

Neurotropic Flaviviruses

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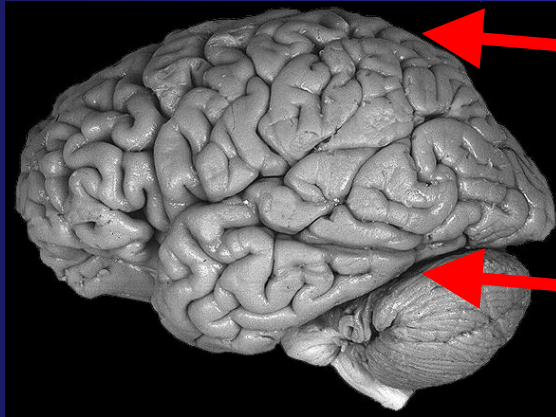
**Division of High-Consequence
Pathogens and Pathology**

**National Center for Emerging
and Zoonotic Infectious
Diseases**

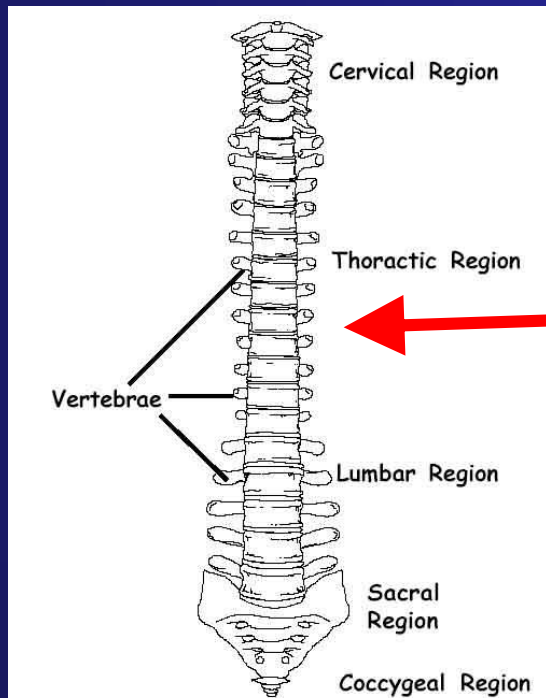
**U.S. Centers for Disease
Control and Prevention**



Definition of Terms



- **“Meningitis”:**
Inflammation of the
covering of the brain
- **“Encephalitis”:**
Inflammation of the brain
itself



- **“Meningoencephalitis”**
- **“Myelitis”:** Inflammation
of the spinal cord

Neurotropic Flaviviruses

- Japanese encephalitis virus
- West Nile virus / Kunjin
- Dengue virus(es)
- Zika virus
- Saint Louis encephalitis virus
- Murray Valley encephalitis virus
- Tick Borne encephalitis virus

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Japanese Encephalitis Serocomplex

Virus	Geographic Distribution	# cases / year	Human disease	Population at greatest risk
Japanese encephalitis virus	South and southeast Asia, China, Indonesia, northern Australia	Est. 70,000	Encephalitis, meningitis, anterior myelitis	Children
West Nile virus (including Kunjin)	Africa, Middle East, Europe, Americas, South / Southeast Asia, Australia	Approx. 1,000* *(>3,000 during 2003 epidemic in US)	Encephalitis, Meningitis, anterior myelitis, fever, rash	Elderly, immunosuppressed
Saint Louis encephalitis virus	Americas	Occasional large outbreaks with hundreds of cases, but usually few sporadic cases	Encephalitis, Meningitis	Elderly, Immunosuppressed
Murray Valley encephalitis virus	Australia, Papua New Guinea	Few sporadic cases, occasional small outbreaks	Encephalitis	All ages

Features of JEV and WNV

Feature	Japanese Encephalitis Virus	West Nile Virus
Geographic area	South / Southeast Asia, Pacific Rim, Northern Australia	Africa, Middle East, South Asia, Eastern Europe, Australia, North / Central / South America
Main vectors	<i>Culex tritaeniorhynchus</i> , <i>C. vishnui</i> , <i>C. pipiens</i>	<i>C. pipiens</i> , <i>C. tarsalis</i> , <i>C. quinquefasciatus</i>
Main Vertebrate hosts	Migrating birds, domestic fowl, pigs	Birds of family Corvidae and other passerine birds
Groups at risk	Children in endemic areas, nonimmune adults	Elderly, immunocompromised
Approximate Incidence	50,000 – 70,000 cases annually in Asia	Sporadic cases in Africa, Europe; larger outbreaks (30 – 3000) in Middle East and North America
Ratio of symptomatic / asymptomatic infections	1 in 25 (nonimmune adults); 1 in 250 – 1000 (children)	1 in 150
Patients presenting with encephalitis (%)	60 - 75	58 - 62
Case fatality rate (%)	20 - 30	5 - 15

