic fever (CCHF).

Key facts

For 2018, EU/EEA countries reported eight cases of Crimean–Congo haemorrhagic fever (CCHF). Bulgaria reported six locally-acquired confirmed cases, Greece one travel-related confirmed case and Spain one locally-acquired probable case.

Key facts

- For 2019, Bulgaria reported two cases of Crimean-Congo haemorrhagic fever.

Monsalve-Arteaga L. *PLOS NTDs* 2020

Suitability map for CCHFV in Europe

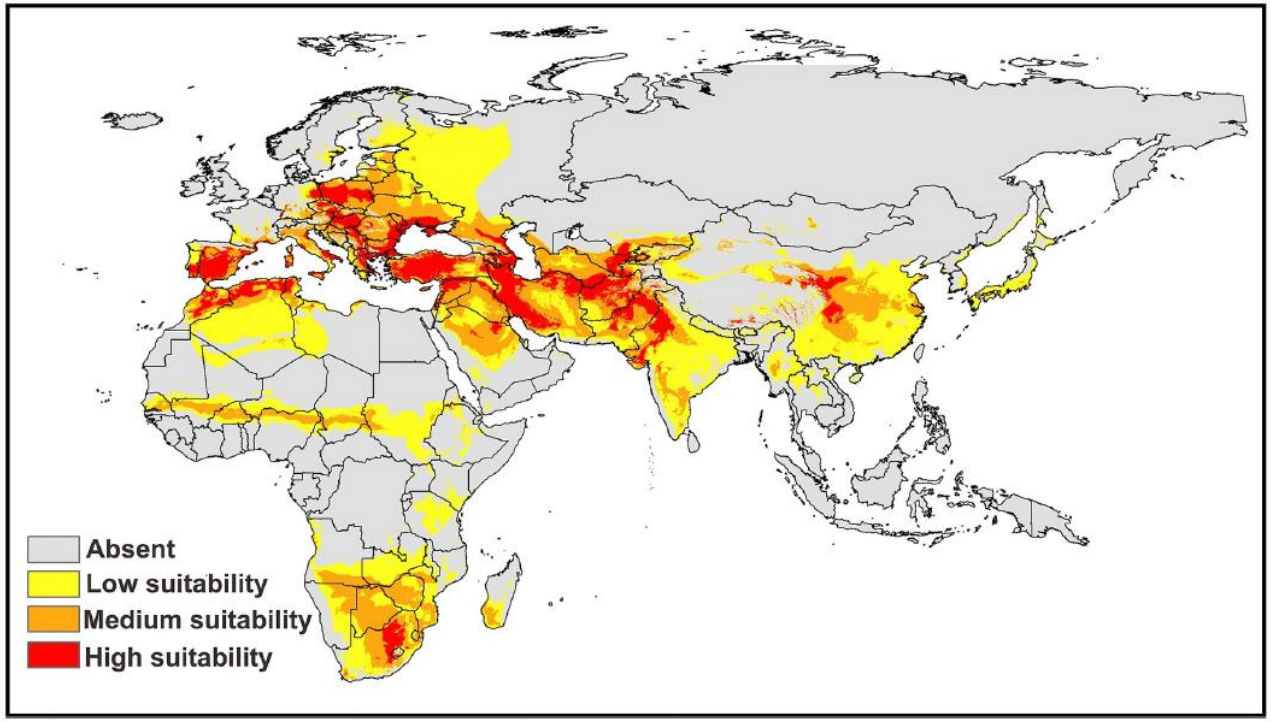


Fig. 1. Environmental suitability map of Crimean-Congo hemorrhagic fever in the Old World.

Dengue virus, global distribution

Aedes mosquito

- Most important arboviral disease in humans
- Global incidence has grown dramatically with ± 50% of the world's population at risk
- Around 400 million infections annually, including about 100 million clinically apparent (Bath et al. *Nature*, 2013)
- The disease is now endemic in 129 countries (70% of global burden in Americas, South-East Asia & Western Pacific
- The largest number of dengue cases ever reported globally was in 2019

Expert Reviews in Molecular Medicine

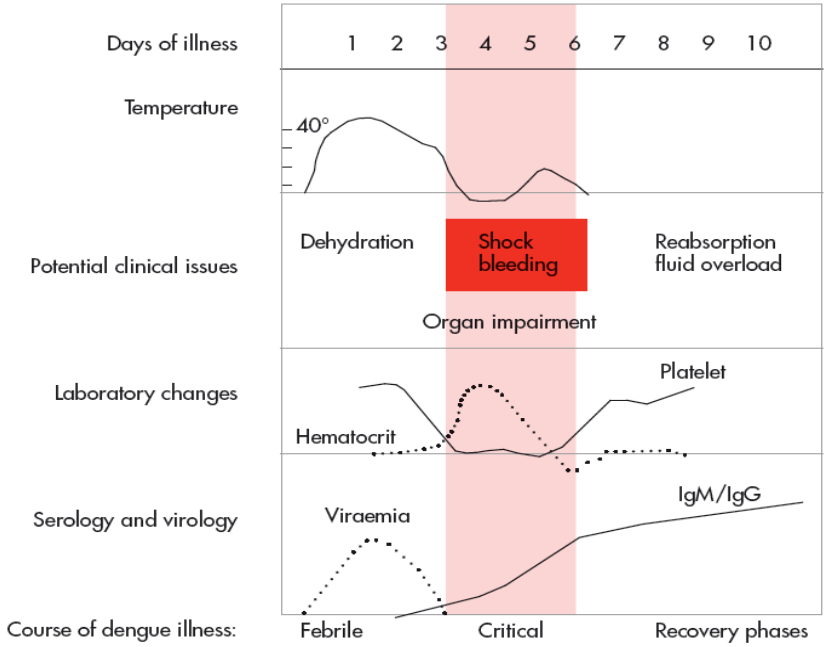
2018

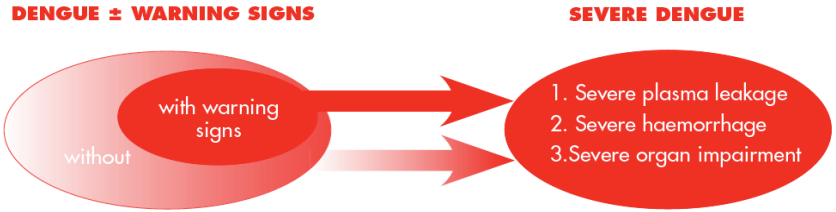
Arbovirus lifecycle in mosquito: acquisition, propagation and transmission

Pa Wu[1,2], Xi Yu[1,2], Penghua Wang[3] and Gong Cheng[1,2]

