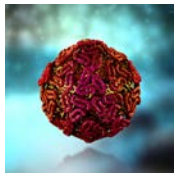
"INFEÇÃO PELO VÍRUS WEST NILE: REVISÃO DOS ASPETOS CLÍNICOS ATUAIS MAIS IMPORTANTES"

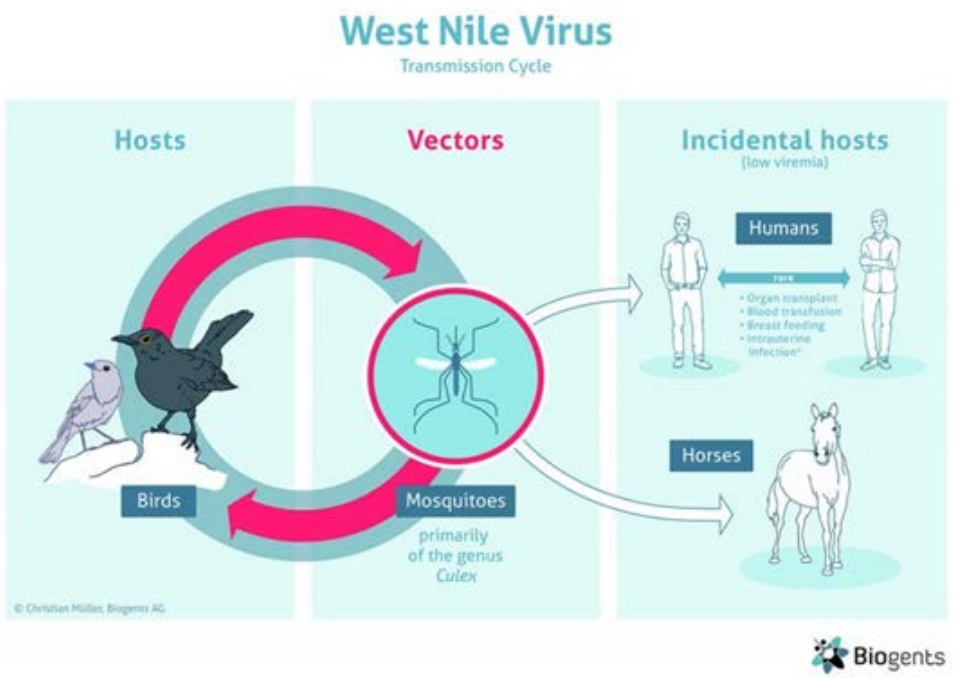
José M D Poças

Diretor do SDI do CHS

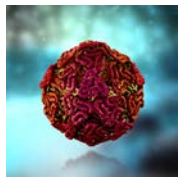
Seminários
Ricardo Jorge



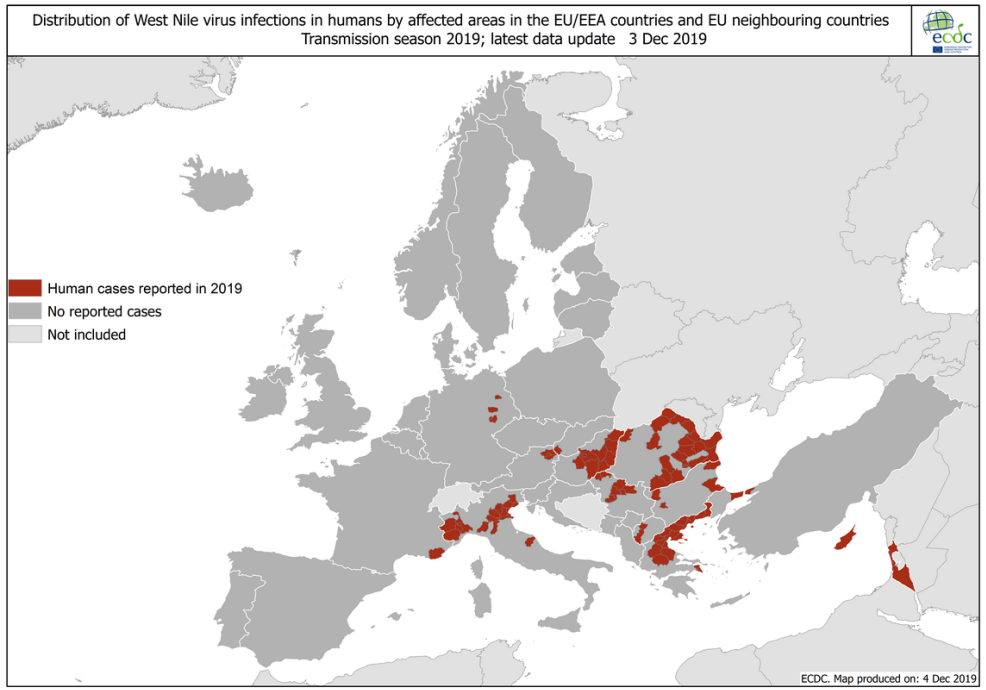
INTRODUÇÃO- ASPETOS EPIDEMIOLÓGICOS I

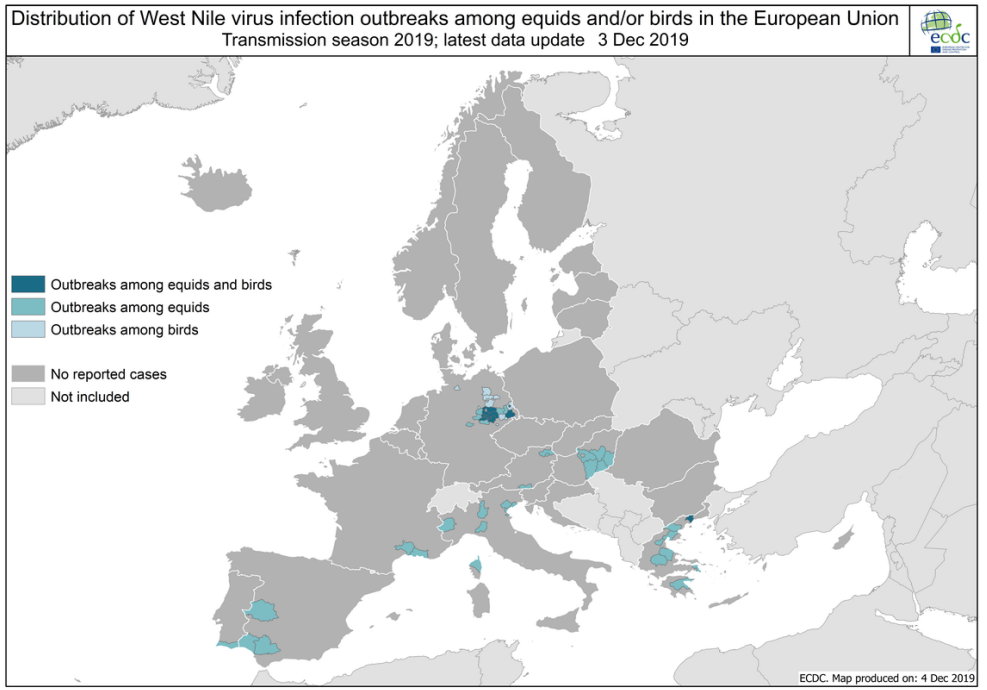


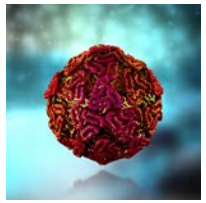
- 1º Isolamento
  - 1937- Uganda
- Expansão geográfica
  - 1969- Portugal (Barragem do Roxo)
  - 1999- Estado de NY (EUA)
- Vetores transmissores
  - Mosquitos *Culex (Anopheles, Aedes)*
- Outros vetores (não transmissores)
  - Carraças (*Ixodidiae* e *Argasidiae*)
- Outras formas de transmissão (transfusões de sangue, transplantes, mãe-filho)



INTRODUÇÃO-
ASPETOS EPIDEMIOLÓGICOS II







INTRODUÇÃO- ASPETOS EPIDEMIOLÓGICOS III

Viruses **2013**, *5*, 3021-3047; doi:10.3390/v5123021

OPEN ACCESS

viruses

ISSN 1999-4915

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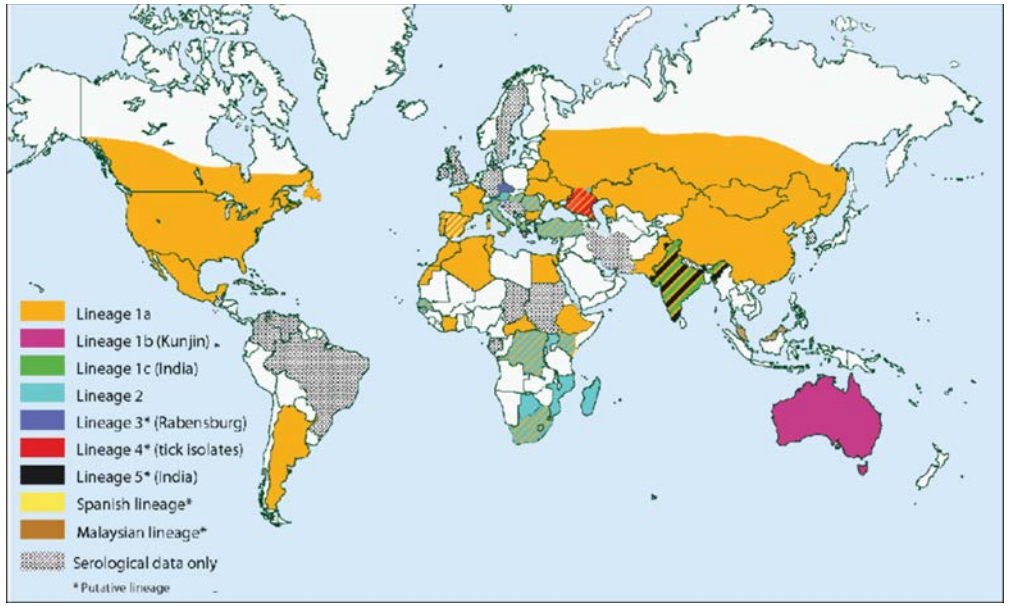
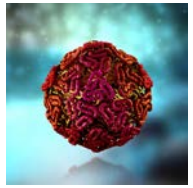
Review

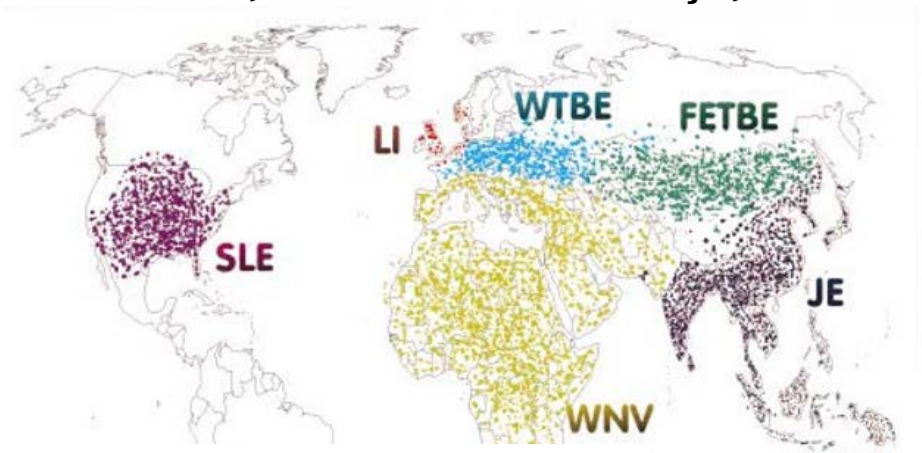
Vector-Virus Interactions and Transmission Dynamics of West Nile Virus