Adapted from Solomon, NEJM 2004;351(4):372

Japanese encephalitis (JE) Epidemiology

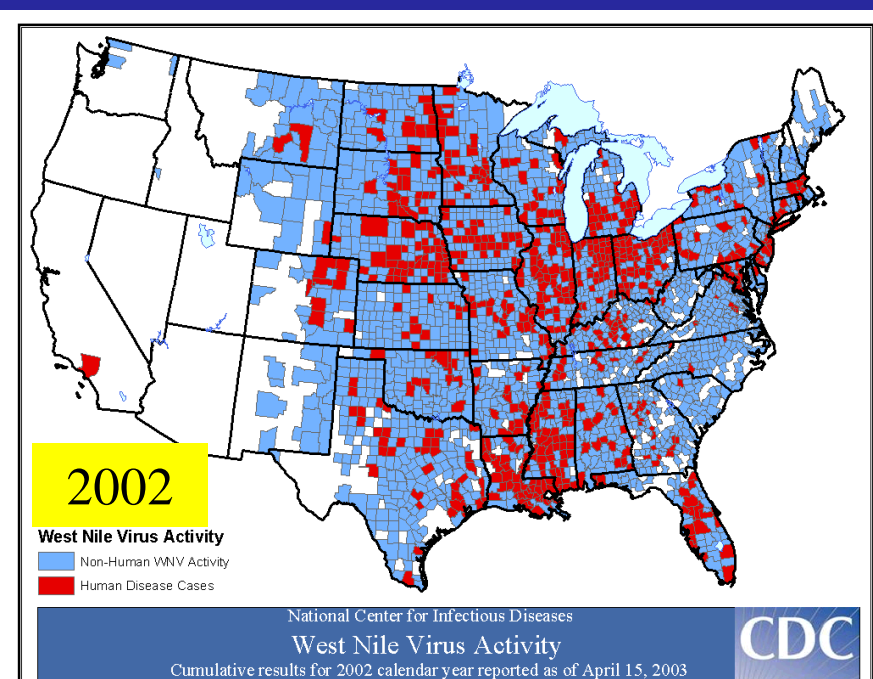
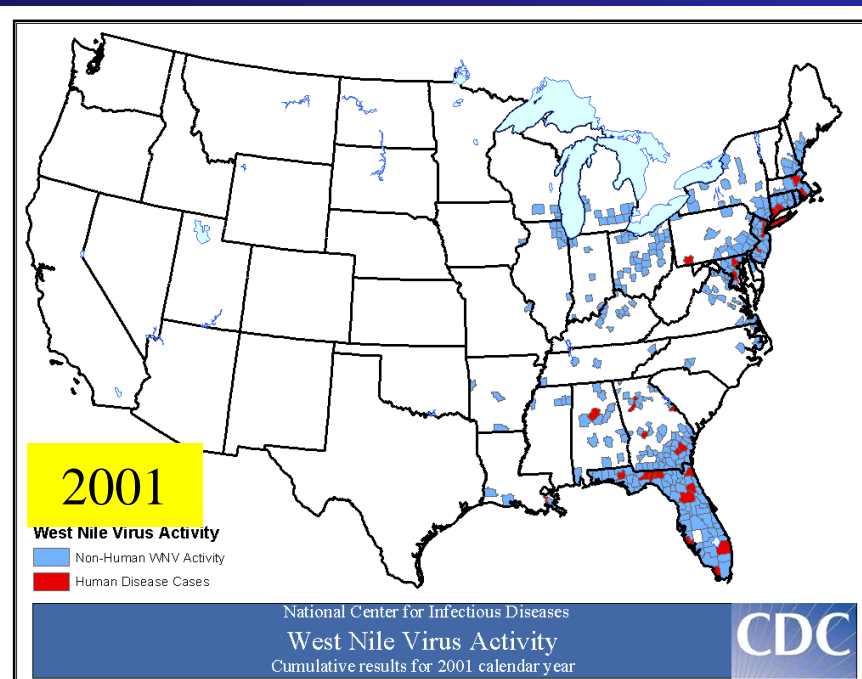
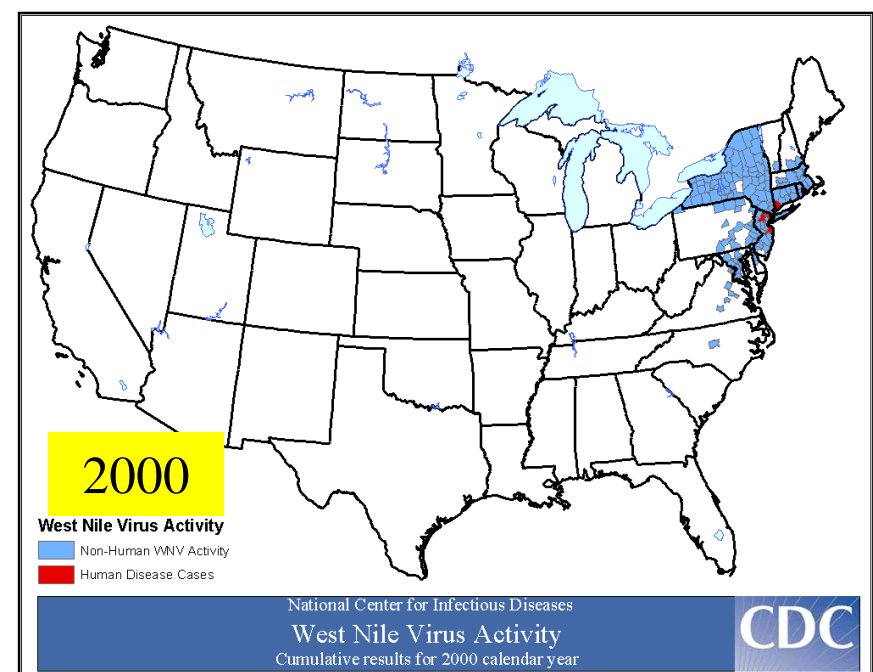
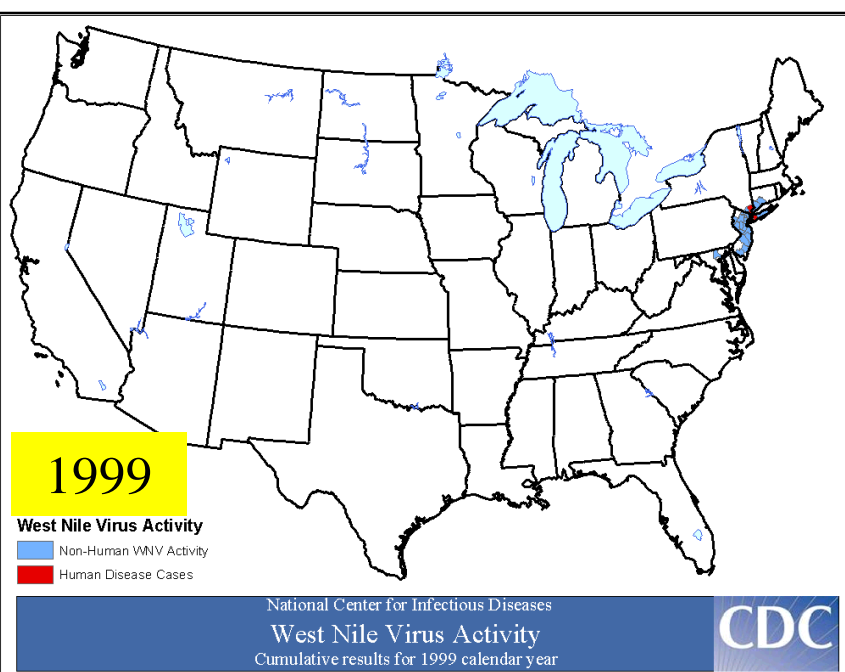
- Leading cause of viral encephalitis in Asia
- 50,000 – 70,000 cases reported annually to WHO
- Primarily in children
- Case fatality 20-30%
- 10,000-15,000 deaths estimated per year
- 30-50% of survivors have significant neurologic sequelae