Dengue, clinical

25% of infections are symptomatic





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
- Leukopenia
- 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 enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

Dengue, clinical

Fever After a Stay in the Tropics

Diagnostic Predictors of the Leading Tropical Conditions

Emmanuel Bottieau, MD, Jan Clerinx, MD, Erwin Van den Enden, MD, Marjan Van Esbroeck, MD, Robert Colebunders, MD, PhD, Alfons Van Gompel, MD, and Jef Van den Ende, MD, PhD

	Adjusted LR+
• Leukopenia	3.3
• Skin rash	2.8
• Thrombocytopenia	2.0

Dengue, diagnosis

- Antibody-based test (IgM/IgG)
  - Sensitivity: 70-80%
- PCR for viremia (reference centres)
  - Sensitivity: 50-80%
- Rapid Diagnotic Test (RDT) NS1 antigen
  - Sensitivity: 50-80%
- RDT Duo NS1 Ag/antibody
  - Sensitivity: > 90%

Dengue, diagnosis (use of RDT in travelers)

Open Forum Infectious Diseases

MAJOR ARTICLE

Clinical Utility of the Nonstructural 1 Antigen Rapid Diagnostic Test in the Management of Dengue in Returning Travelers With Fever

Ralph Huits,[1] Patrick Soentjens,[1] Ula Maniewski-Kelner,[1] Caroline Theunissen,[1] Steven Van Den Broucke,[1] Eric Florence,[1] Jan Clerinx,[1] Erika Vlieghe,[1,2] Jan Jacobs,[1,3] Lieselotte Cnops,[1] Dorien Van Den Bossche,[1] Marjan Van Esbroeck,[1] and Emmanuel Bottieau[1]

[1]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium; [2]Unit of Tropical Diseases, University Hospital of Antwerp, Belgium; and [3]Department of Microbiology and Immunology, University of Leuven, Belgium

Table 1. Performance of the NS1 Antigen Rapid Diagnostic Test for the Diagnosis of Dengue in 308 Tested Travelers With Fever

		Samples Tested by NS1 Antigen RDT		
Diagnostic Under Evaluation	Result RDT	Confirmed Dengue Case	No Dengue	Total
NS1 antigen RDT	positive	43	1	44
	negative	9	255	264
		52	256	308
		sensitivity: 43/52 = 82.7% (95% CI, 74.4–93.0)	specificity: 255/256 = 99.6% (95% CI, 98.8–100)	

Sens: 83%

Spec: >99%

Compared to historical controls

- Less hospital admissions
- Less empirical antibiotics

Chikungunya, global distribution

Aedes mosquito

Chikungunya Virus and the Global Spread of a Mosquito-Borne Disease

Scott C. Weaver, Ph.D., and Marc Lecuit, M.D., Ph.D.

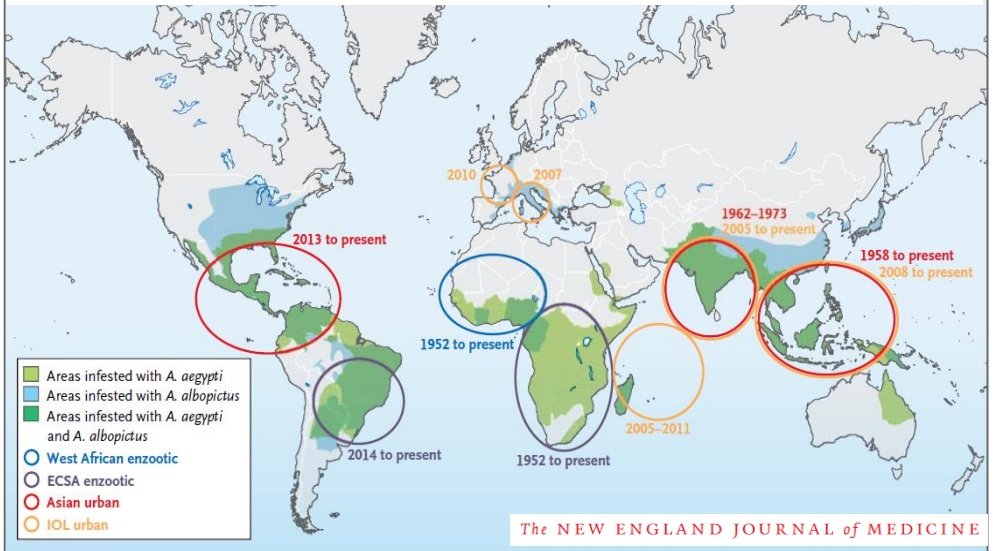


Figure 2. Origin, Spread, and Distribution of Chikungunya Virus and Its Vectors.

The map shows the African origins of enzootic chikungunya virus strains and the patterns of emergence and spread of the Asian lineage and Indian Ocean lineage (IOL) of the virus during epidemics since the 1950s, based on phylogenetic studies.[4,5] The distributions of the peridomestic vectors, *Aedes aegypti* and *A. albopictus*, are also shown. ECSA denotes eastern, central, and southern African.

2003-2018: ≥ 5 million cases

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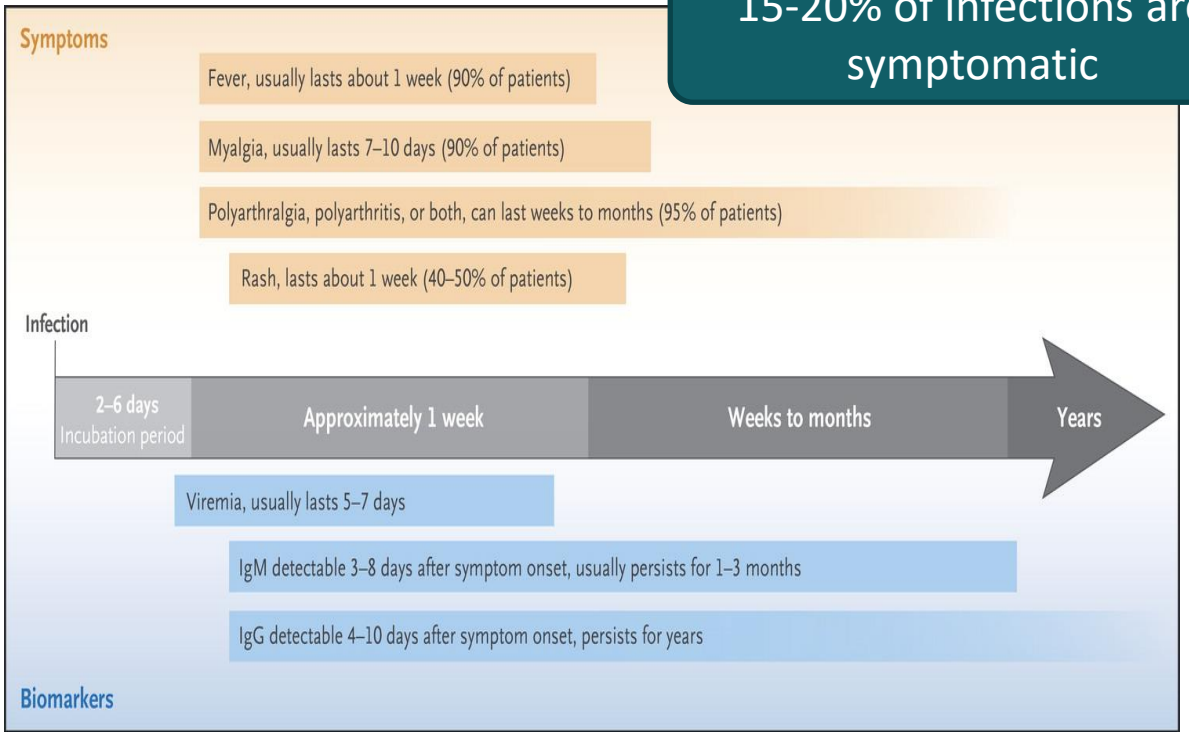
cambridge.org/erm