Alexander T. Ciota [1] and Laura D. Kramer [1,2,*]





- **Flavivírus**
  - **Grupo "Encefalite Japonesa"**
    - **JEV, WNV, Murray Valley, Usutu, St. Louis, Encefalite da Carraça, etc**



J Neurol Neurosurg Psychiatry 2000;68:405–415

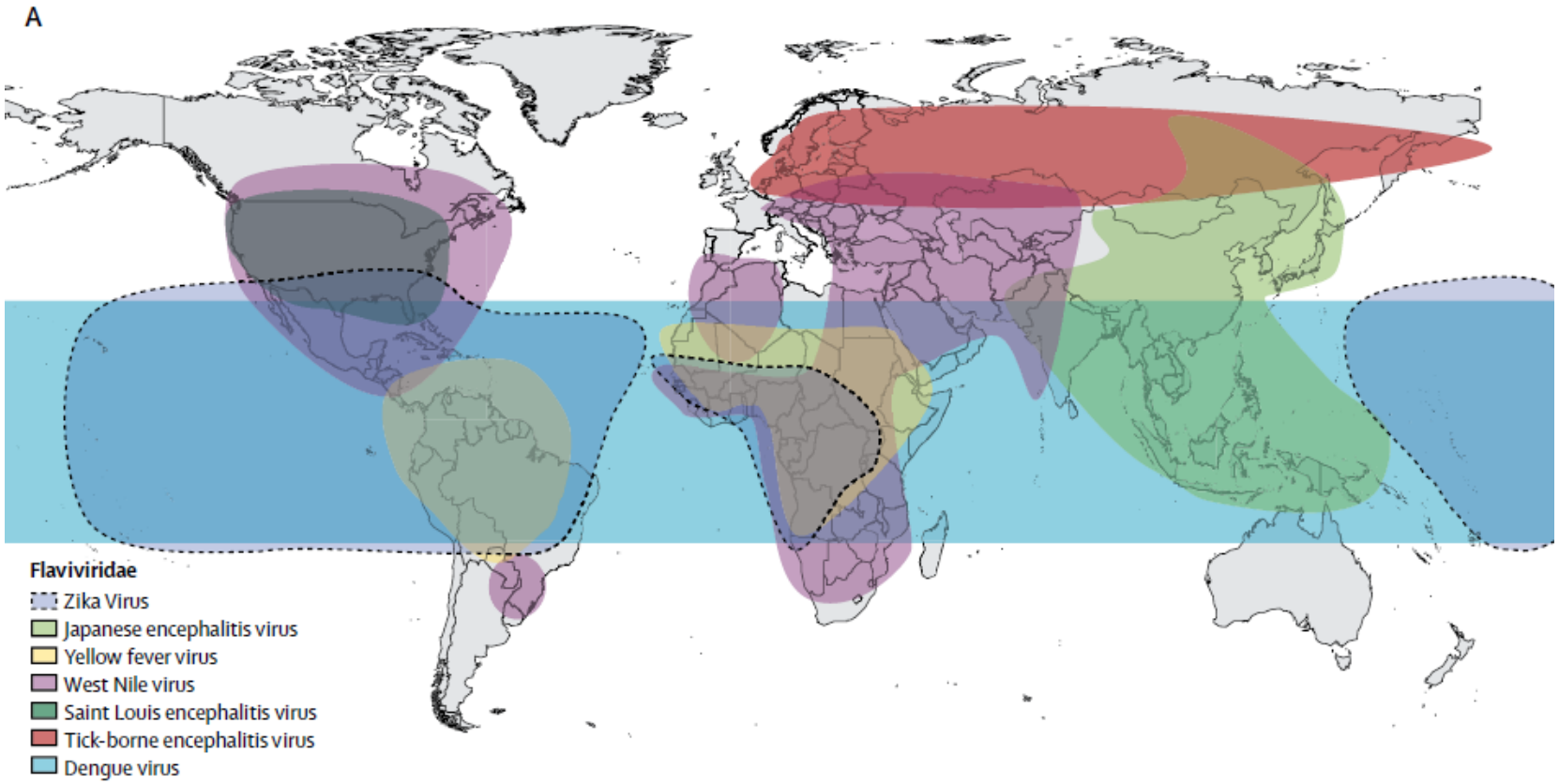
NEUROLOGICAL ASPECTS OF TROPICAL DISEASE

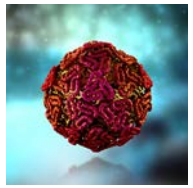
Japanese encephalitis

Tom Solomon, Nguyen Minh Dung, Rachel Kneen, Mary Gainsborough, David W Vaughn, Vo Thi Khanh

Figure 1 Map showing approximate global distribution of major neurotropic flaviviruses; JE=Japanese encephalitis; MVE=Murray valley encephalitis; WN=West Nile; WTBE=Western tick-borne encephalitis; FETBE=Far Eastern tick-borne encephalitis; LI=Louping Ill virus; SLE=St Louis encephalitis.

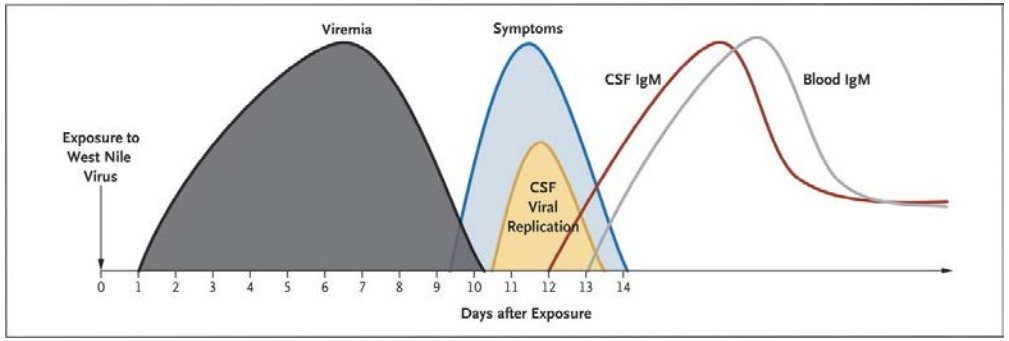
INTRODUÇÃO-
ASPETOS EPIDEMIOLÓGICOS IV

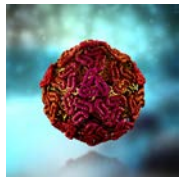




DIAGNÓSTICO LABORATORIAL

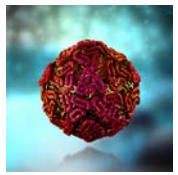
- **Sangue e LCR**
  - **PCR (RNA)**
    - **1° dia de febre**
    - **Até 2-3 semanas depois do início dos sintomas**
    - **Viremia mais prolongada em imunodeprimidos (até 2-3 anos)**
  - **Serologia**
    - **ELISA**
    - **IFA**
    - **Hemaglutinação**
    - **Neutralização**





MANIFESTAÇÕES CLÍNICAS

- **PI: 2 a 14 dias**
- **Frequentemente sub-clínicas (70-80%)**
- **Sintomatologia inespecífica (20-30%)**
- **Auto-limitadas (até 1 semana)**
  - **Febre**
  - **Cefaleias**
  - **Mialgia**
  - **Artralgia**
  - **Anorexia**
  - **Astenia, Adinamia**
  - **Rash cutâneo maculopapular**
  - **Poliadenopatias**
  - **Dor ocular**
  - **Náuseas, Vómitos, Diarreia**
  - **Hepatite**
  - **Pericardite**
  - **Pneumonite**



- **Formas clínicas graves (0,5-1%; > idosos; alcoólicos, d. crónica e imunodeprimidos, 50% c/ sequelas posteriores; 6-25% Mortalidade)**
  - **SNC**
    - **Encefalites**
    - **Meningite**
    - **Mielite**
    - **Poliradiculopatia**
    - **Doenças do Movimento (Parkinson-like, etc)**
    - **Sindroma de Guillam Barré**
    - **Sindroma de Disautonomia**
    - **Epilépsia**
    - **Coma**
  - **Mais raramente**
    - **Nevrite Ocular, Vitrine, Corioretinite**
    - **Miocardite**
    - **Pancreatite**
    - **Rabdomiólise**
    - **Diabetes insípida**
    - **“Pos-WN Syndrome”- Miastenia Gravis, Encefalopatia auto-imune, etc.**

DOENÇA NEUROINVASIVA: IMAGIOLOGIA

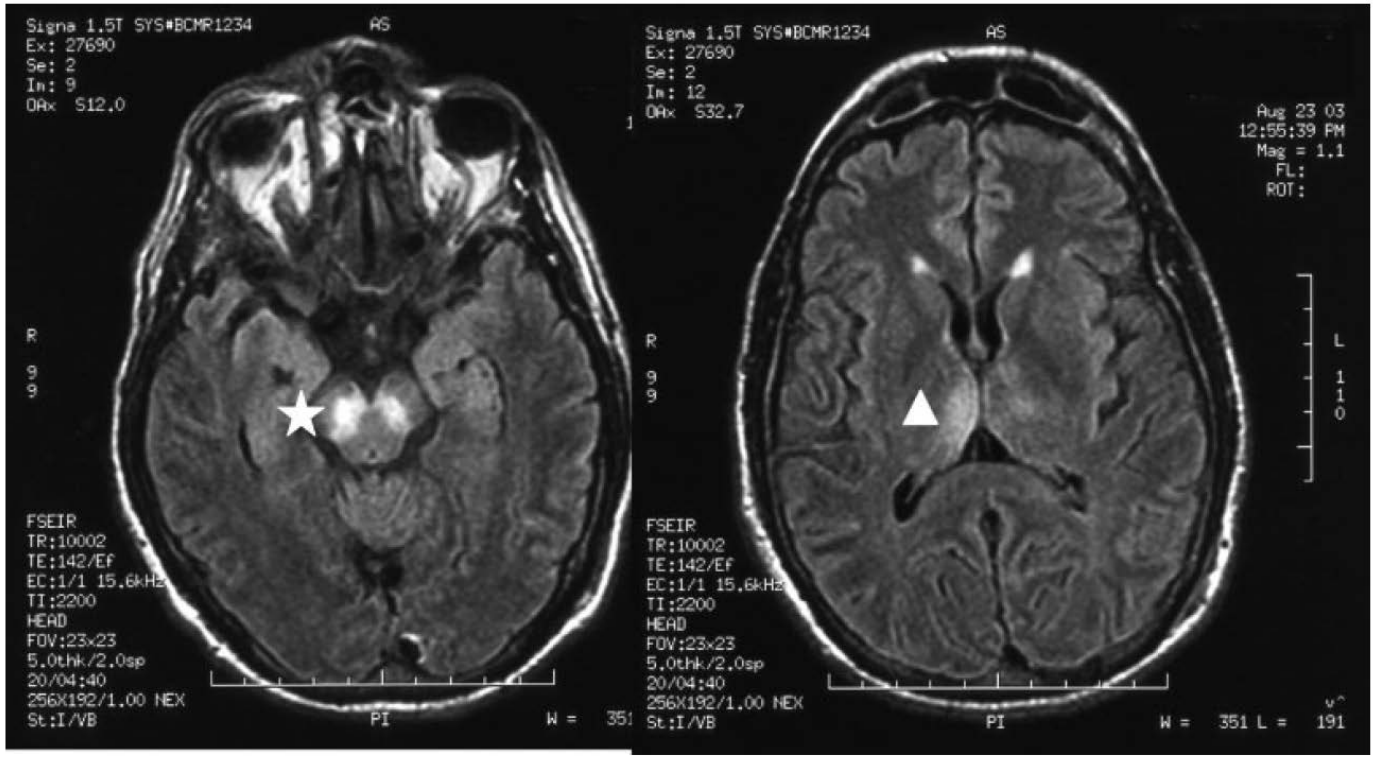


Figure 3. Axial T2-weighted brain magnetic resonance image of a patient with West Nile virus encephalitis and severe tremor and parkinsonism, displaying increased signal in the basal ganglia (*) and posterior thalami (Δ)