Geographic range of Japanese encephalitis

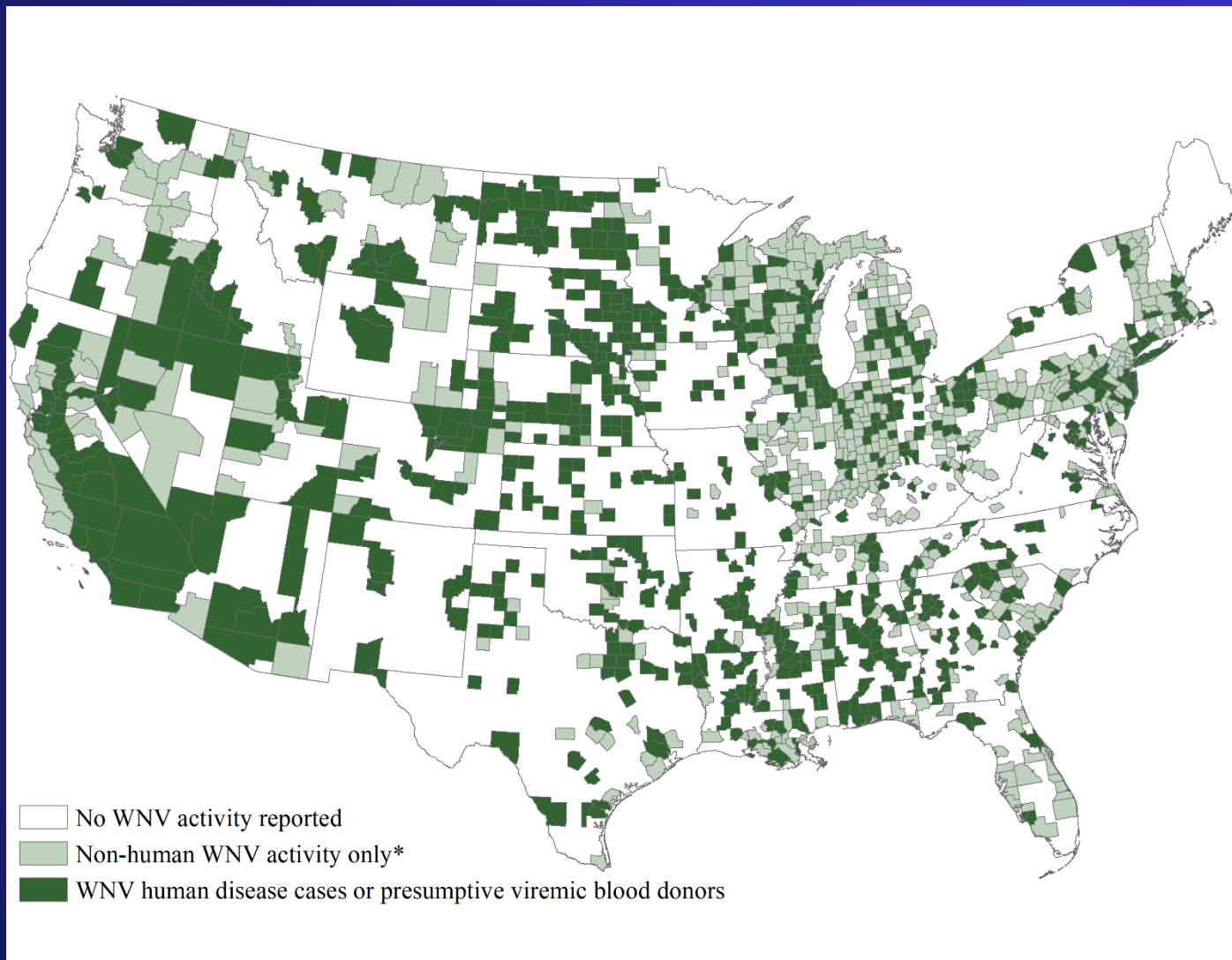


West Nile Virus Epidemiology

- Isolation in 1937, West Nile district of Uganda
- **HISTORICALLY** (e.g., prior to 1996):
 - Infrequent outbreaks
 - Mild, dengue fever-like illness
 - CNS involvement rare
 - Wide distribution throughout Asia, Eastern Europe, Africa, Middle East



