

**Project:** Ghana Emergency Medicine Collaborative

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# Central Nervous System INFECTIONS (NOT MENINGITIS)

## Cerebrospinal Fluid DISORDERS

Geetika Gupta, MD

May 18, 2011

## **CNS Infections**

- Meningitis
  - Inflammation of the pia and arachnoid
- Encephalitis
  - Inflammation of the brain
- Brain Abscess
  - Usually encapsulated structure with inflammatory cells and pathogen
- Parameningeal Infections

## **CSF Disorders**

- aqueductal stenosis
- tumoral hydrocephalus
- isolated ventricles
- arachnoid cysts
- multiloculated hydrocephalus
- fourth ventricular outlet obstructions

# Differential diagnosis of infections of the CNS

## Meningitis

### Bacterial

Aseptic: infections with a negative Gram stain and culture or noninfectious causes

#### Infections

##### Viral

Bacteria with negative Gram stain and culture: bacteria with negative Gram stain with usual stain and technique and not culturable with usual media

Organisms not able to grow on routine culture media: Mycobacteria, Treponema (syphilis), Mycoplasma (tuberculosis), Chlamydia, Borrelia burgdorferi (Lyme disease)

##### Nonviral

##### Fungal

Meningeal inflammation secondary to adjacent pyogenic infections

Eosinophilic meningitis (parasitic CNS infections)

#### Noninfectious cause

Neoplasms (meningeal carcinomatosis or leptomeningeal carcinomatosis)

Systemic diseases that affect the CNS: systemic lupus erythematosus, sarcoidosis,

Drugs (intrathecal chemotherapy)

## Encephalitis

### Infections

Viral (WNV, EEE, H1N1, WEE, HSV, St Louis, EBV, HZV, CMV)

#### Nonviral

Bacteria: bacteria with negative Gram stain and culture

Rickettsia

Fungi

Protozoa

Helminths

Borrelia

## Brain abscess

### Bacterial

### Nonbacterial

Fungi

Protozoa

Parasites

## Parameningeal infections

Brain abscess

Subdural empyema

Epidural abscess

# Other considerations

Acute disseminated encephalomyelitis  
(ADEM)

CNS disease

Hemorrhage

Strokes

Venous thrombosis

Aneurysms

Migraines/Other headaches

Hematologic disorders

Hyperviscosity syndromes

Polycythemia

Leukocytosis/leukostasis

Platelet disorders

Thrombocytosis

Coagulopathy

Encephalopathies

Metabolic

Hypoxia

Ischemia

Intoxications

Organ dysfunction

Systemic infection

Delirium/dementia

Seizures

Nonconvulsive status epilepticus

Legionnaire disease

Posttransplant lymphoproliferative disorder

Prion diseases

Epstein-Barr virus

Posterior fossa syndrome

# Case

13 yo male arrives in ED with chief complaint of vomiting and fever for 2 days.

In ED patient has labs, CT and LP.

Diagnosis: Viral meningitis

Disposition: Home with supportive therapy

Outcome: Patient died 2 days later

Autopsy: meningoencephalitis

Etiology.....

# Arboviral Encephalitis

Geetika Gupta, MD

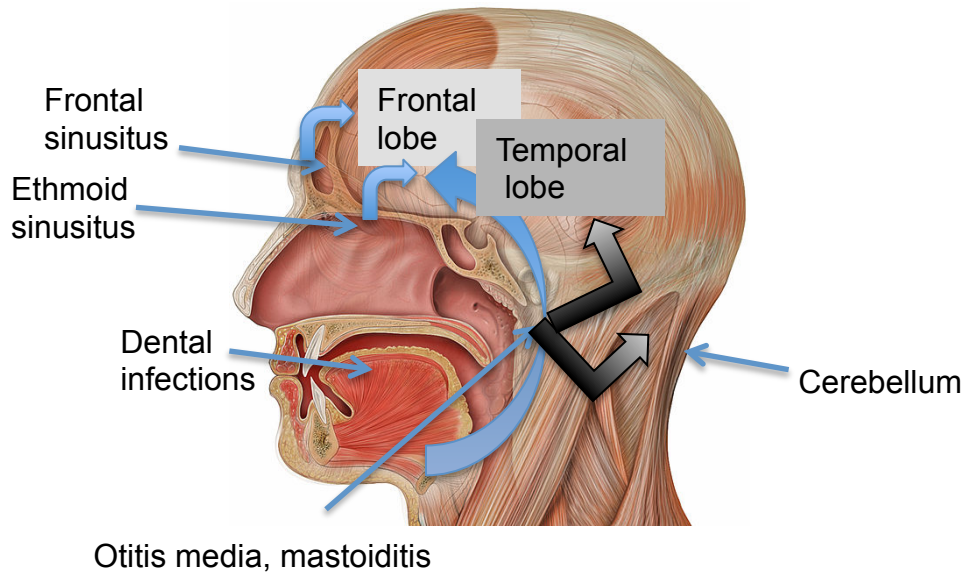
University of Michigan Health System  
St Joseph Mercy Health System