VARIANTES DA DOENÇA NEUROINVASIVA I

Movement Disorders
CLINICAL PRACTICE
REVIEW

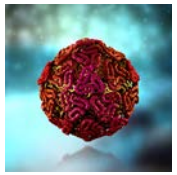
Spectrum of Movement Disorders in Patients With Neuroinvasive West Nile Virus Infection

Abhishek Lenka, MD, PhD,[1] *Anuja Kamat, MD,[2]* *and Shivam Om Mittal, MD[3]*

TABLE 4 *Studies that have reported parkinsonism in patients with West Nile virus infection*

Author, Year, Reference	Subjects (age/gender)	Other Involuntary Movements	MRI/CT	Outcome
Sejvar et al. 2003[20]	11 in a cohort of 16 (WNM, 5; WNE, 8; AFP, 3)	Myoclonus and tremor	Imaging abnormality Correlated with parkinsonism in 2 patients	Parkinsonism persisted in 5/11 patients
Robinson et al. 2003[41]	71/female	Nil	Normal	Recovered within 3 weeks
	81/female	Intention tremor, myoclonus	Normal	Resolution of symptoms by sixth day
Pepperell et al. 2003[42]	2 in a cohort of 64 hospitalized patients	Details NA	NA	NA
Burton et al. 2004[40]	72/male	Nil	Normal (CT)	Resolution of symptoms in weeks
Kleinschmidt-DeMasters et al. 2004[12]	56/male (s/p: liver transplantation)	Postural and intentional tremor, myoclonus	Signal changes in left hippocampus	Died after 6 months
	61/male (s/p: lung transplantation)	Postural and intentional tremor, myoclonus	White-matter changes in subcortical area	Resolution of parkinsonism after few months

MRI, magnetic resonance imaging; CT, computed tomography; WNM, West Nile meningitis; WNE, West Nile encephalitis; AFP, acute flaccid paralysis; s/p, status post.



VARIANTES DA DOENÇA NEUROINVASIVA II

RESEARCH

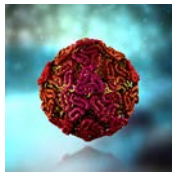
Acute Flaccid Paralysis and West Nile Virus Infection

James J. Sejvar,* A. Arturo Leis,† Dobrivoje S. Stokic,† Jay A. Van Gerpen,‡
Anthony A. Marfin,* Risa Webb,§ Maryam B. Haddad,* Bruce C. Tierney,* Sally A. Slavinski,§
Jo Lynn Polk,† Victor Dostrow,† Michael Winkelmann,† and Lyle R. Petersen*

Table 4. Clinical characteristics of patients with West Nile virus–associated acute flaccid paralysis compared with patients with typical Guillain-Barré syndrome (25–27)[a]

Characteristic	West Nile virus–associated flaccid paralysis	Guillain-Barré syndrome
Timing of onset	Acute phase of infection	1–8 weeks after acute infection
Fever and leukocytosis	Present	Absent
Weakness distribution	Asymmetric; occasional monoplegia	Generally symmetric; proximal and distal muscles
Sensory symptoms	Absence of numbness, paresthesias, or sensory loss; occasional myalgias	Painful distal paresthesias and sensory loss
Bowel/bladder involvement	Often present	Rare
Concurrent encephalopathy	Often present	Absent
CSF profile	Pleocytosis and elevated protein	No pleocytosis; elevated protein (albuminocytologic dissociation)
Electrodiagnostic features	Anterior horn cell/motor axon: reduced/absent CMAPs, preserved SNAPs; asymmetric denervation	Demyelination: marked slowing of conduction velocity; conduction block, temporal dispersion; reduced SNAPs

[a]CSF, cerebrospinal fluid; CMAPs, compound muscle action potentials; SNAPSs, sensory nerve action potentials.



ETIOPATOGENIA

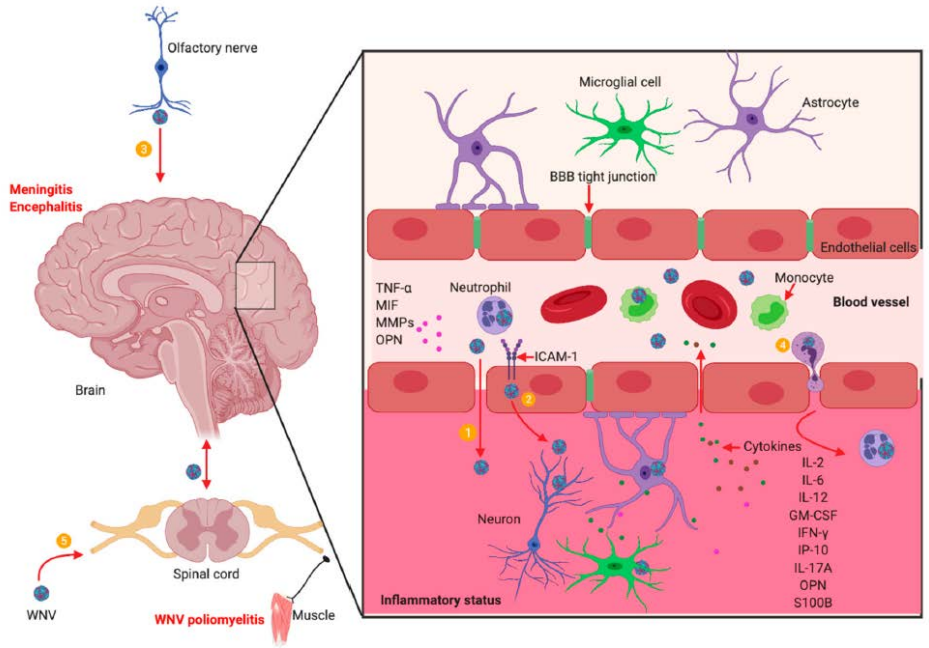
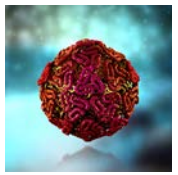


Figure 1. West Nile virus (WNV) neuroinvasion and neuropathogenesis.



pathogens

MDPI

Review

Current Understanding of West Nile Virus Clinical Manifestations, Immune Responses, Neuroinvasion, and Immunotherapeutic Implications

Fengwei Bai [1,*], E. Ashley Thompson [1], Parminder J. S. Vig [2] and A. Arturo Leis [3]

1 Department of Cell and Molecular Biology, University of Southern Mississippi, Hattiesburg, MS 39406, USA; elizabeth.a.thompson@usm.edu
2 Departments of Neurology, University of Mississippi Medical Center, Jackson, MS 39216, USA; pvig@umc.edu
3 Methodist Rehabilitation Center, Jackson, MS 39216, USA; aleis@mmrcrehab.org
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WNV replication in the peripheral organs and the blood cells, such as neutrophils and monocytes, generates viremia in the blood circulation that may lead to infection in the CNS. WNV infection in the CNS can result in meningitis, encephalitis, and acute flaccid paralysis, including WNV poliomyelitis. The possible mechanisms by which WNV enters the CNS include: ① WNV infection induces the expression of TNF-α, MIF, MMP9, ICAM-1 and Opn, which directly or indirectly increase the permeability of the BBB allowing the virus to penetrate to the CNS; ② WNV may infect endothelial cells in the cerebral microvasculature, from which progeny viruses may be released into the CNS; ③ WNV may enter the CNS from infected olfactory bulbs via olfactory neurons; ④ WNV-infected leukocytes, such as neutrophils via a "Trojan horse" transport of WNV to the CNS; and ⑤ WNV may be transported to the CNS through the infected peripheral nerves. In the CNS, WNV may infect neurons, microglia, and astrocytes producing cytokines and chemokines and leading to inflammation, neuron apoptosis and necrosis. Some molecules including IL-2, IL-6, IL-12, GM-CSF, IFN-γ, IP-10, S100B, IL-17A and OPN, remain persistently elevated in the blood for months after clearance of WNV from the body, which can lead to a post-infectious pro-inflammatory state that may promote autoimmune diseases, such as myasthenia gravis. The illustration was created in Biorender.com.

FATORES GENÉTICOS DE SUSCETIBILIDADE I

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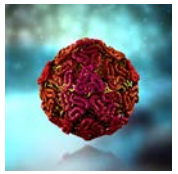
West Nile Virus: Biology, Transmission, and Human Infection

Tonya M. Colpitts,[a] Michael J. Conway,[a] Ruth R. Montgomery,[b] and Erol Fikrig[a,c]

Department of Internal Medicine, Section of Infectious Diseases[a] and Section of Rheumatology,[b] Yale University School of Medicine, New Haven, Connecticut, USA, and Howard Hughes Medical Institute, Chevy Chase, Maryland, USA[c]

TABLE 2 Genes and corresponding SNPs important in human WNV infection

Gene(s)	SNP(s)	Comparison groups (*n*)	Study results	Reference
OASL	rs3213545	WNV^+ cases (33) vs healthy controls (16)	Associated with increased susceptibility to WNV infection	236
CCR5	Δ32 deletion	WNV^+ cases (395) vs WNV^- (1,463)	Increased risk of symptomatic WNV infection	69
		WNV^+ cases (224) vs healthy controls (1,318)	Increased risk of symptomatic WNV infection	113
		WNV^+ cases (634) vs WNV^- (422)	Not a risk factor for WNV initial infection; associated with symptomatic WNV infection	114
OAS1	rs10774671	WNV^+ cases (501) vs healthy controls (552)	A risk factor for initial infection with WNV	112
IRF3, MX1, OAS1	rs2304207, rs7280422, rs34137742	Symptomatic cases (422) vs asymptomatic cases (331)	Associated with symptomatic WNV infection	19
RFC1, SCN1A, ANPEP	rs2066786, rs2298771, rs25651	Severe WNV cases (560) vs mild WNV cases (950)	Associated with neuroinvasive disease in patients infected with WNV	123



FATORES GENÉTICOS DE SUSCETIBILIDADE II

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Published in final edited form as:
J Infect Dis. 2010 January 15; 201(2): 178–185. doi:10.1086/649426.