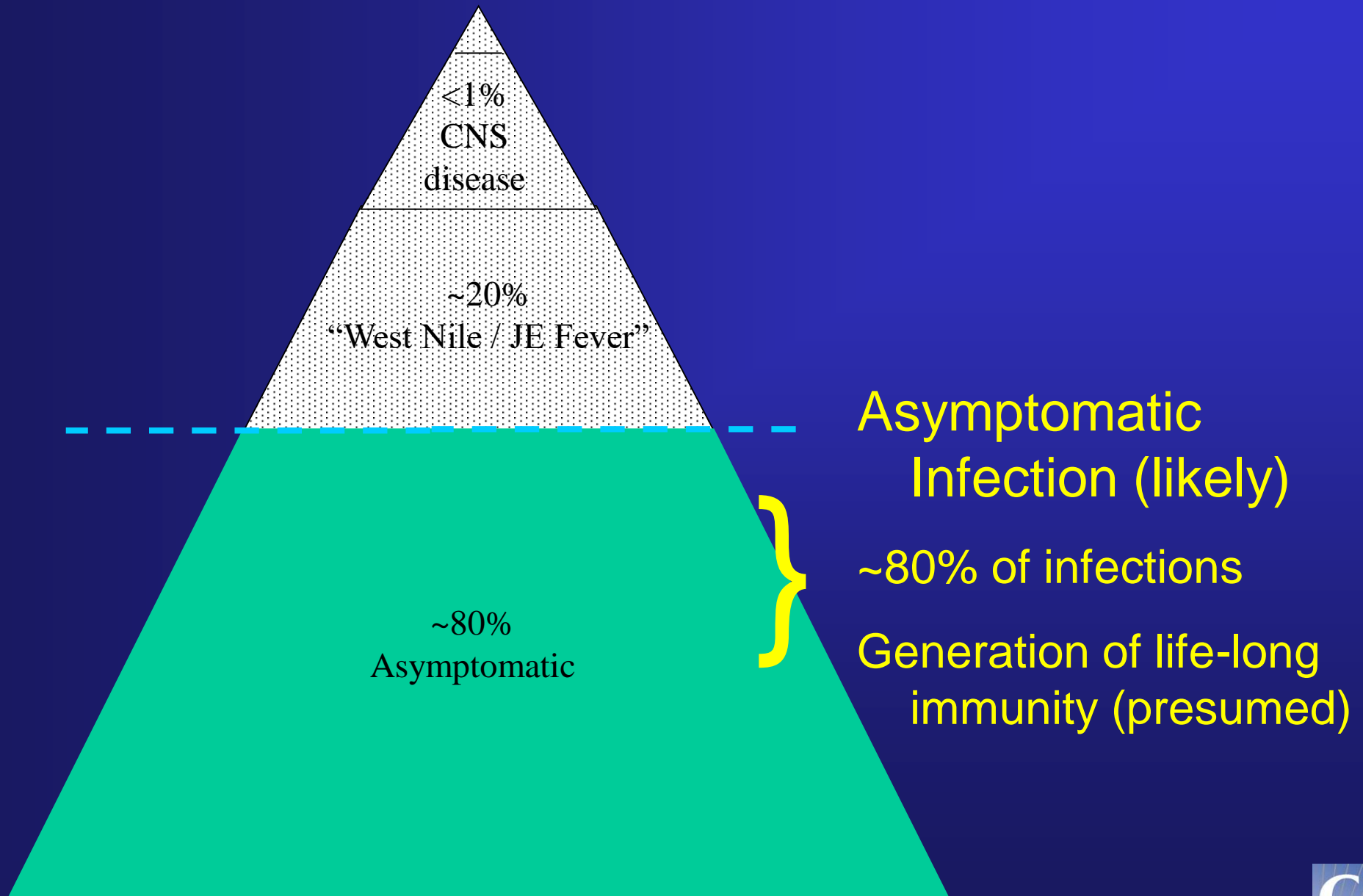
WNV Activity, 2017



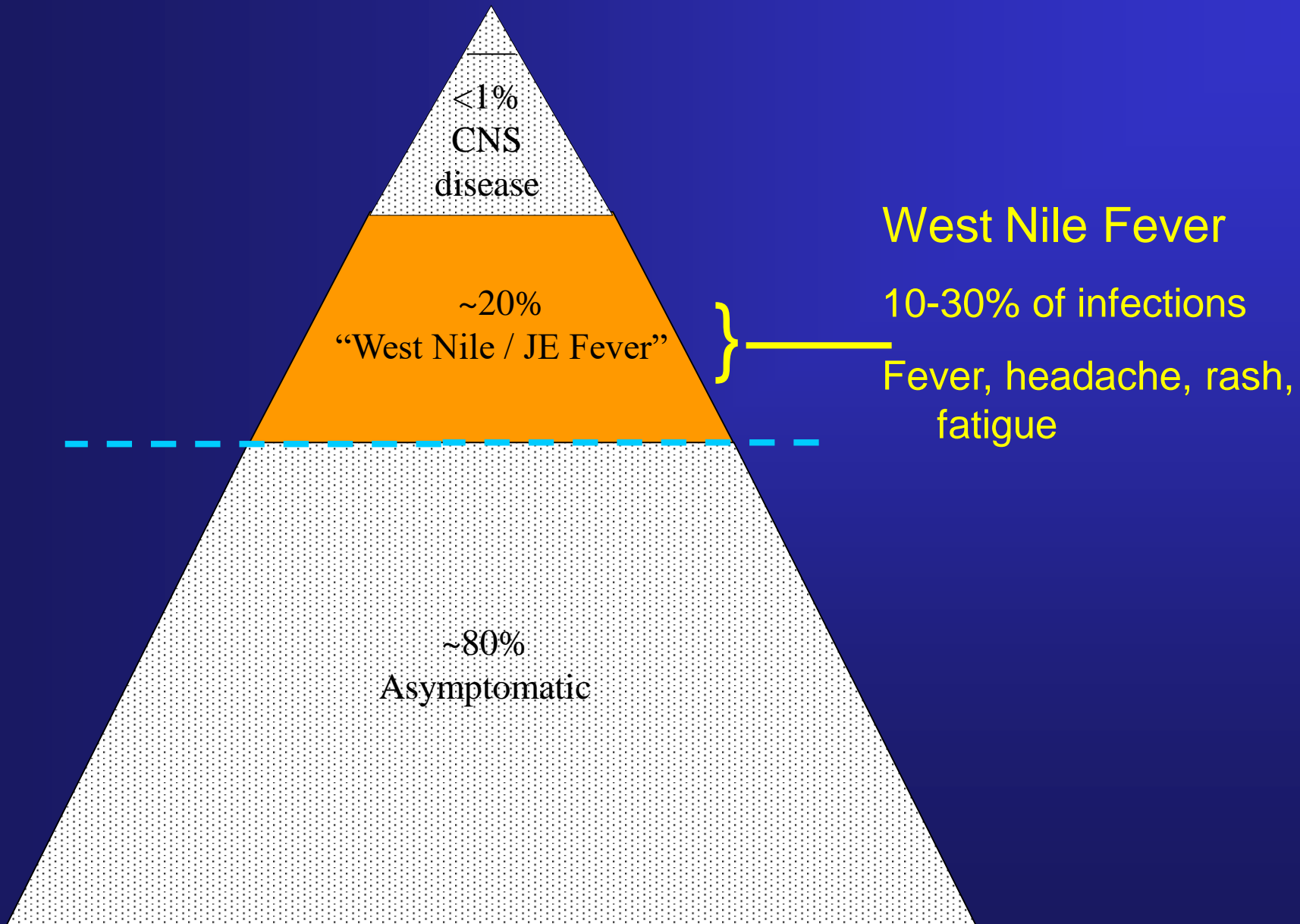