Arbovirus lifecycle in mosquito: acquisition, propagation and transmission

Pa Wu[1,2], Xi Yu[1,2], Penghua Wang[3] and Gong Cheng[1,2]

Chikungunya, clinical

15-20% of infections are symptomatic



Weaver SC. *N Engl J Med* 2015

Simon. *Curr Infect Dis Rep*. 2011

Chikungunya, diagnosis (serology, E1 antigen)

Evaluation of Commercially Available Serologic Diagnostic Tests for Chikungunya Virus

Christine M. Prat, Olivier Flusin, Amanda Panella, Bernard Tenebray, Robert Lanciotti, and Isabelle Leparc-Goffart

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 12, December 2014

TABLE 2 Summarized results from the IC test with specimens from suspected chikungunya fever cases

Country	No. of patients	Genotype	RNA result (*n*)	IC test result			
				No. positive	No. negative	Sensitivity (%)	Specificity (%)
Thailand	50	ECSA[b]	Positive (34)	31	3	91.2	93.8
			Negative (16)	1	15		
Laos	54	ECSA	Positive (34)	29	5	85.3	95.0
			Negative (20)	1	19		
Indonesia	2	Asian	Positive (2)	2	0		
			Negative (0)	0	0		
Senegal	6	West African	Positive (6)	6	0		
			Negative (0)	0	0		
Total	112		Positive (76)	68	8	89.4	94.4
			Negative (36)	2	34		

[a] OAA, overall agreement with RT-PCR assays.

Clinical Microbiology and Infection 24 (2018) 78–81

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Diagnostic accuracy of a rapid E1-antigen test for chikungunya virus infection in a reference setting

R. Huits [1,*], T. Okabayashi [2], L. Cnops [1], B. Barbé [1], R. Van Den Berg [4], K. Bartholomeeusen [3], K.K. Ariën [3], J. Jacobs [1,5], E. Bottieau [1], E.E. Nakayama [2], T. Shioda [2], M. Van Esbroeck [1]

Performance highly dependent of genotype

Summary of E1-antigen test results

Test panel	CHIKV RT-PCR positive (*n*)	E1-Ag positive	E1-Ag negative	Sensitivity (%) (95% CI)[a]	Specificity (%) (95% CI)[a]
Chikungunya, ECSA genotype, *n*=9	9	8	1	88.9% (56.5-98.0)	
Chikungunya, Asian genotype, *n*=30	30	10	20	33.3% (19.2-51.2)	
Endemic controls, *n*=26	ND	6	20	-	76.9% (57.9-89.0)
Selected pathogens,[b] *n*=20	ND	5	15	-	75.0% (53.1-88.8)
Reference panel (spiked sera),[c] *n*=12	ND	1[d]	11	-	91.7% (64.6-98.5)

Zika, global distribution

Aedes mosquito

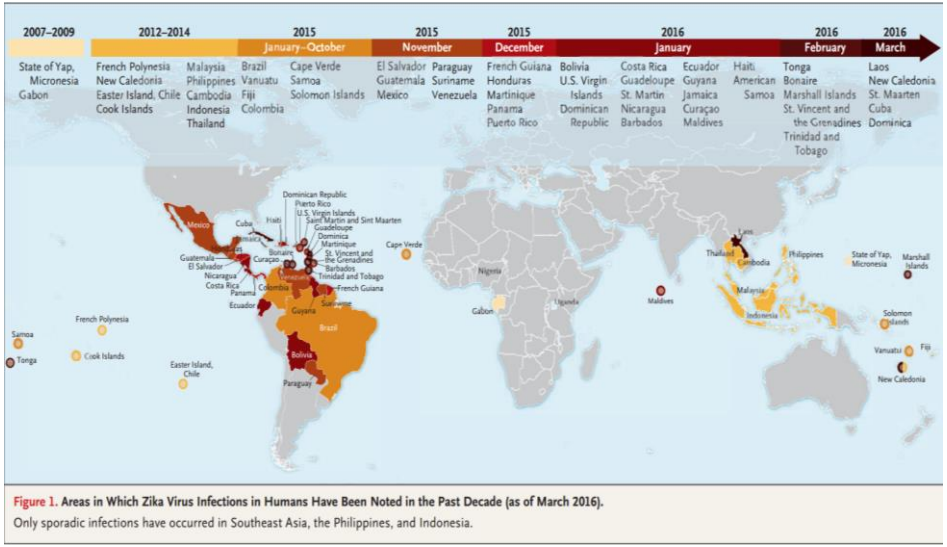


Figure 1. Areas in Which Zika Virus Infections in Humans Have Been Noted in the Past Decade (as of March 2016).
Only sporadic infections have occurred in Southeast Asia, the Philippines, and Indonesia.

2018

Expert Reviews in Molecular Medicine

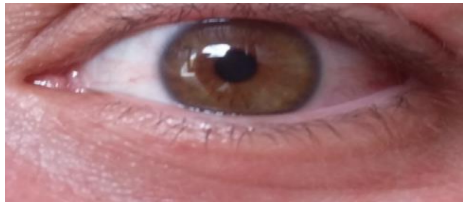
cambridge.org/erm

Arbovirus lifecycle in mosquito: acquisition, propagation and transmission

Pa Wu[1,2], Xi Yu[1,2], Penghua Wang[3] and Gong Cheng[1,2]

Petersen LR. *N Engl J Med* 2016

Zika, clinical



Comparison of selected clinical findings in chikungunya, dengue and Zika infections

Clinical presentation	Chikungunya	Dengue	Zika
Fever	+++	+++	+
Rash	++	++	+++
Myalgia	+	+++	+
Arthralgia	+++	+	++
Oedema	–	–	++
Retro-orbital pain	+	++	+
Conjunctivitis	+++	–	+++
Lymphadenopathy	++	++	+
Hepatomegaly	+++	–	–
Haemorrhage	–	+	–

Adapted and modified with permission from [33,34].
+++, very common; ++, frequently observed; +, sometimes observed; –, not typical.