CCR5 Deficiency is a Risk Factor for Early Clinical Manifestations of West Nile Virus Infection, but not for Infection *per se*

Jean K. Lim[1], **David H. McDermott**[1], **Andrea Lisco**[2], **Gregory A. Foster**[3], **David Krysztof**[3], **Dean Follmann**[4], **Susan L. Stramer**[3], and **Philip M. Murphy**[1]

[1]Molecular Signaling Section, Laboratory of Molecular Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892

[2]Section on Intercellular Interactions, Laboratory of Cellular and Molecular Biology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892

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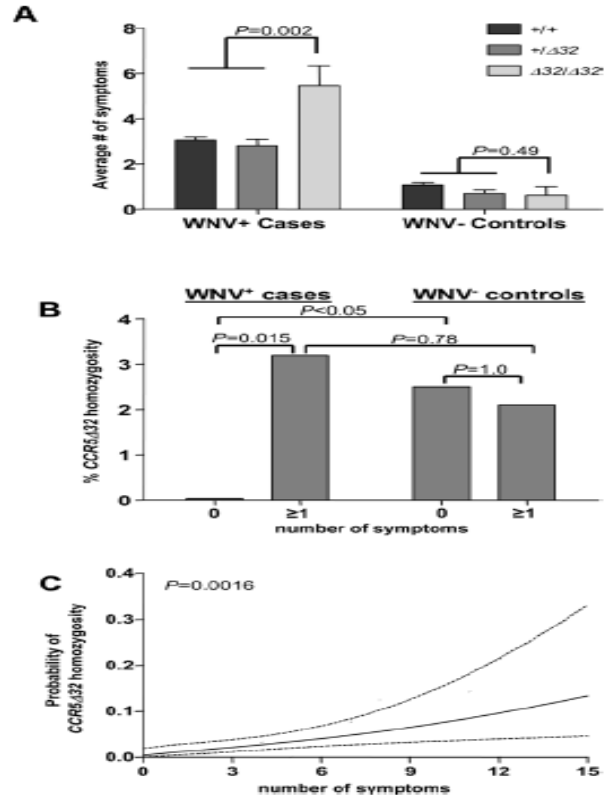

Figure 2.
Association of *CCR5Δ32* homozygosity and West Nile virus-related symptoms. (**A**) The number of symptoms reported among WNV+ cases and WNV− controls was averaged (±SEM) according to *CCR5* genotype. An unpaired *t*-test was used to calculate significance of the difference between *CCR5Δ32* homozygotes versus *CCR5Δ32* heterozygotes and *CCR5* wild-type individuals. +, *CCR5* wild-type allele; *Δ32*, *CCR5Δ32* allele. (**B**) *CCR5Δ32* homozygous frequency among WNV+ cases or WNV− controls with 0 symptoms was compared to individuals reporting ≥1 symptoms. (**C**) The predicted probability curve (solid line) along with upper and lower 95% confidence intervals (dotted lines) of *CCR5Δ32* homozygotes is plotted as a function of the number of symptoms.

DA FISIOPATOLOGIA PARA O TRATAMENTO

frontiers in Medicine

CASE REPORT
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doi: 10.3389/fmed.2019.00081

Lazarus Effect of High Dose Corticosteroids in a Patient With West Nile Virus Encephalitis: A Coincidence or a Clue?

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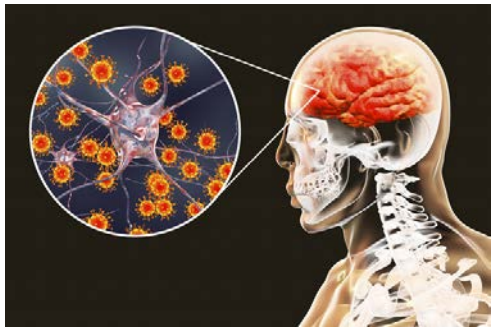
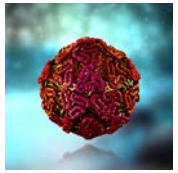
[1] *Center for Neuroscience and Neurological Recovery, Methodist Rehabilitation Center, Jackson, MS, United States,*
[2] *Mississippi Baptist Medical Center, Jackson, MS, United States*





OS PRIMEIROS DOIS CASOS HUMANOS EM PORTUGAL

Eurosurveillance
Europe's journal on infectious disease epidemiology, prevention and control
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Eurosurveillance, Volume 8, Issue 32, 05 August 2004

Articles

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Two linked cases of West Nile virus (WNV) acquired by Irish tourists in the Algarve, Portugal

Jeff Connell[1], Paul McKeown[2](Paul.McKeown@ndsc.ie), Patricia Garvey[2], Suzanne Cotter[2], Aileen Conway[1], Darina O'Flanagan[2], Brian P. O'Herlihy[3], Dilys Morgan[4], Angus Nicoll[4] and Graham Lloyd[5]

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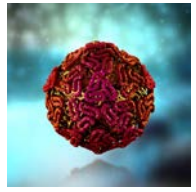

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CASO CLÍNICO / *CLINICAL CASE*

Infecção por vírus *West Nile* (Flavivírus) em Portugal

Considerações acerca de um caso clínico de síndrome febril com exantema

West Nile virus (Flavivirus) infection in Portugal

Considerations about a clinical case with febrile syndrome and rash

/ M. J. Alves[1] / J. M. D. Poças[2] / T. Luz[1] / F. Amaro[1] / L. Zé-Zé[1] / H. Osório[1]

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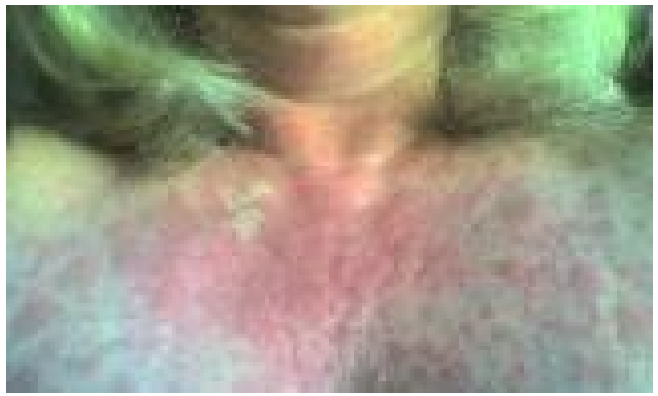
/ Resumo

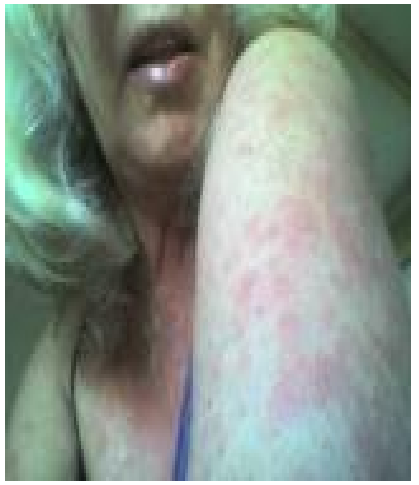
O vírus *West Nile* (WN) é um flavivírus transmitido por mosquitos e agente etiológico de febre e de doença neuroinvasiva. O vírus WN mantém-se na natureza em ciclos enzoóticos que envolvem mosquitos ornitofílicos, como vectores primários, e algumas espécies de aves como reservatório primário.

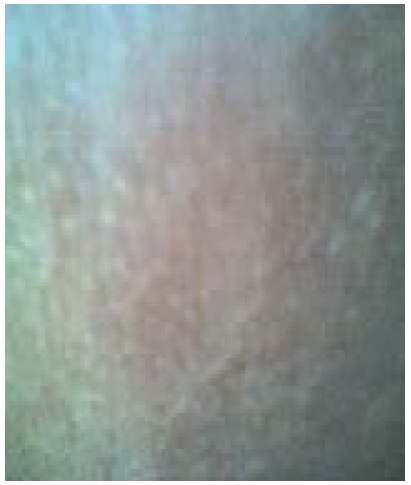
A sua presença em Portugal é conhecida, surgindo esporadicamente alguns casos de infecção em equinos e humanos. Em 2010 foi identificado um caso humano na região sul de Portugal, tendo sido o único caso humano detectado em toda a época de actividade de mosquitos nesse ano.

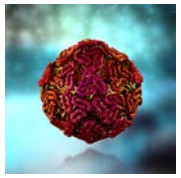
Neste caso a paciente apresentava quadro febril com hiperpirexia muito irregular, por vezes com calafrios e picos de febre superiores a 39ºC, cefaleias, mialgias, adinamia e astenia acentuada, adenomegalias volumosas e dolorosas na região cervical, assim como exantema eritematoso difuso com maior expressão no tronco. Os exames laboratoriais identificaram seroconversão de anticorpos IgM contra o vírus *West Nile*.

Palavras-chave: vírus *West Nile*; síndrome febril; zoonoses.









O ÚLTIMO CASO HUMANO EM PORTUGAL

RAPID COMMUNICATIONS

Human case of West Nile neuroinvasive disease in Portugal, summer 2015

L Zé-Zé [1,2], P Proença [3,4], HC Osório [1], S Gomes [1], T Luz [1], P Parreira [1], M Fevereiro [5], MJ Alves [1]

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Zé-Zé L, Proença P, Osório HC, Gomes S, Luz T, Parreira P, Fevereiro M, Alves MJ. Human case of West Nile neuroinvasive disease in Portugal, summer 2015. Euro Surveill. 2015;20(38):pii=30024. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.38.30024

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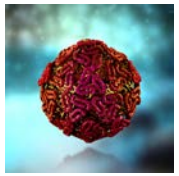
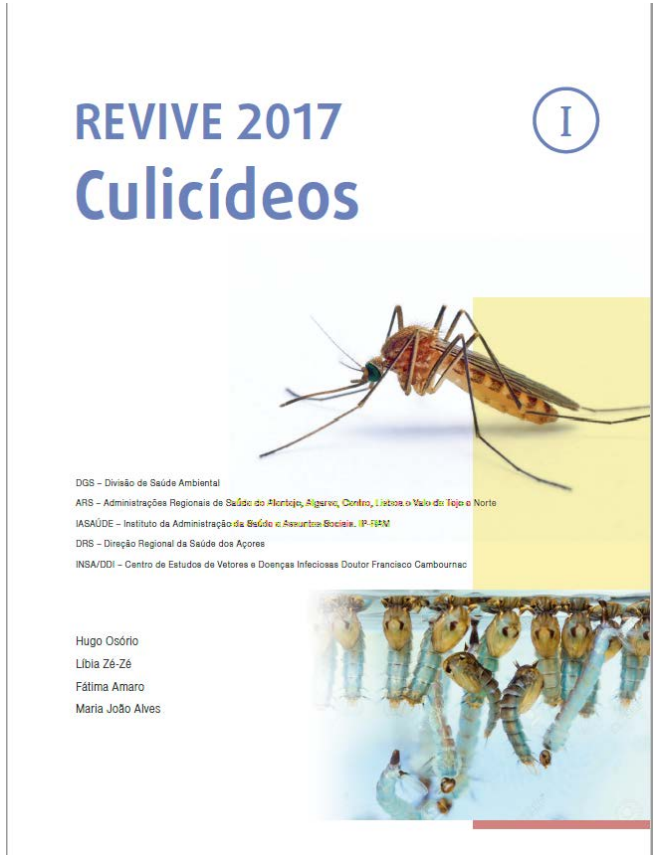
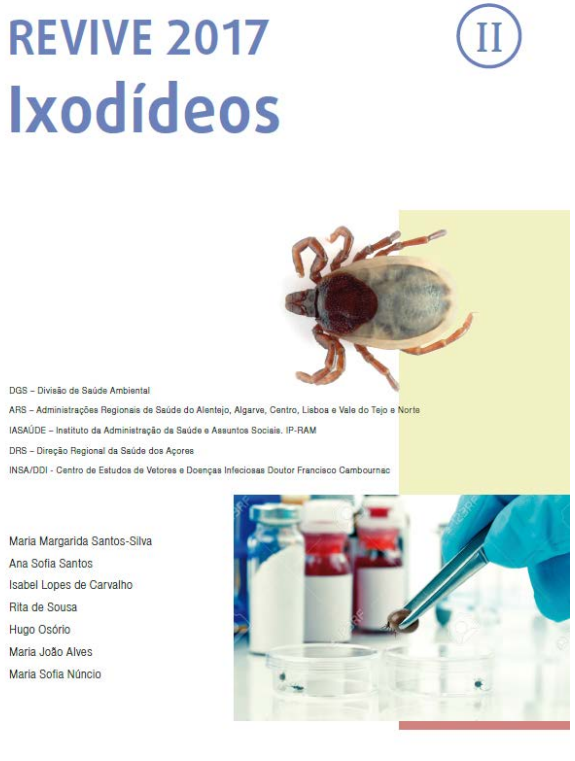