WNV in Europe



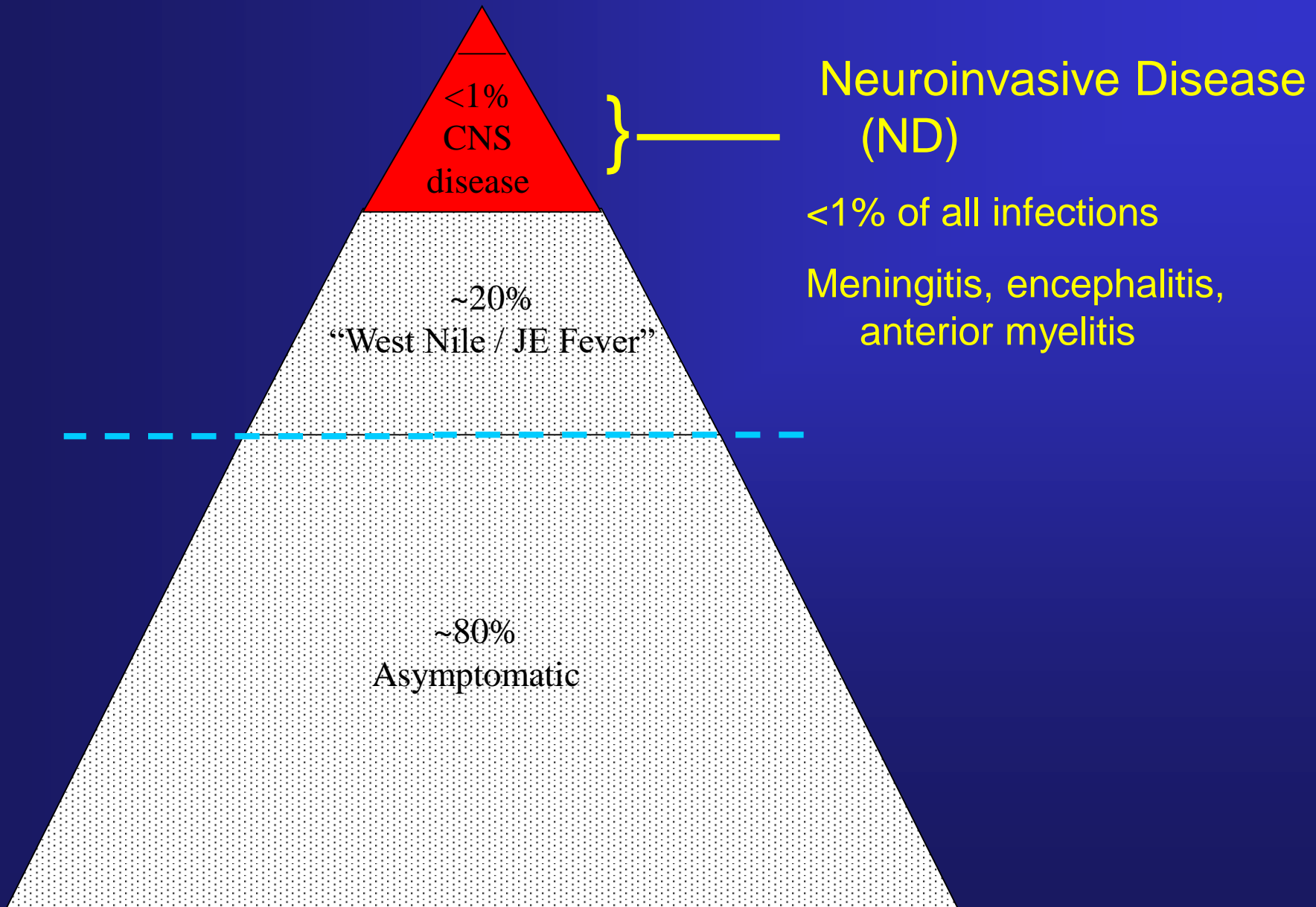
JEV / WNV Human Infection “Iceberg”