# Objective

- Understand arboviral encephalitis as it pertains to EM
- Questions
  1. Are there specific clinical features to be considered for *arboviral* encephalitis
  2. Are there any laboratory/ radiology studies *from the ED that are crucial*
  3. Does *specific* management change outcome
  4. Upcoming considerations

## Direct Spread

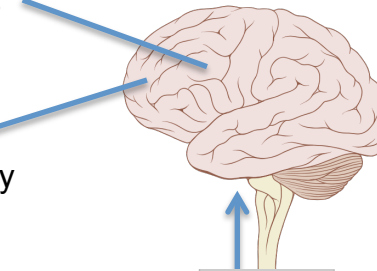


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## Hematogenous Seeding

Brain abscess

Middle cerebral artery



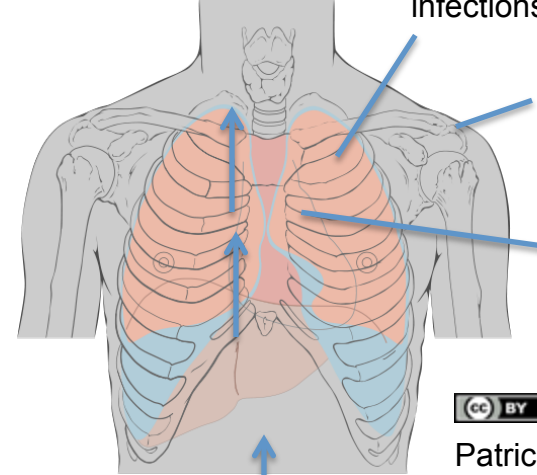


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Chronic pulmonary infections

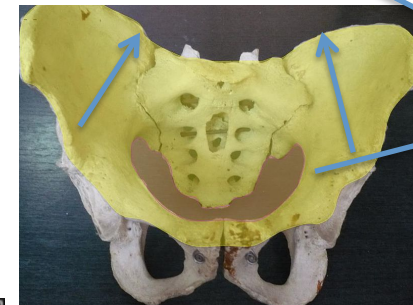
Skin infections

Endocarditis  
Congenital heart disease





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Hematogenous via  
arthropod vector bite  
(ex. arboviruses) into  
the bloodstream



Lee Ostrom,  
[Wikimedia Commons](#)



Alvesgaspar, [Wikimedia Commons](#)



Inhalation  
(ex. LCMV, *C.  
psittacosis*)  
into the  
respiratory  
system



Tompw, [Wikimedia Commons](#)



National Institutes of Health,  
[Wikimedia Commons](#)

Neutral via animal vector bite  
(ex. rabies virus) into the skin

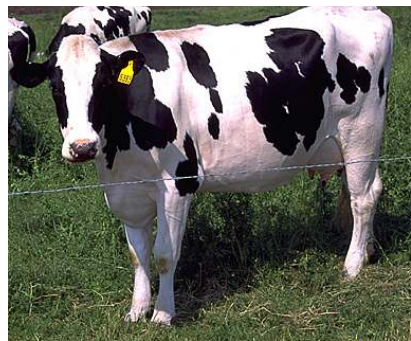


Latorilla,  
[Wikimedia Commons](#)



CDC/Barbara Andrews  
[Wikimedia Commons](#)

Gastrointestinal  
via infected dairy  
food into the  
gastrointestinal  
system (ex.  
brucellosis)



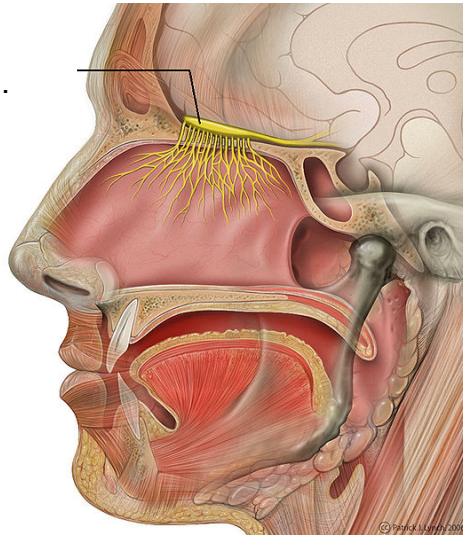
United States Department of Agriculture,  
[Wikimedia Commons](#)