A IMPORTÂNCIA DA VIGILÂNCIA ENTOMOLÓGICA I- EM PORTUGAL





A IMPORTÂNCIA DA VIGILÂNCIA ENTOMOLÓGICA II- NA EUROPA

SCIENTIFIC REPORT

APPROVED: 19 November 2019

doi: 10.2903/j.efsa.2019.5926

The European Union One Health 2018 Zoonoses Report

European Food Safety Authority and European Centre for Disease Prevention and Control (EFSA and ECDC)

Abstract

This report of the European Food Safety Authority and the European Centre for Disease Prevention and Control presents the results of zoonoses monitoring activities carried out in 2018 in 36 European countries (28 Member States (MS) and 8 non-MS). The first and second most commonly reported zoonoses in humans were campylobacteriosis and salmonellosis, respectively. The European Union (EU) trend for confirmed human cases of these two diseases was stable during 2014–2018. The proportion of human salmonellosis cases due to *Salmonella* Enteritidis was at the same level in 2018 as in 2017. Of the 27 reporting MS, 16 met all *Salmonella* reduction targets for poultry, whereas 11 MS failed meeting at least one. The EU flock prevalence of target *Salmonella* serovars in breeding hens, laying hens, broilers and fattening turkeys decreased during recent years but stalled in breeding turkeys. *Salmonella* results from Competent Authorities for pig carcasses and for poultry tested through National Control Programmes were more frequently positive compared with food business operators. Shiga toxin-producing *Escherichia coli* (STEC) infections in humans were the third most commonly reported zoonosis in the EU and increased from 2014 to 2018. Yersiniosis was the fourth most frequently reported zoonosis in humans in 2018 with a stable trend in 2014–2018. The number of reported confirmed listeriosis cases further increased in 2018, despite *Listeria* rarely exceeding the EU food safety limit tested in ready-to-eat food. In total, 5,146 food- and waterborne outbreaks were reported. *Salmonella* was the most commonly detected agent with *S.* Enteritidis causing one in five outbreaks. *Salmonella* in eggs and egg products was the highest risk agent/food pair. A large increase of human West Nile virus infections was reported in 2018. The report further updates on bovine tuberculosis, *Brucella*, *Trichinella*, *Echinococcus*, *Toxoplasma*, rabies, *Coxiella burnetii* (Q fever) and tularaemia.

Keywords: *Campylobacter*, *Listeria*, food-borne outbreaks, monitoring, parasites, *Salmonella*, zoonoses

Requestor: European Commission

Question number: EFSA-Q-2019-00006

Correspondence: zoonoses@efsa.europa.eu

Table 69: Summary of WNV infection statistics related to humans, birds and equidae, EU, 2014–2018

	2018	2017	2016	2015	2014	Data source
Humans						
Total number of cases	1,605	208	240	128	78	ECDC
Total number of cases/100,000 population (notification rates)	0.38	0.05	0.06	0.03	0.02	ECDC
Number of reporting MS	26	26	26	26	24	ECDC
Infection acquired in the EU	1,567	205	227	122	76	ECDC
Infection acquired outside the EU	24	2	4	0	2	ECDC
Unknown travel status or unknown country of infection	14	1	9	6	0	ECDC
Animals						
Total number of outbreaks notified by MS in ADNS	315	84	173	92	31	ADNS
Total number of MS notified outbreaks to the ADNS	12	7	5	6	4	ADNS
Birds						
Number of units tested	14,216	11,525	8,258	8,594	10,246	EFSA
Number of units positive for IgM by ELISA	1	0	0	0	–*	EFSA
Number of units positive in PCR	425	93	75	74	–*	EFSA
Number of countries reporting surveillance/ monitoring data	11	8	4	7	7	EFSA
Number of outbreaks notified in ADNS	22	0	0	0	0	ADNS
Number of countries notified outbreaks to the ADNS	6	0	0	0	0	ADNS
Equids						
Number of units tested	13,785	11,670	9,751	12,619	13,751	EFSA
Number of units positive for IgM by ELISA	393	110	189	65	12	EFSA
Number of units positive in PCR	7	1	2	0	0	EFSA
Number of countries reported data to EFSA	12	12	9	9	12	EFSA
Number of outbreaks notified in ADNS	292	84	173	92	31	ADNS

TERAPÊUTICA

International Journal of
Molecular Sciences

MDPI

Review

Development of Antibody Therapeutics against Flaviviruses

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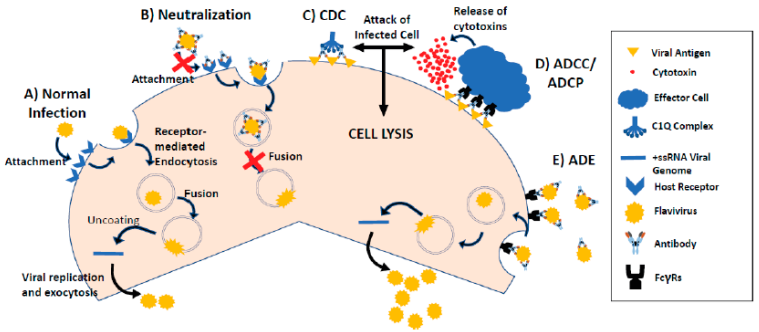
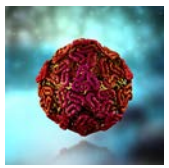


Figure 1. Flavivirus infection cycle and mechanisms of mAb neutralization and enhancement. The entry of flaviviruses into host cells is initiated with the attachment of the E protein with its receptor on the target host cell, which leads to endocytosis of flavivirus virions (**A**). The low pH in the endosome triggers the fusion of the viral envelope with the endosomal membrane, releasing the viral genome to the cytoplasm where viral replication and assembly occur (**A**). MAbs can neutralize flaviviruses by blocking viral attachment, endocytosis, or membrane fusion (**B**). MAbs can eliminate flavivirus-infected cells through antibody Fc effector functions such as complement dependent cytotoxicity (CDC) (**C**) and antibody-dependent cell cytotoxicity (ADCC) (**D**). Some non-neutralizing or subneutralizing anti-flavivirus mAbs can enhance viral infection in Fc receptor-expressing cells via the mechanism of antibody-dependent enhancement (ADE) (**E**).



PROFILAXIA

vaccines

MDPI

Review

Current Progress of Avian Vaccines Against West Nile Virus

Nereida Jiménez de Oya, Estela Escribano-Romero, Ana-Belén Blázquez, Miguel A. Martín-Acebes and Juan-Carlos Saiz *

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check for updates

viruses

MDPI

Review

Twenty Years of Progress Toward West Nile Virus Vaccine Development

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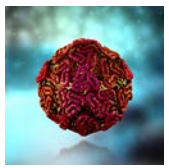

ASPETOS CONTROVERSOS I SEGURANÇA TRANSFUSIONAL

EUROROUNDUP

One Health approach for West Nile virus surveillance in the European Union: relevance of equine data for blood safety

Johanna J Young[1], Denis Coulombier[1], Dragoslav Domanović[1], European Union West Nile fever working group[2], Hervé Zeller[1], Céline M Gossner[1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm
2. Members of the European Union West Nile fever working group are listed at the end of the article

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Young Johanna J, Coulombier Denis, Domanović Dragoslav, European Union West Nile fever working group, Zeller Hervé, Gossner Céline M, European Union West Nile fever working group. One Health approach for West Nile virus surveillance in the European Union: relevance of equine data for blood safety. Euro Surveill. 2019;24(16):pii=1800349. https://doi.org/10.2807/1560-7917.ES.2019.24.16.1800349

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Semenza *et al. Environmental Health* 2016, **15**(Suppl 1):28
DOI 10.1186/s12940-016-0105-4

Environmental Health

RESEARCH **Open Access**

Climate change projections of West Nile virus infections in Europe: implications for blood safety practices

Jan C. Semenza[1*], Annelise Tran[2], Laura Espinosa[1], Bertrand Sudre[1], Dragoslav Domanovic[1] and Shlomit Paz[3]

From The 11th International Conference on Urban Health
Manchester, UK. 6 March 2014

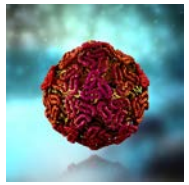
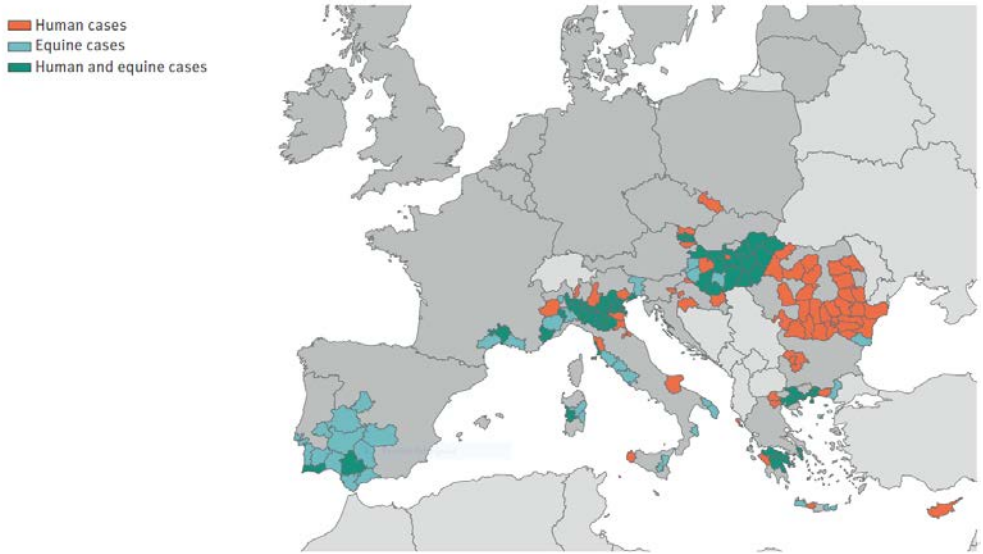


FIGURE 1

Distribution of human (n = 847) and equine (n = 553) West Nile virus infections in the European Union countries, 2013–2017, (n = 1,400)