- Guillain-Barre syndrome / neurological disorders (<1%)
- Fetal loss/birth defects (5-10%)

zika, transmission

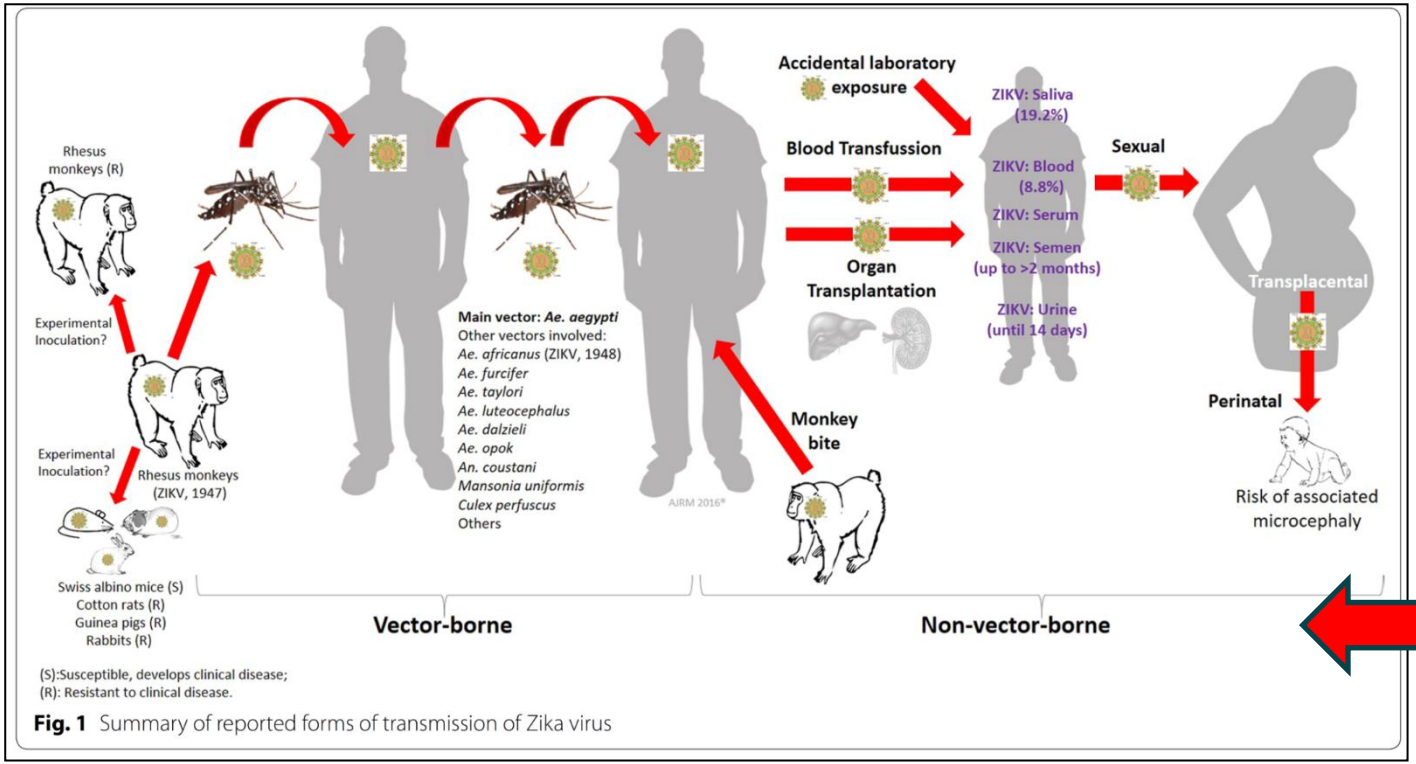
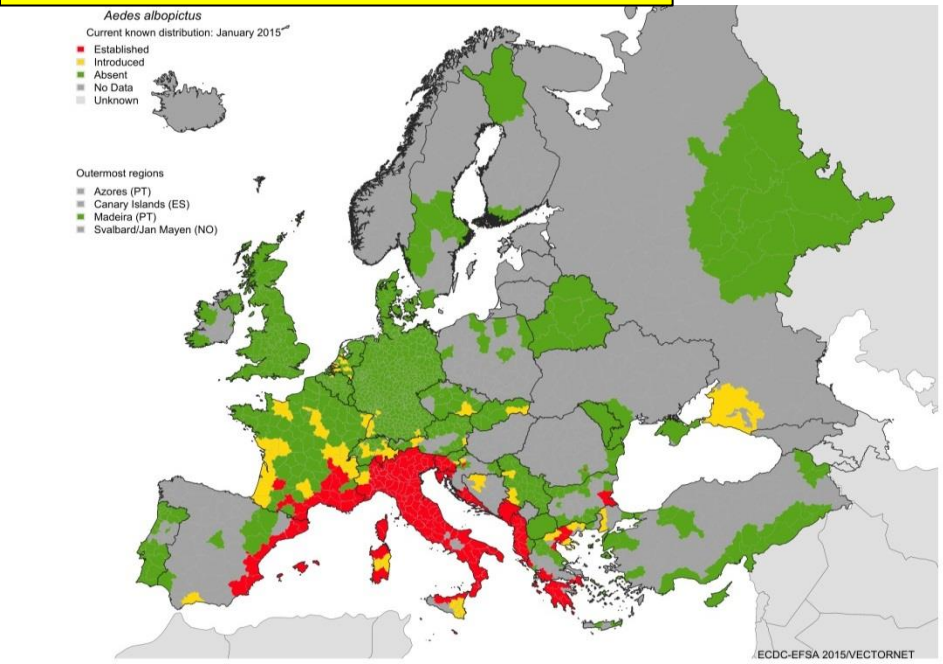