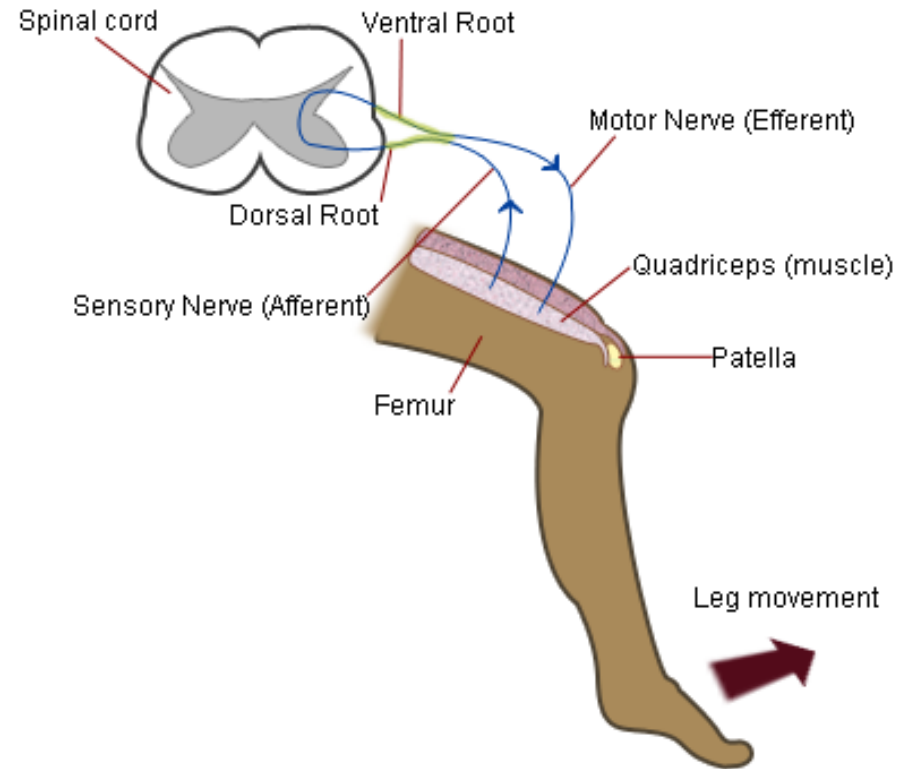
Tompw, [Wikimedia Commons](#)

# HSV and Rabies Virus

Herpes simplex virus via olfactory tract or trigeminal n.



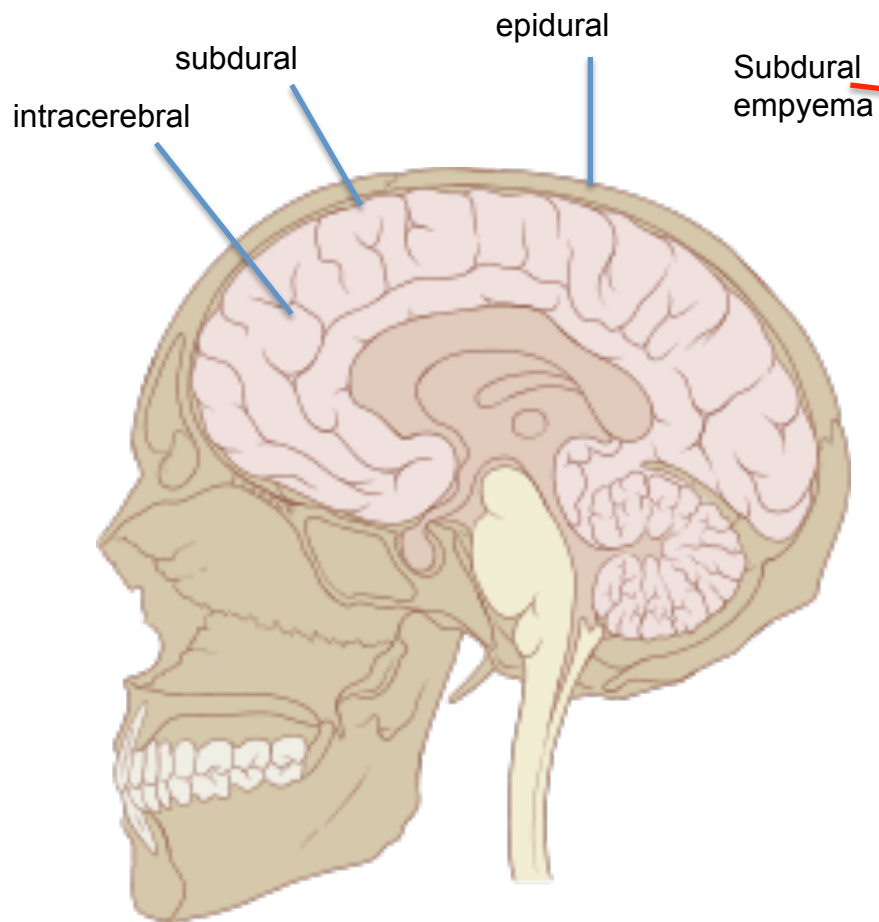
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Rabies viruses transmission via peripheral wound to dorsal root ganglion to brain