ASPETOS CONTROVERSOS II
SEGURANÇA TRANSFUSIONAL

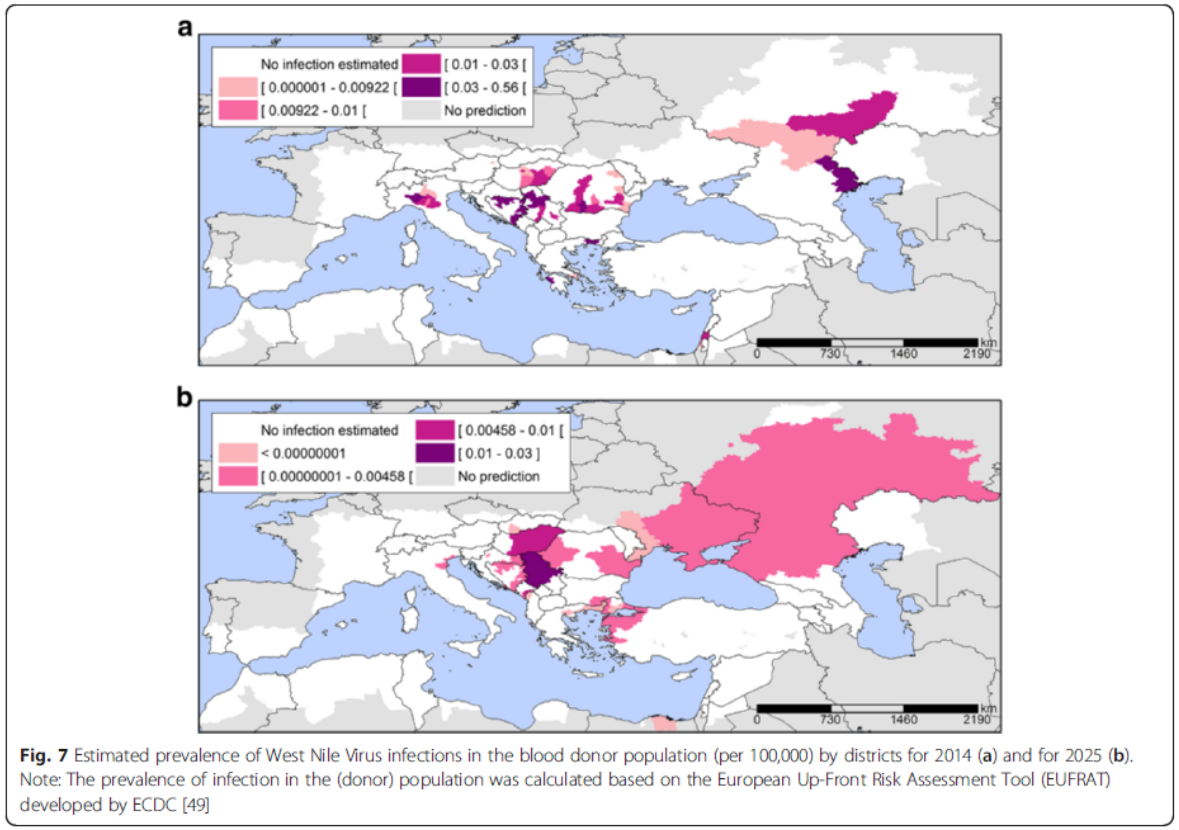
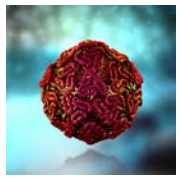


Fig. 7 Estimated prevalence of West Nile Virus infections in the blood donor population (per 100,000) by districts for 2014 (**a**) and for 2025 (**b**). Note: The prevalence of infection in the (donor) population was calculated based on the European Up-Front Risk Assessment Tool (EUFRAT) developed by ECDC [49]



ASPETOS CONTROVERSOS III
A INFEÇÃO NA GRÁVIDA

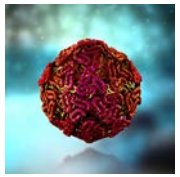
Arboviruses and pregnancy: maternal, fetal, and neonatal effects

Lancet Child Adolesc Health 2017; 1: 134-46

Review

Caroline Charlier, Marie-Claude Beaudoin, Thérèse Couderc, Olivier Lortholary, Marc Lecuit

Arboviruses are an expanding public health threat, with pregnant women facing unique complications from arbovirus infections. These infections, such as dengue and Crimean–Congo haemorrhagic fever, can be more severe in pregnant women than in the general population. Vertical transmission is reported for many arboviruses and can severely affect pregnancy outcome. Indeed, arboviruses—particularly flaviviruses and alphaviruses—are associated with increased risks of fetal loss and premature birth. Arboviruses can be teratogenic, as is the case for Zika virus and Venezuelan equine encephalitis virus. Finally, intrapartum transmission can result in severe neonatal infections, as is true for chikungunya virus. Although the global burden of arboviruses is well recognised, few studies have provided data on arbovirus infection specifically in the context of maternal and child health. Epidemiological and clinical studies are therefore needed to better assess the burden of arbovirus infections during pregnancy and to improve the prevention and clinical management of these viral infections. In this Review, we analyse the information available and identify gaps in knowledge that require further assessment.



	Geographical area	Main vectors	Maternal risk	Antenatal consequences of mother-to-child transmission	Perinatal consequences of mother-to-child transmission
Dengue virus (DENV)	Tropical and subtropical areas worldwide	Mosquito (*Aedes* spp)	Documented risk of severe infection; increased risk of haemorrhagic fever/shock syndrome compared with non-pregnant women of reproductive age (odds ratio 3·38, 95% CI 2·10–5·42)[11,23-26]	Transmission documented; increased fetal losses in the first half of pregnancy (data from multiple cohorts, substantiated by a meta-analysis)[27-29]	Documented, incidence unknown; severe neonatal infection with sepsis-like symptoms and acute respiratory distress reported in case reports[30,31]
Japanese encephalitis virus (JEV)	Asia, Australia	Mosquito (*Culex* spp)	No data	Transmission documented and severe; incidence unknown; fetal losses documented only in maternal infections occurring <22 weeks of gestation[32]	No data
Kyasanur Forest disease virus (KFDV), Alkhurma haemorrhagic fever virus (AHFV)	Asia (Middle East, India, southeast, and western Asia)	Tick (*Haemophysalis* spp)	No data	No data	No data
Murray Valley encephalitis virus (MVEV)	Australia, Papua New Guinea	Mosquito (*Culex* spp)	No data	No data	No data
Powassan virus	North America	Tick (*Ixodes* spp)	No data	No data	No data
Saint Louis encephalitis virus (SLEV)	America (North and Central)	Mosquito (*Culex* spp)	No data	No data	No data
Tick-borne encephalitis virus (TBEV)	Northern Europe and northern Asia (in a belt extending from eastern Europe to Japan)	Tick (*Ixodes* spp)	No data	No data	No data
West Nile virus (WNV; also known as Kunjin virus in Oceania)	Worldwide, most prevalent in America and Africa, low prevalence in Europe	Mosquito (*Culex* spp)	No data	Transmission documented; extremely rare; one case of congenital chorioretinitis and encephalitis after maternal infection at 27 weeks of gestation;[33] no significant increase in fetal losses or adverse long-term neurological outcome in US cohort studies[34-36]	Uncertain; two cases with encephalitis that developed 6–10 days after birth (maternal symptoms 21–6 days before delivery, no documentation of viral infection at birth);[35] one case with transient rash at birth and positive IgM 1 month later (maternal symptoms at birth)[35]
Yellow fever virus (YFV)	Sub-Saharan Africa, South America	Mosquito (*Aedes* spp or *Haemagogus* spp)	No data	Transmission documented; extremely rare; two cases of fatal and maternal infection at 4–5 months of pregnancy with lesions compatible with yellow fever virus in the fetuses[37]	Documented, probably extremely rare; one report of fatal neonatal infection (maternal symptoms onset 3 days before delivery)[38]
Zika virus (ZIKV)	South Pacific area, Latin America, Caribbean, USA (Florida and Puerto Rico)	Mosquito (*Aedes* spp)	..	Transmission documented; incidence of 1–13% brain abnormalities at birth;[39,40] teratogenic according to multiple case reports and case series;[41] severe microcephaly and other brain lesions;[39,42,43] retinal lesions;[44] prematurity or fetal losses;[45] organogenesis and weight usually preserved;[45] and impaired postnatal neurological development with poor cranial growth, irritability, pyramidal or extrapyramidal symptoms, and epilepsy[46]	Documented; probably extremely rare; two French Polynesian case reports of possible perinatal transmission (one asymptomatic, one with mild rash)[47]

Miscarriages refer to fetal losses before 28 weeks of gestation. Stillbirths refer to fetal losses at 28 weeks of gestation or later.

Table 2: **Classification, maternal risk, and consequences of mother-to-child transmission of major Flaviviridae viruses**

ASPETOS CONTROVERSOS IV
A TRANSMISSIBILIDADE TRANSPLACENTÁRIA

Published in final edited form as:
Birth Defects Res A Clin Mol Teratol. 2016 August ; 106(8): 716–723. doi:10.1002/bdra.23523.

Prospective Study of Pregnancy and Newborn Outcomes in Mothers with West Nile Illness during Pregnancy

Gabriella Pridjian[1,*], **Patricia A. Sirois**[1], **Scott McRae**[1], **Alison F. Hinckley**[2], **Sonja A. Rasmussen**[3], **Patricia Kissinger**[1], **Pierre Buekens**[1], **Edward B. Hayes**[2], **Dan O'Leary**[2], **Stephanie Kuhn**[2], **Kenneth F. Swan**[1], **Xu Xiong**[1], and **Dawn M. Wesson**[1]

[1]Tulane University, New Orleans, Louisiana

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[3]Centers for Disease Control and Prevention, Atlanta, Georgia

	West Nile virus illness $N = 28$	Uninfected women $N = 25$	p-Value
Presence of umbilical cord blood WNV antibody[a]			
IgM negative	28	-	
IgG negative	-	25	
Gestational age at birth, weeks (mean ± SD)	38.6 ± 1.9	38.6 ± 1.1	0.924
Preterm birth	1	0	1.000
Live birth	28	25	1.000
Neonatal death	1	0	1.000
APGAR[b] median (range)			
1 min	8 (3 – 9)	9 (4–9)	0.377
5 min	9 (8 –10)	9 (7–9)	0.472
Birth weight,[b] gm (mean ± SD)	3384 ± 374	3501 (± 515)	0.365
Birth length, cm (mean ± SD)	50.5 ± 3.1	50.1 ± 2.4	0.620
Birth head circumference, cm (mean ± SD)	34.3 ± 1.2	34.4 ± 2.0	0.982
Small for gestational age[b]	0	0	1.000
Respiratory distress	2	2	1.000
Signs of infection at birth[c]	0	1	0.481
Hearing test passed[d]	26	23	1.000
Birth defects-major[e]	1 (pyloric stenosis)	0	0.481
Birth defects-minor	1 (umbilical hernia)	1 (patent foramen ovale)	1.000

[a]Newborns from WNV illness mothers not tested for IgG; newborns from uninfected mothers not tested for IgM.

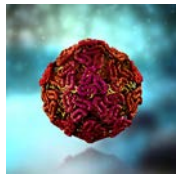
[b]A preterm birth with neonatal death not included; two missing WNV group birth weight entries.

[c]Includes sepsis, pneumonia, seizures, skin rash, thrombocytopenia, cataracts.

[d]Two missing entries in each group; one in the WNV illness group because of neonatal death.

[e]The mother of the child with pyloric stenosis also had hypertrophic pyloric stenosis.