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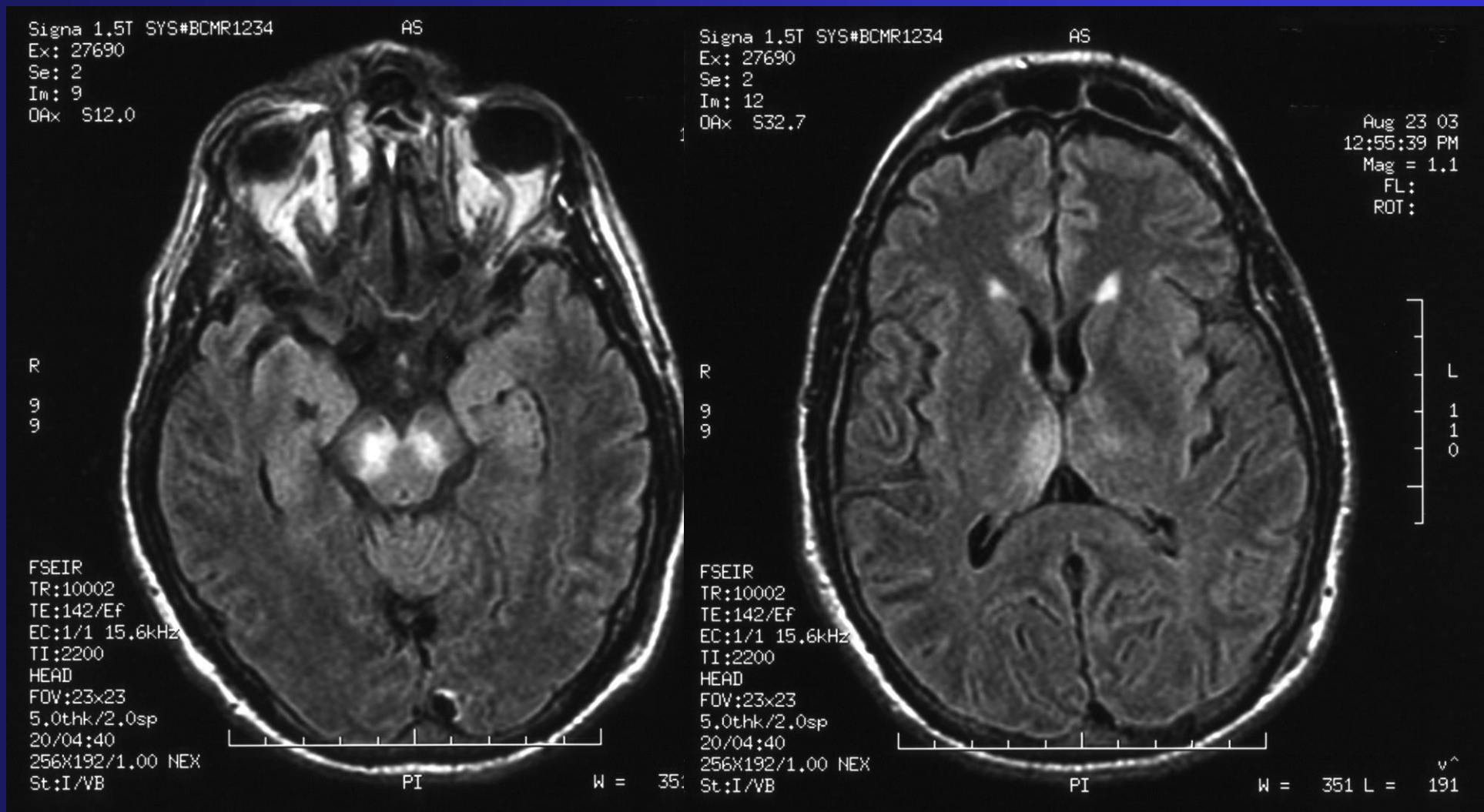
Clinical features of Japanese encephalitis / West Nile Virus

- Fever, headache, vomiting
 - Milder febrile illness, uncomplicated meningitis likely underestimated
- Altered mental status
- Movement disorders (25%)
- Cranial nerve palsies (10%)
- Generalized weakness
 - Anterior myelitis somewhat more common with WNV
- Seizures (more common with JEV)



JEV / WNV and Movement Disorders

- **Tremor**
 - Sometimes associated with other viral infections
 - Coarse; postural / kinetic
 - Occasionally functionally impairing
- **Myoclonus**
 - Quick, uncontrolled muscle twitching
 - Upper extremities, face
 - Bothersome to patients
- **Parkinsonism**
 - “Cogwheel” rigidity, bradykinesia, postural instability
 - Functionally impairing
- **OUTCOMES: JE with poorer prognosis**
 - Ongoing disability: JEV = 50%, WNV = 15-20%



Sejvar et al. JAMA 2003

JEV / WNV Anterior Myelitis

- Involvement of anterior horn cells-- acute, asymmetric paralysis (generally no sensory loss)
- Relatively infrequent - ~12% of cases of WNND; less frequent in JE
- May be younger in age, previously healthy



Dengue 'Encephalitis': the Case For and Against

- Dengue: flavivirus closely related to several other neurotropic viruses (WNV, JEV)
 - WNV, JEV – associated with hundreds of thousands of cases of neurotropic disease worldwide
 - Dengue – relatively few reports, despite its tremendous worldwide illness burden
- Many reports of 'encephalitis' unaccompanied by signs of CNS inflammation, or evidence of CNS viral invasion
- “Neurologic” signs associated with dengue may simply be temporally related; ‘causality’ difficult to substantiate

Challenges to Diagnosis of 'Dengue Encephalitis'