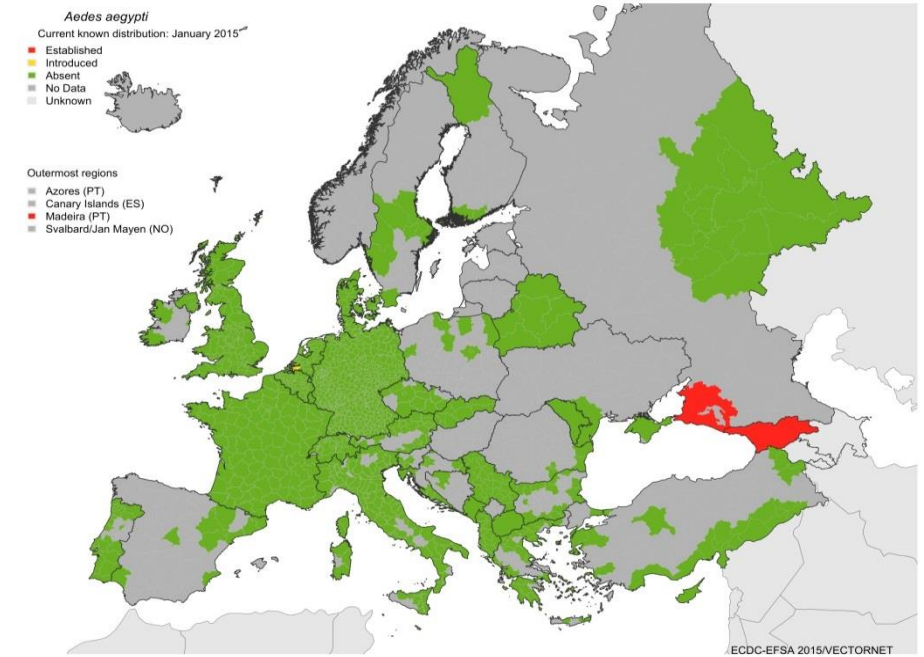
Fig. 1 Summary of reported forms of transmission of Zika virus

Distribution of invasive *Aedes* in Europe (2015)

Aedes albopictus

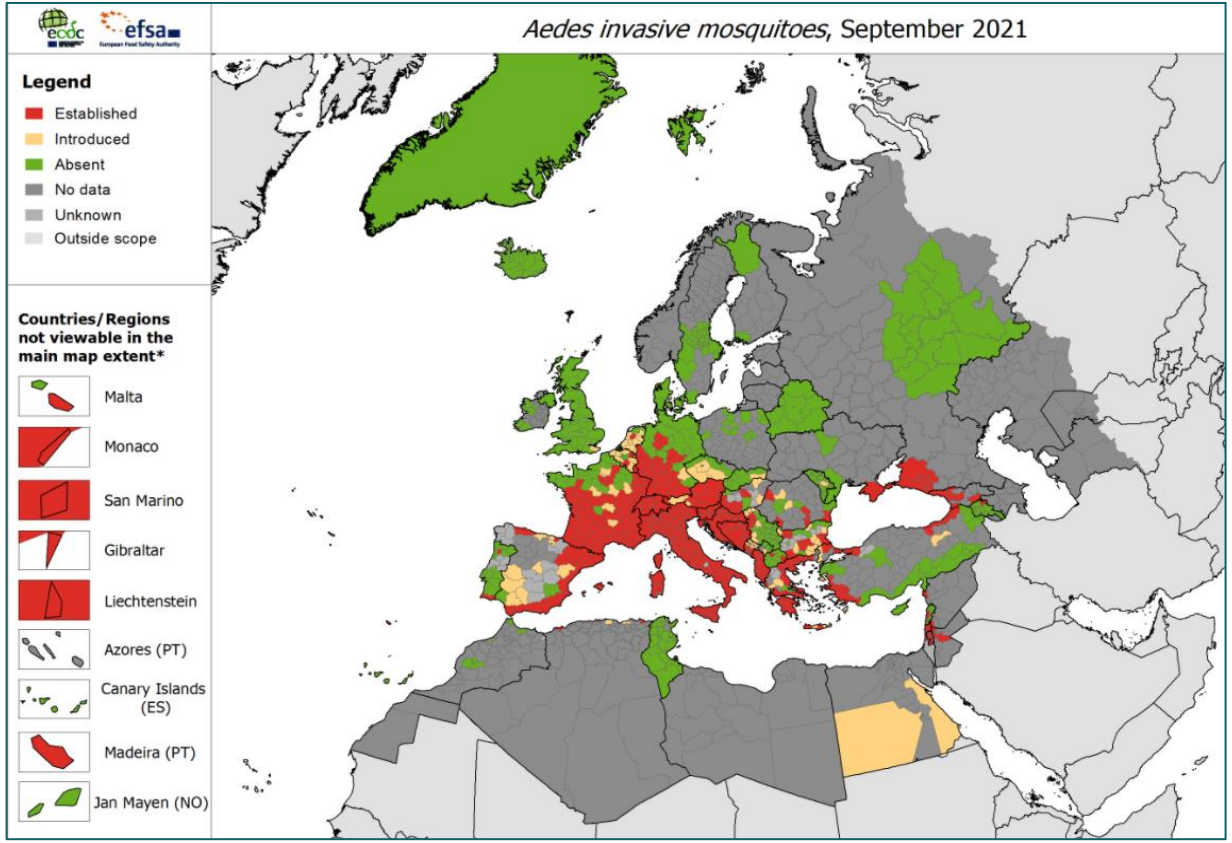


Aedes aegypti

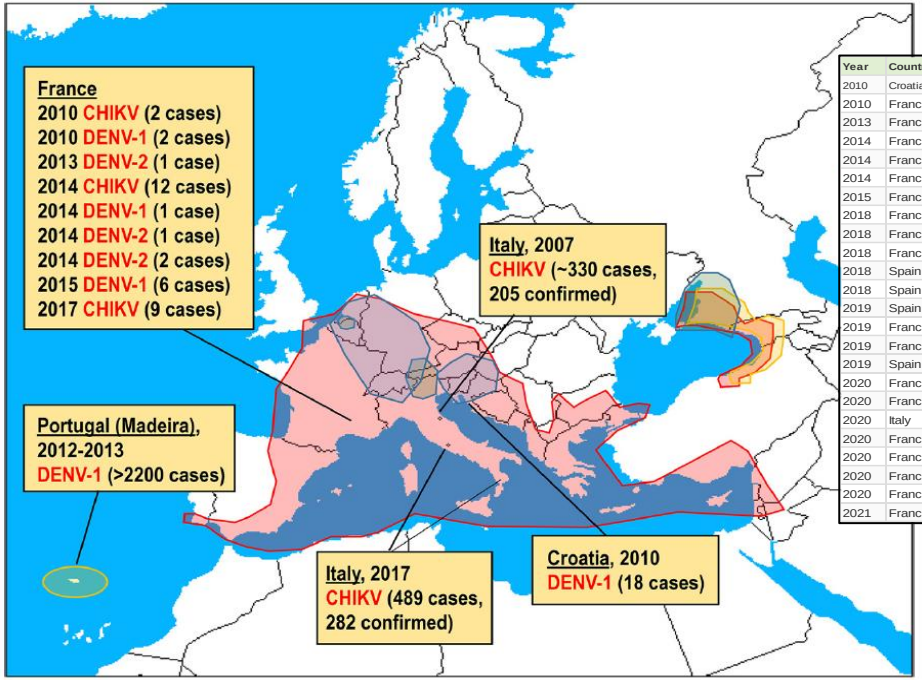


Distribution of invasive *Aedes* in Europe (2021)