IgG, immunoglobulin G; IgM, immunoglobulin M; WNV, West Nile virus.



ASPETOS CONTROVERSOS V
A TRANSMISSIBILIDADE PELO LEITE MATERNO

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Breast Milk Transmission of Flaviviruses in the Context of Zika Virus: A Systematic Review

Table 1b

Cases of possible, probable, or confirmed transmission of a flavivirus or flaviviral vaccine virus by breast feeding

Author	Case Number for cases with evidence of transmission	Certainty of transmission through breast feeding	Maternal illness onset	Maternal PCR (days post maternal illness onset or vaccination)*	Maternal serology (days post maternal illness onset or vaccination)*	Period of infant exposure to potentially contaminated milk*	Cord blood test results	Infant's illness onset*	Infant PCR (days post infant illness onset)**	Infant serology (days post infant illness onset)**
Zika Virus										
Besnard 2014[15] (n=2)	Case 1	Unlikely (Infant only breast fed 1 day prior to positive test). Perinatal transmission more likely, vector-borne transmission not excluded. *Endemic region*	Day 2 BD	Serum+ (4) Saliva+ (4)	Not reported	Days 2–5	Not reported	Asymptomatic	Serum+ (5)*, Saliva + (5)*	Not reported
	Case 2	Unlikely (Infant only breast fed 1 day prior to onset). Perinatal infection not excluded. *Endemic region*	Day 3 AD	Serum+ (−2,2) Urine+ (4)	Not reported	Days 0–1	Not reported	Day 1	Serum+ (0,3)[b], Urine + (4)	Not reported
Blohm 2017[18]	Single Case	Possible. Vector-borne transmission not excluded. *Endemic region*	~Month 5 AD	Serum+ (3) Urine+ (3)	Not reported	Days 0–3	Not applicable	Asymptomatic	Serum+ (3)*, Urine + (3)*	Not reported
Dengue Virus										
Barthel 2013[20]	Single Case	Possible. Cord blood was negative by PCR, but perinatal infection not excluded. *Endemic Region*	Day 2 BD	Blood+ (2–8)	IgM+ (8), IgG+ (2)	Days 4–6	PCR−	Day 6	Serum+[b] (0–9)	IgM+ (21)
Arragain 2016[21] (n=16)	Case 1	Possible. Cord blood was negative by PCR, but perinatal and vector-borne transmission not excluded. *Endemic Region*	Day 2 AD	Serum+ (−4, 1, 4, 6, 8)	Not reported	Day −2–4	PCR−	Day 5	Serum+ (−3,−1,3, 5)	Not reported
West Nile Virus										
CDC 2002[22]	Single Case	Probable. Perinatal and vector-borne transmission not excluded, although unlikely. *Endemic region*	Day 10 AD (Day 9 after receiving WNV contaminated blood)	Not reported	IgM+ in CSF	Days ~10–6	Not reported	Asymptomatic	Not reported	IgM+ (15)*
Hinckley 2007[23] (n=8)	Case 1[#]	Unlikely. Not supported by time-order of mother and infant symptom onsets. Vector-borne transmission likely. *Endemic region*	~ 1 month after infant onset (Month 9 AD)	Not reported	IgM+ (Not reported)	Infant onset prior to maternal onset	Not applicable	Month 8[c]	Not reported	IgM+ (~14)
	Case 2[#]	Unlikely. Perinatal and vector-borne transmission not excluded. *Endemic region*	Day 5 BD	Not reported	IgM+ (7)	Not reported	Not reported	Day 5 (Born symptomatic)	Not reported	IgM+ (~60, ~240), NT+ (~60; ~240, titer 4-fold higher)
	Case 3[#]	Possible Perinatal and vector-borne transmission not excluded. *Endemic region*	Day 6 BD	Serum (12)	IgM+ (12), IgG+ (12), NT+ (12)	Not reported	IgM−, IgG−, NT−	Day 16	Not reported	IgM+ (9) in serum and CSF

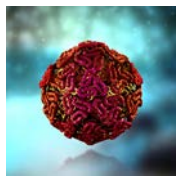

Table 1a

Detection of flaviviral ribonucleic acid (RNA) and virus in human milk

Author	Case Number for cases with flaviviral RNA detected	RNA detected (days post maternal illness onset)*	Virus cultured (days post maternal illness onset)*
Zika Virus			
Besnard 2014[15] (n=2)	Case 1	Yes (5)	No (5)
	Case 2	Yes (5)	No (5)
Dupont-Rouzeyrol 2016[16]	Single Case	Yes (4)	Yes (4)
Cavalcanti 2017[17] (n=4)	Case 1	Yes (3)	Yes (3)
Blohm 2017[18]	Single Case	Yes (3)	Yes (3)
Sotello 2017[19]	Single Case	Yes (14[b],23,32)	Yes (14[b],32)
Dengue Virus			
Barthel 2013[20]	Single Case	Yes (6,8)	Yes (6,8)
Arragain 2016[21] (n=12)	Case 1	Yes (3)	No (3)
	Case 2	Yes (2–10)	No (2–10)
	Case 3[a]	Yes (1,3–7)	No (1,3–7)
	Case 4[a]	Yes (4,6–8,10)	No (4,6–8,10)
	Case 5[a]	Yes (7–9,12)	No (7–9,12)
	Case 6[a]	Yes (2–11,14)	No (2–11,14)
	Case 7[a]	Yes (3)	No (3)
	Case 8[a]	Yes (1–6)	No (1–6)
	Case 9[a]	Yes (9)	No (9)
West Nile Virus			
CDC 2002[22]	Single Case	Yes (6)	No (6)
Hinckley 2007[23] (n=45)	Case 1	Yes (50[b])	Not attempted due to low viral load
	Case 2	Yes (70[b])	Not attempted due to low viral load
Paisley 2016[24] (n=9)	Case 1[a]	Equivocal (Not reported)	Not reported

RNA= ribonucleic acid,

*Day 0 considered day of maternal illness onset unless otherwise indicated,

[a]case number assigned differs from the case number reported in cited study due to excluded cases,

[b]Colostrum sample

ASPETOS CONTROVERSOS VI
O IMPACTO DAS ALTERAÇÕES CLIMÁTICAS

insects

MDPI

Review

Effects of the Environmental Temperature on *Aedes aegypti* and *Aedes albopictus* Mosquitoes: A Review

Joanna M. Reinhold [1], Claudio R. Lazzari [2] and Chloé Lahondère [1,*]

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[2] Institut de Recherche sur la Biologie de l'Insecte, UMR CNRS 7261, Université de Tours, 37200 Tours, France; claudio.lazzari@univ-tours.fr
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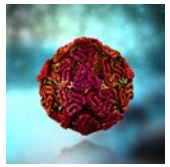
Climate change impacts on West Nile virus transmission in a global context

Shlomit Paz

Table 1. Impacts of climatic variables as drivers in the epidemiology of WNV.

climatic variable	impacts on the epidemiology of WNV	
temperature	correlates positively with:	
	—viral replication rates	
	—seasonal phenology of mosquito host populations	
	—growth rates of vector populations	
	—viral transmission efficiency to birds	
	—geographical variations in human case incidence	
	correlates negatively with:	
	—interval between blood meals	
	—incubation time from infection to infectiousness in mosquitoes	
precipitation (*contradictory findings*)	above average, floods	—leads to higher mosquito abundance
		—reduces potential by flushing drainage channels used by *Culex* larvae
		—correlates positively with potential for disease outbreaks in humans
	below average, drought	—facilitates population outbreaks of some mosquito species
		—'rich' standing water attracts several species of mosquitoes and birds; this increases the bird–mosquito interaction and accelerates the epizootic cycling and amplification of WNV within these populations
relative humidity	correlates positively with:	
	—vector population dynamics	
	—morbidity in humans	
wind	contributes to virus spread by impact on wind-blown mosquitoes and on the arboviruses they transmit	
	affects bird migration through changes in the patterns of storm tracks	



ASPETOS CONTROVERSOS VII
O CASO DO CONTINENTE EUROPEU

Semenza *et al. Environmental Health* 2016, **15**(Suppl 1):28
DOI 10.1186/s12940-016-0105-4

Environmental Health

RESEARCH Open Access

Climate change projections of West Nile virus infections in Europe: implications for blood safety practices

Jan C. Semenza[1*], Annelise Tran[2], Laura Espinosa[1], Bertrand Sudre[1], Dragoslav Domanovic[1] and Shlomit Paz[3]

From The 11th International Conference on Urban Health
Manchester, UK. 6 March 2014

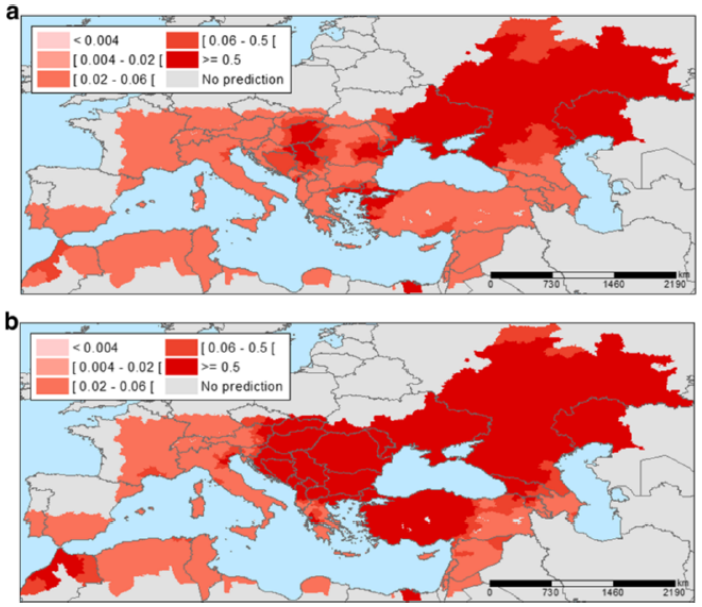
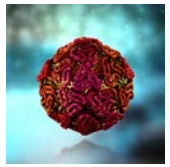


Fig. 5 Predicted probability of districts with West Nile Virus infections based on July temperatures for A1B scenario projections for 2025 (**a**) and 2050 (**b**). Note: Among IPCC scenarios, the A1 scenario groups are distinguished by their technological emphasis. A1B represent a balance across all energy sources (intensive fossil and non-fossil energy)



ASPETOS CONTROVERSOS VIII
RESERVATÓRIOS NA NATUREZA

viruses

MDPI

Review

West Nile Virus Associations in Wild Mammals: An Update

J. Jeffrey Root [1,*] and Angela M. Bosco-Lauth [2]

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Common Name	Scientific Name	Detection Type	Location	Reference
Virginia opossum[a]	*Didelphis virginiana*	Virus	MO, USA	[31]
		Viral RNA/histopathologic	Quebec, CA	[32]
Raccoon	*Procyon lotor*	Antibodies[b]	NY, USA	[19]
		Antibodies	Ontario, CA	[33]
Striped skunk	*Mephitis mephitis*	Antibodies	Ontario, CA	[33]
Black bear	*Ursus americanus*	Antibodies	MD, USA	[34]
Eurasian brown bear	*Ursus arctos arctos*	Antibodies	Slovakia	[35]
Red fox	*Vulpes vulpes*	Antibodies[b]	Spain	[14]

Common Name	Scientific Name	Detection Type	Location	Reference
Black howler	*Alouatta caraya*	Antibodies	Argentina	[26]
Mountain gorilla	*Gorilla beringei beringei*	Antibodies	DRC[a]/Rwanda	[20]
Hoffman's two-toed sloth	*Choloepus hoffmanni*	Antibodies	Costa Rica	[50]
African straw-colored fruit bat	*Eidolon helvum*	Antibodies	Uganda	[51]
Little epauletted fruit bat	*Epomophorus labiatus*	Antibodies	Uganda	[51]
African elephant	*Loxodonta africana*	Antibodies	DRC[a]	[20]

[a] Democratic Republic of the Congo.