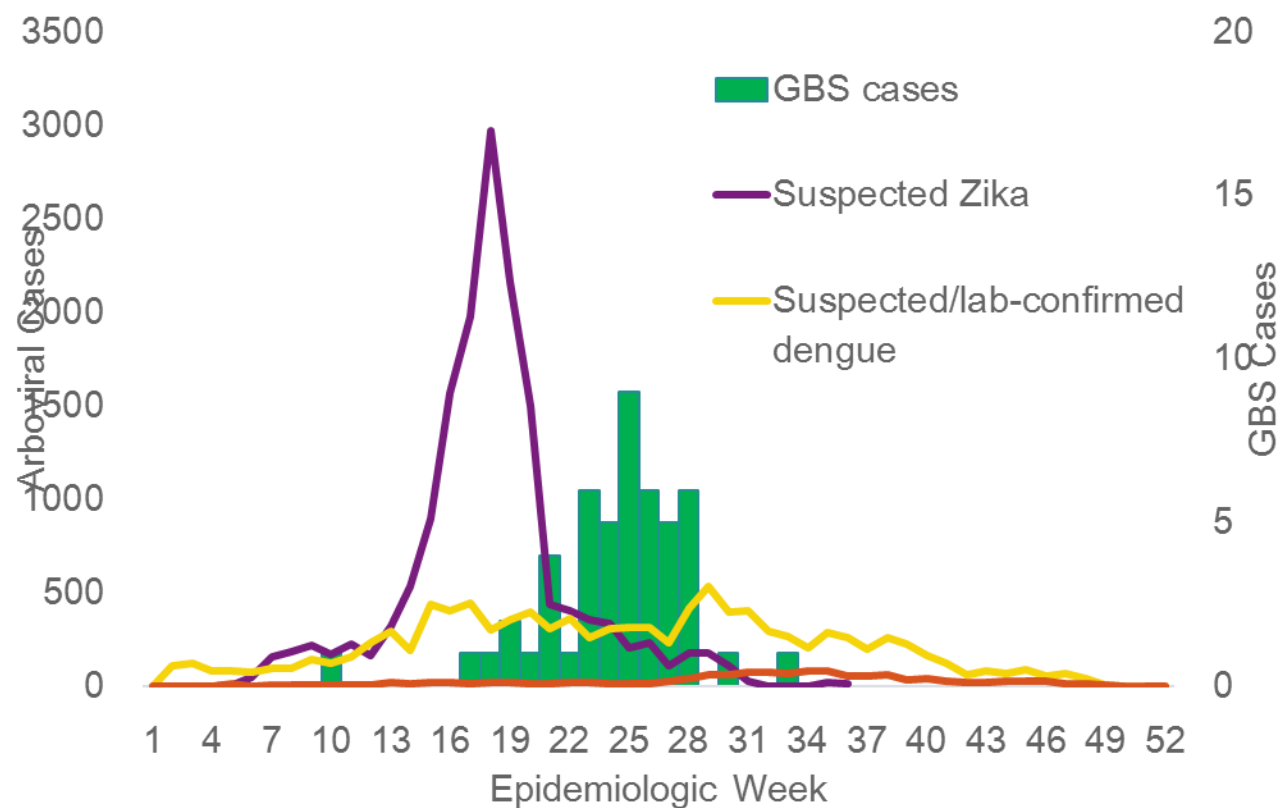
- Lumbar puncture (LP) contraindicated in persons with hemorrhagic illness
- Vascular changes associated with dengue – difficult to differentiate true viral invasion or intrathecal IgM antibody detection from passive transfer across compromised blood-brain barrier
- Advanced neurodiagnostics (LP, neuroimaging, electroencephalography) often unavailable in dengue-endemic areas

Zika Virus

- Human illness identified in 1950's, but associated with sporadic cases of mild rash illness
- 2007 – first sizeable outbreak in Yap
 - 100 cases, no neurologic manifestations
- 2013 – large ZIKV outbreak in French Polynesia
 - 42 Guillain-Barré syndrome (GBS) cases reported, population ~280,000
 - Magnitudes higher than expected incidence of GBS (1.2 cases / 100,000 / year)
 - Many cases testing positive for ZIKV by PCR, MAC-ELISA
- 2015 – Emergence of ZIKV in Brazil
 - Again, increase in GBS in epidemic ZIKV areas



GBS outbreak followed peak in Zika cases in Salvador, Brazil.



Zika Virus and GBS in Americas

- Extremely and unusually high incidence of GBS in areas with Zika virus outbreaks
 - Salvador, Brazil: 7.6 cases / 100,000
 - Barranquilla, Colombia: 5.8 cases / 100,000
 - Puerto Rico: 6.8 / 100,000
- As of November 2018, at least 12 Central/South American and Caribbean countries reporting possible increases of GBS following introduction of Zika virus
 - **Some with laboratory evidence of ZIKV infection**
 - **Strong evidence suggesting ZIKV associated with GBS**
 - 'Cause' of GBS



Zika Virus and Other Neurologic Manifestations

- Anecdotal reports of other neurologic manifestations of ZIKV illness

Meningitis, encephalitis, myelitis, optic neuritis

Generally isolated case reports or small case clusters; difficult to discern from background

Nothing of magnitude seen with GBS

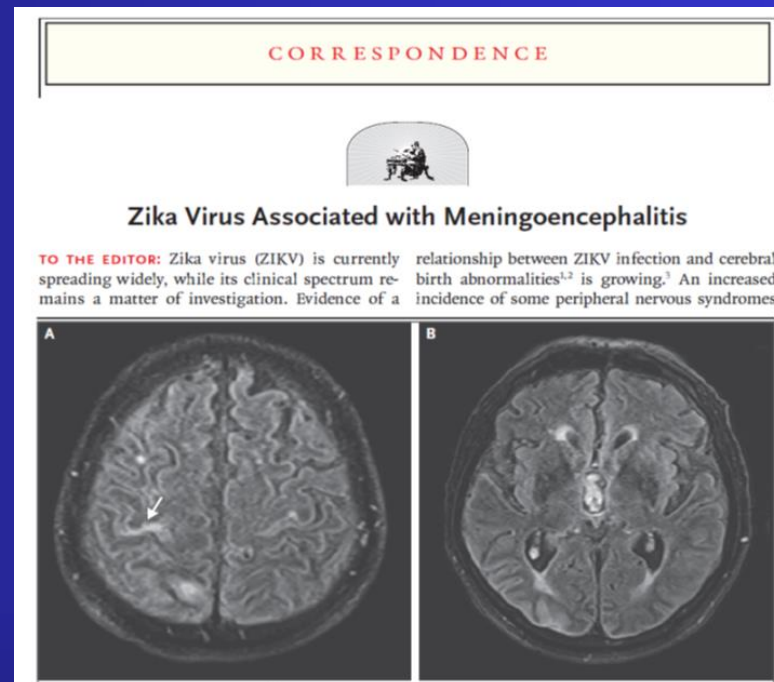
Possible association may become clear with time

- ZIKV as 'neurotropic' virus??