Aedes aegypti
Aedes albopictus
Aedes atropalpus
Aedes japonicus
Aedes koreicus



Dengue, chikungunya, zika: autochthonous cases (Europe)



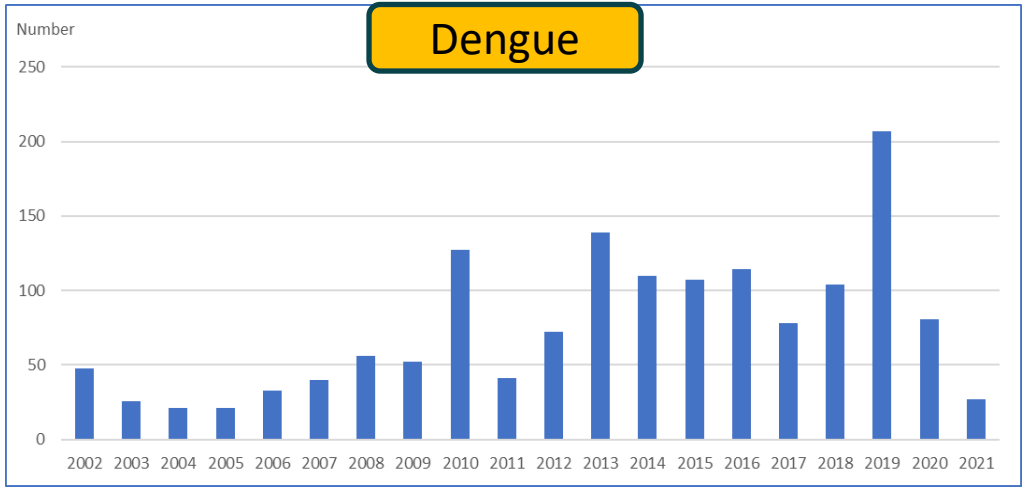
Year	Country	Region, municipalities	
2010	Croatia	Korčula Island and the Pelješac peninsula	
2010	France	Alpes-Maritimes department, Nice	
2013	France	Bouches–du-Rhône department, Venelles	
2014	France	Var department, Toulon	1
2014	France	Var department, Toulon	1
2014	France	Bouches-du-Rhône department, Aubagne	2
2015	France	Gard department, Nîmes	8
2018	France	Alpes Maritimes department, Saint-Laurent-du-Var	5
2018	France	Hérault department, Clapiers	2
2018	France	Gard department, Nîmes	1
2018	Spain	Murcia region or province of Cádiz	5
2018	Spain	Catalonia region	1
2019	Spain	Catalonia region	1
2019	France	Alpes-Maritimes department, Vallauris	7
2019	France	Rhône department, Caluire-et-Cuire	2
2019	Spain	Municipality of Madrid	1
2020	France	Hérault department, Cessenon-sur-Orb	1
2020	France	Var department, la Croix Valmer	3
2020	Italy	Veneto region, Montecchio Maggiore	11
2020	France	Alpes-Maritime department, Nice	5
2020	France	Gard department, Saint-Jean-de-Valériscle	1
2020	France	Alpes-Maritime department, Saint-Laurent-du-Var	2
2020	France	Hérault department, Montpellier, or Gard department, Cabrières	1
2021	France	Var department, Toulon	0

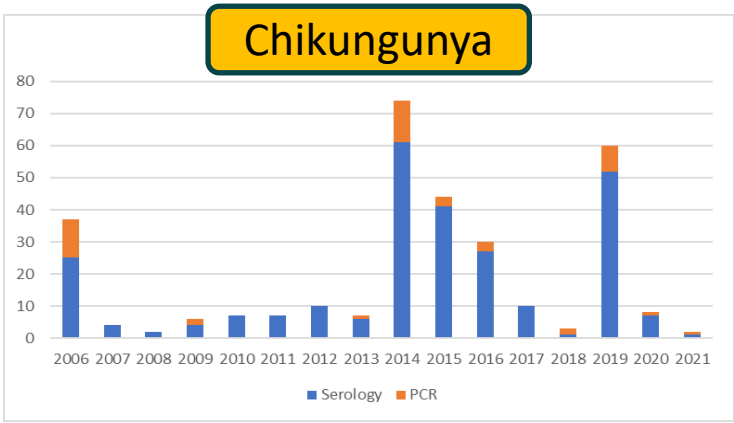

RAPID COMMUNICATION

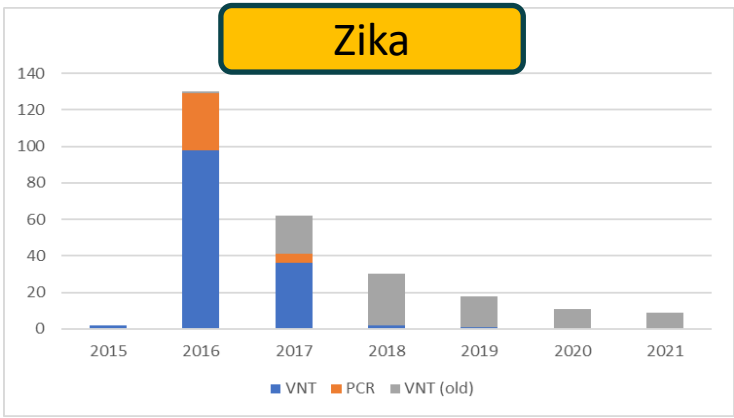
First autochthonous dengue outbreak in Italy, August 2020