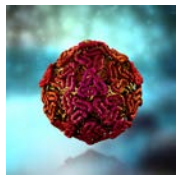

Table 1. Recently reported natural exposures of artiodactyls to West Nile virus.

Common Name	Scientific Name	Detection Type	Location	Reference
Wild boar	*Sus scrofa*	Antibodies	Serbia	[12]
		Antibodies	Czech Republic	[13]
		Antibodies[a]	Spain	[14]
		Antibodies[a]	Spain	[15]
Roe deer	*Capreolus capreolus*	Antibodies	Serbia	[12]
		Antibodies	Czech Republic	[13]
Red deer	*Cervus elaphus*	Antibodies	Czech Republic	[13]
		Antibodies[b]	Spain	[16]
		Antibodies[a]	Spain	[15]
Fallow deer	*Dama dama*	Antibodies	Czech Republic	[13]
		Antibodies[b]	Spain	[16]
Mouflon	*Ovis* sp.	Antibodies	Czech Republic	[13]
		Antibodies[b]	Spain	[16]
Dromedary camel	*Camelus dromedarius*	Antibodies[a,c]	Spain	[17]
		Virus	UAE[d]	[18]
"Camel"	Not listed[e]	Antibodies[a,c]	USA[f]	[19]
African forest buffalo	*Syncerus caffer nanus*	Antibodies	DRC[g]	[20]
White-tailed deer	*Odocoileus virginianus*	Antibodies	Multiple USA	[21]
Reindeer	*Rangifer tarandus tarandus*	Antibodies[a,c]	Alberta, CA	[22]

[a] Indicates that a single test (e.g., enzyme-linked immunosorbent assay [ELISA]) was used, samples were not tested against multiple flaviviruses, or it is unclear if samples were tested against multiple flaviviruses. Therefore, all detections may or may not represent WNV. [b] Data were presented as WNV and antigenically related flaviviruses. [c] Animals were from a privately owned collection. [d] United Arab Emirates. Original paper did not list specific location of animal and if animal was privately owned of feral. [e] Species of camel was not listed in original paper. Animals were privately owned. [f] Serum samples were sent to a diagnostic laboratory. The actual locations of where the privately owned animals were sampled was not listed in the original paper. [g] Democratic Republic of the Congo.

Common Name	Scientific Name	Detection Type	Location	Reference
Fox Squirrel	*Sciurus niger*	Viral RNA	MI, USA	[44]
Eastern gray squirrel	*Sciurus carolinensis*	Antibodies	Italy[a]	[45]
		Antibodies	GA, USA	[43]
Groundhog	*Marmota monax*	Antibodies	Ontario, CA	[33]
Yellow-necked field mouse	*Apodemus flavicollis*	Antibodies	Italy	[46]
		Virus	Europe[b]	[47]
Bank vole	*Myodes glareolus*[c]	Virus	Europe[b]	[47]

[a] Species is introduced into Italy. [b] Reference did not give a specific location. [c] Listed in original paper as *Clethrionomys glareolus*.

ASPETOS CONTROVERSOS VIII
AS IMPLICAÇÕES DAS COINFEÇÕES

VECTOR-BORNE AND ZOONOTIC DISEASES
Volume 11, Number 8, 2011

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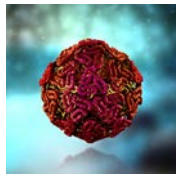
Culex Flavivirus and West Nile Virus Mosquito Coinfection and Positive Ecological Association in Chicago, United States

Christina M. Newman,[1] Francesco Cerutti,[2] Tavis K. Anderson,[1] Gabriel L. Hamer,[3] Edward D. Walker,[3] Uriel D. Kitron,[4] Marilyn O. Ruiz,[5] Jeffery D. Brawn,[5] and Tony L. Goldberg[1]

Abstract

Culex flavivirus (CxFV) is an insect-specific flavivirus globally distributed in mosquitoes of the genus *Culex*. CxFV was positively associated with West Nile virus (WNV) infection in a case–control study of 268 mosquito pools from an endemic focus of WNV transmission in Chicago, United States. Specifically, WNV-positive *Culex* mosquito pools were four times more likely also to be infected with CxFV than were spatiotemporally matched WNV-negative pools. In addition, mosquito pools from residential sites characterized by dense housing and impermeable surfaces were more likely to be infected with CxFV than were pools from nearby urban green spaces. Further, 6/15 (40%) WNV-positive individual mosquitoes were also CxFV positive, demonstrating that both viruses can coinfect mosquitoes in nature. Phylogenetic analysis of CxFV from Chicago demonstrated a pattern similar to WNV, consisting of low global viral diversity and lack of geographic clustering. These results illustrate a positive ecological association between CxFV and WNV, and that coinfection of individual mosquitoes can occur naturally in areas of high flaviviral transmission. These conclusions represent a challenge to the hypothesis of super-infection exclusion in the CxFV/WNV system, whereby an established infection with one virus may interfere with secondary viral infection with a similar virus. This study suggests that infection with insect-specific flaviviruses such as CxFV may not exclude secondary infection with genetically distinct flaviviruses such as WNV, and that both viruses can naturally coinfect mosquitoes that are epidemic bridge vectors of WNV to humans.

Key Words: Arboviruses—Epidemiology—*Flavivirus*—Mosquito-only *Flavivirus*—West Nile.



ASPETOS CONTROVERSOS IX
AS IMPLICAÇÕES DAS COINFEÇÕES

PLOS BIOLOGY

UNSOLVED MYSTERY

Arbovirus coinfection and co-transmission: A neglected public health concern?

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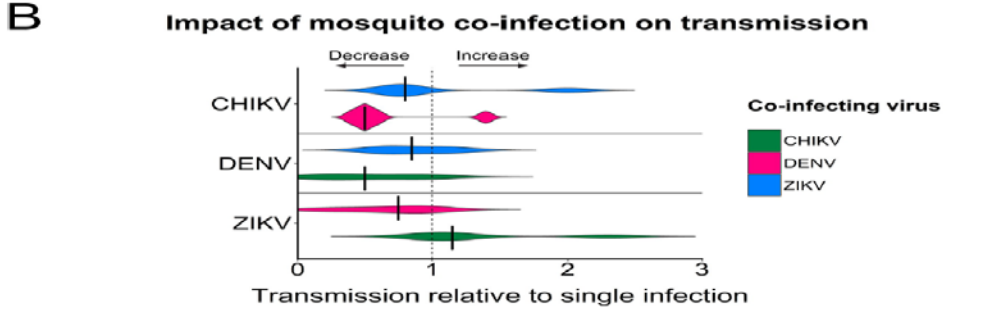


Fig 3. Effects of coinfection on clinical disease in humans and virus transmission by mosquitoes. (**A**) Clinical outcomes were obtained from studies providing sufficient information for both single infected and coinfected patients [22,25,32,46,47,50,52,56,58,61,63,65,67–69]. "Dengue-like illness" summarizes all cases of febrile illness with a range of additional symptoms including arthralgia, myalgia, rash, headache, gastrointestinal symptoms, thrombocytopenia, and conjunctivitis. Hemorrhagic fever includes all patients with clear signs of hemorrhage ranging from mild to severe, and dengue shock syndrome includes patients with hypotension, ascites, and pleural effusion. (**B**) Data on mosquito transmission were compiled from studies that made a direct comparison between mosquitoes exposed to a single or multiple viruses [82–84,87]. Transmission of coexposed mosquitoes was calculated relative to single exposed mosquitoes, with relative transmission being defined as transmission rate of virus X in mosquitoes coexposed to virus X and Y divided by transmission rate of virus X in single exposed mosquitoes. Transmission is expressed as the percentage of mosquitoes with virus in their saliva out of the total number of exposed mosquitoes. Relative transmission of 1 indicates that no difference was observed between transmission rates of single exposed or coexposed mosquitoes. Vertical black bars indicate the median. Data used to calculate relative co-transmission are available at https://github.com/grubaughlab/paper_2019_co-infection. CHIKV, chikungunya virus; DENV, dengue virus; ZIKV, Zika virus.

https://doi.org/10.1371/journal.pbio.3000130.g003

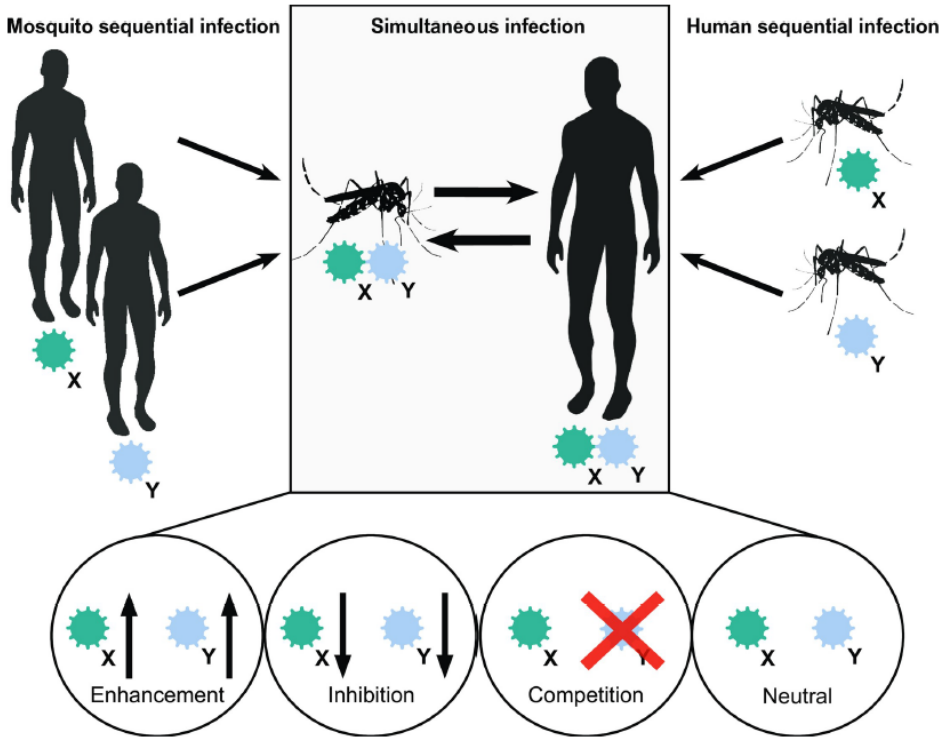
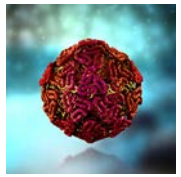


Fig 2. Mosquito and human coinfections occur as a result of simultaneous or sequential infection. Coinfection may either be the result of simultaneous transmission of multiple viruses between mosquitoes and humans (central panel) or sequential transmission during multiple mosquito bites. Four scenarios may explain the consequences of virus coinfection inside mosquito vectors and human hosts: enhancement, inhibition, competition, or neutral.

https://doi.org/10.1371/journal.pbio.3000130.g002



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