GBS: immune-mediated syndrome, not due to direct viral neuroinvasion

ZIKV Congenital Malformations: Fetal brain is 'different'; no evidence of inflammation in ZIKV – associated congenital anomalies

ZIKV does not 'appear' to have same neurotropism as some other flaviviruses



Case Report

Acute myelitis due to Zika virus infection

Sylvie Mécharles, Cécile Hermann, Pascale Poullain, Tuan-Huy Tran, Nathalie Deschamps, Grégory Mathon, Anne Landais, Sébastien Breurec, Annie Lannuzel

In January, 2016, a 15-year-old girl with a history only of an ovarian cyst was admitted to hospital in Pointe-à-Pitre, Guadeloupe, with left hemiparesis. 7 days previously she had presented to the emergency department with left arm pain, frontal headaches, and conjunctival hyperemia, but

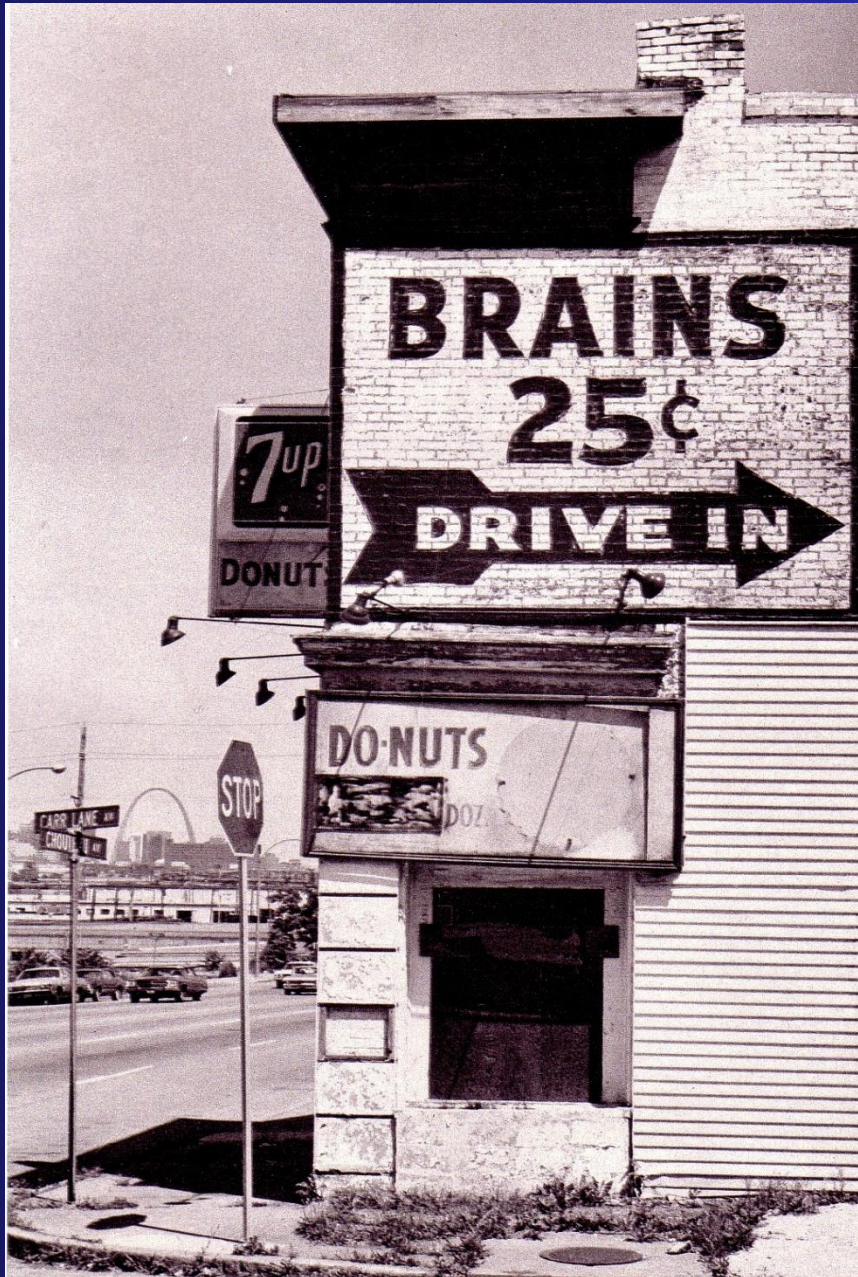
myelitis suggests that this virus might be neurotropic. In addition to the usual clinical picture of myelitis she had severe pain. Absence of intrathecal immunoglobulins and normal brain MRI excluded acute disseminated encephalomyelitis. The neurotropic of flaviviruses such



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Service de Neurologie

Tick-Borne Encephalitis Virus

- Vectored by *Ixodes* ticks
 - Rarely, transmission from consumption of unpasteurized dairy products
- Geographic distribution temperate areas of Europe and Asia
- Two important genotypes – European and Far Eastern
- 2 / 3 of infections asymptomatic
- Clinical illness
 - European – biphasic course in 20 – 30%; initial mild illness with fever, myalgias, headache, then ~1 week asymptomatic period, followed by neurologic illness – encephalitis, meningitis, myelitis
 - Mortality 0.5 – 2%; neurologic sequelae in 10%
 - Far Eastern – more severe illness, monophasic
 - Mortality 20%; higher rates of neurologic sequelae
- Vaccine - adult and pediatric formulations; licensed in Europe, Canada



Thank You