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

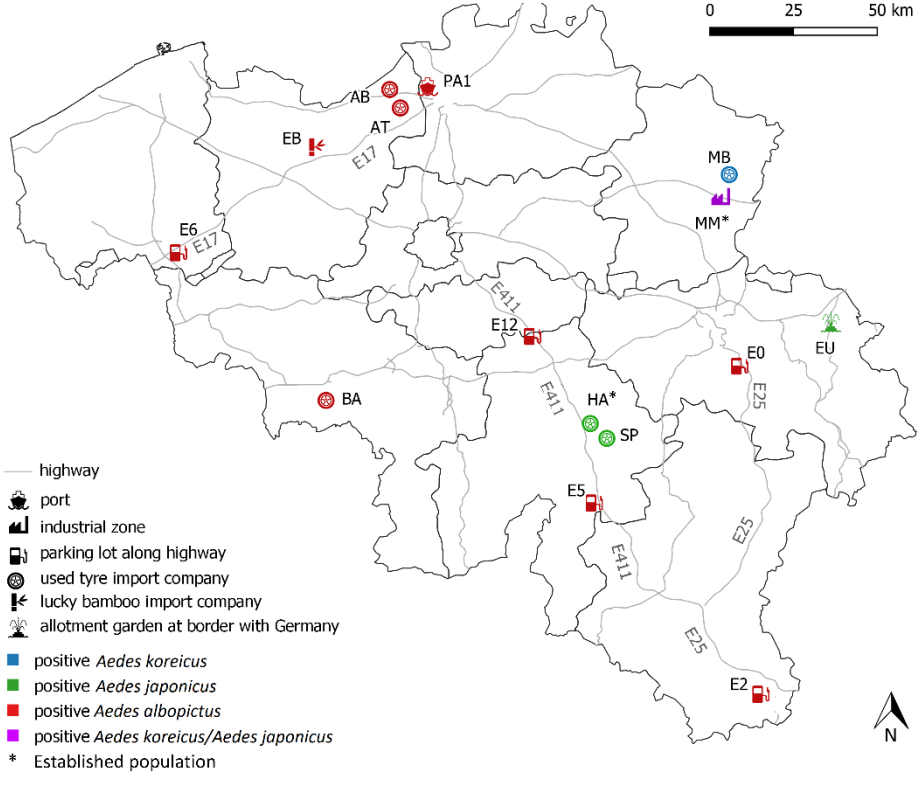
Dengue, chikungunya, zika in Belgium







Active monitoring of invasive *Aedes* in Belgium



		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
	EU														
	HA														
	SP														
	MB														
	MM														

Deblauwe et al. submitted (light grey: no monitoring, dark grey: monitoring)

And still more: Japanese encephaltis

Travel Medicine and Infectious Disease 34 (2020) 101580

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

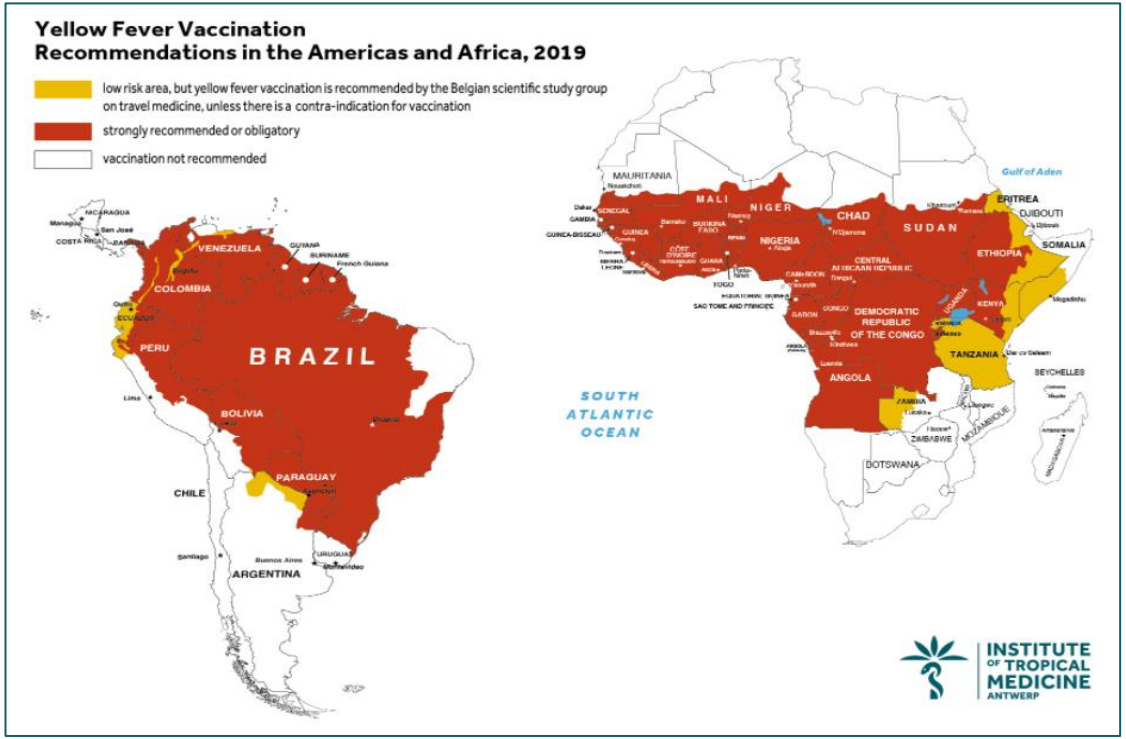
Diagnostic Challenge

Japanese encephalitis in a young traveler returning from a short-term holiday in Khao Lak, Thailand

Ralph Huits[a,*], Yeleni Eelen[b], Philippe G. Jorens[b], Kevin K. Ariën[c,d], Marjan Van Esbroeck[a], Els LIM. Duval[b]

And still more: yellow fever

Aedes mosquito



BRIEF REPORT • **CID 2002:35 (15 November)** • e113

A Belgian Traveler Who Acquired Yellow Fever in The Gambia

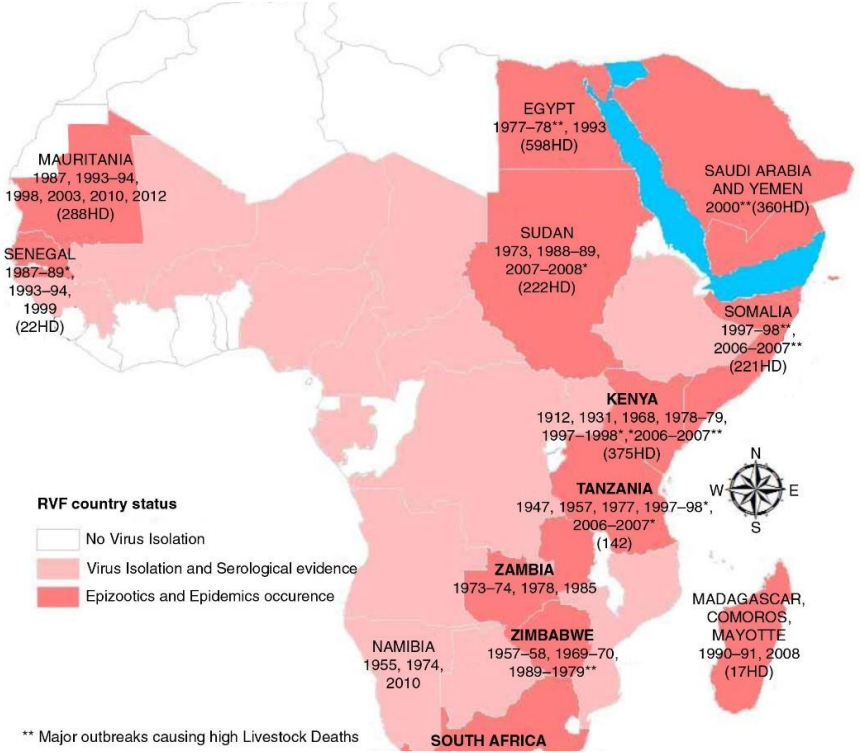
R. Colebunders,[1,2] J.-L. Mariage,[3] J.-Ch. Coche,[3] B. Pirenne,[3] S. Kempinaire,[3] Ph. Hantson,[4] A. Van Gompel,[1] M. Niedrig,[5] M. Van Esbroeck,[1] R. Bailey,[7] C. Drosten,[6] and H. Schmitz[6]

[1]Institute of Tropical Medicine and [2]University Hospital Antwerp, Antwerp, [3]Clinic St.-Pierre, Ottignies, and [4]St.-Luc Hospital, Université Catholique de Louvain, Brussels, Belgium; [5]Robert Koch Institute, Berlin, and [6]Bernard Nocht Institute for Tropical Medicine, Hamburg, Germany; and [7]Clinical Services Medical Research Council, Fajara, The Gambia

A 47-year-old Belgian woman acquired yellow fever during a 1-week vacation in The Gambia; she had never been vaccinated against yellow fever. She died of massive gastrointestinal bleeding 7 days after the onset of the first symptoms. This dramatic case demonstrates that it is important for

And still more: Rift Valley fever

Aedes, Culex, Anopheles, Mansonia



Symptoms (98% Asymptomatic)

- Aspecific: flue-like, often mild/asymptom.
- **Hemorrhagic** fever
- Renal failure
- **Retina** : vasculitis – hemorrhages - blind
- **Neurologic** complications (lymphocytes in CSF)

Diagnosis:

- Serology IgM
- Virus isolation, PCR

And still more…

Mayaro virus

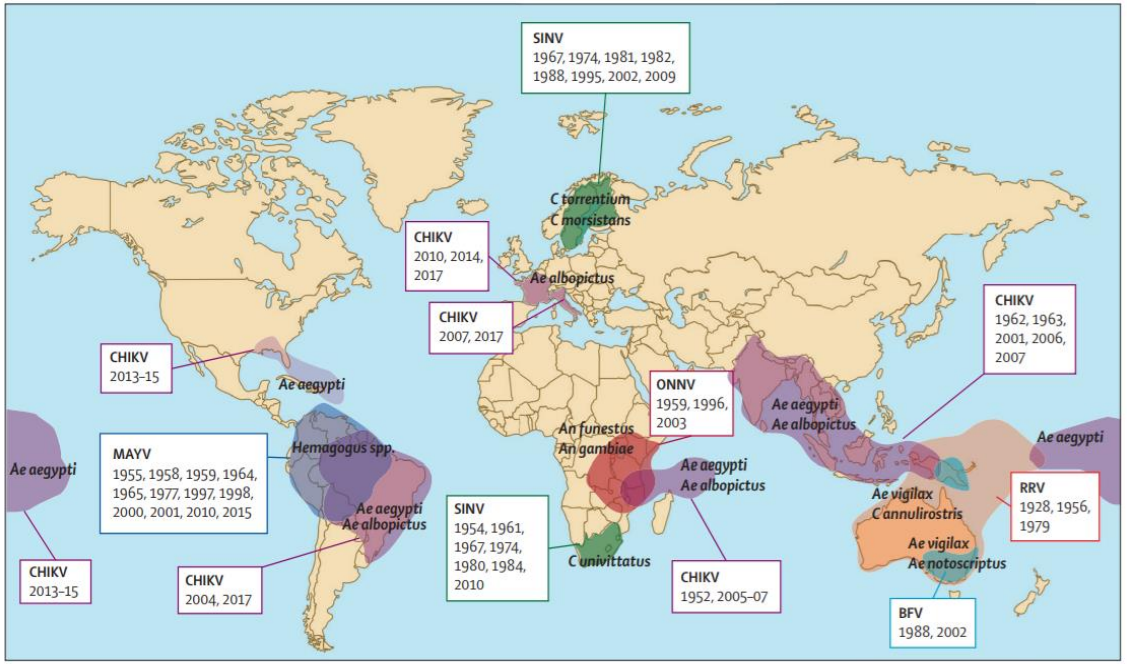
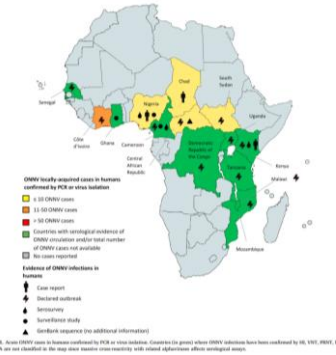


Figure: **Spatiotemporal distribution of arthritogenic alphavirus outbreaks and main mosquito vectors**
Chronological summary of known arthritogenic alphavirus outbreaks, with geographical distribution of most prominent arthritogenic alphaviruses. The main mosquito vector species for each virus and associated outbreaks are indicated. Ae=Aedes. An=Anopheles. BFV=Barmah Forest virus. C=Culex. CHIKV=chikungunya virus. MAYV=Mayaro virus. ONNV=o'nyong-nyong virus. RRV=Ross River virus. SINV=Sindbis virus.

O'nyong-nyong virus



Conclusion: Arboviruses acquired outside Europe

The Lancet Regional Health - Europe 1 (2021) 100001

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journal homepage: www.elsevier.com/lanepe

Research paper

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

Martin P. Grobusch[a,*], Leisa Weld[b], Abraham Goorhuis[a], Davidson H. Hamer[c],

Substantial increase and "diversification" of arboviroses

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	

Conclusion: Arboviruses acquired in Europe

Most infections are asymptomatic (> 90%)

Febrile disease (FD) +

- Arthralgia and/or rash (AR) → Think of sindbis, dengue, chik, (zika)
- Neurological syndrome (NS) → Think of TBE, Toscana, West Nile
- Hemorrhagic syndrome (HS) → Think of dengue, CCHF

Thank you for your attention