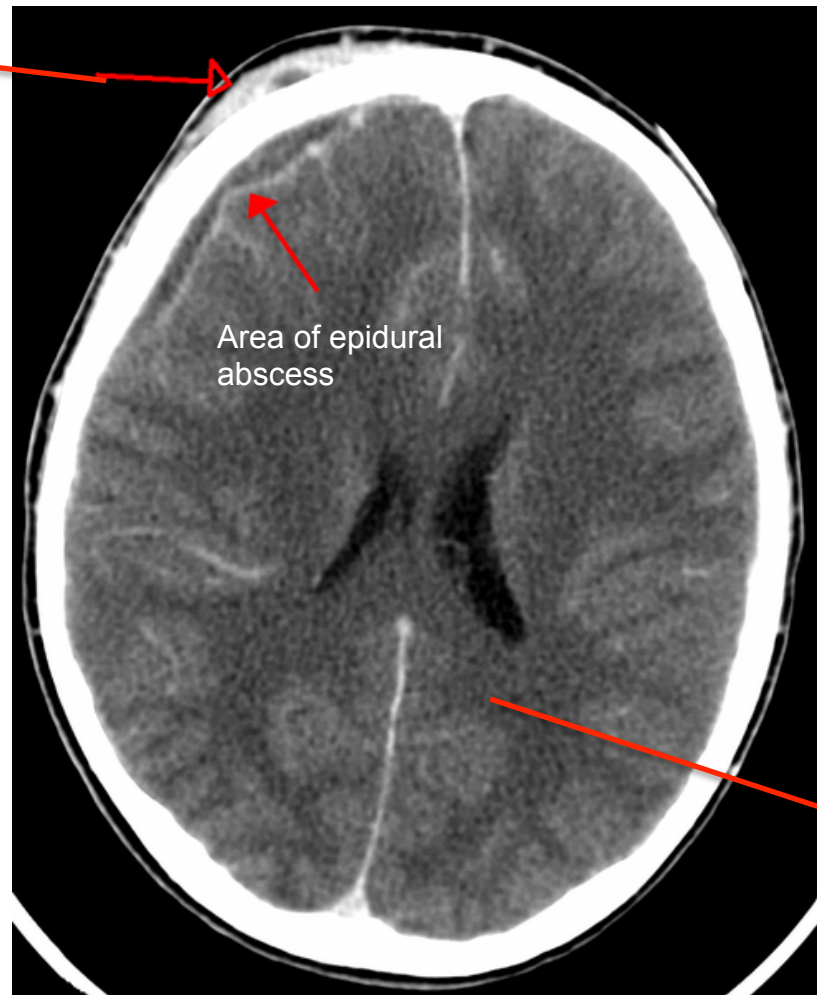


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Subdural  
empyema



James Heilman,  
[Wikimedia Commons](#)

# Pathophysiology


- Cross the blood brain barrier
  - Hematogenous, direct, neuronal
    - transport across the cell by endocytosis (transcellular passage) (eg, meningococci or Streptococcus pneumococci)
    - transport between the cells (paracellular passage) can occur after endothelial injury or following disruption of the intracellular endothelial connections
    - within WBCs during diapedesis.
  - During certain disease states, the endothelial cells become damaged and the blood-brain barrier becomes porous, allowing pathogens to transverse the blood-CSF barrier
- Replicate
- Activate inflammatory cascade via brain cells
  - Release of cytokines → breaks down the blood brain barrier
  - Activation of inflammatory mediators (eg, nitric oxide [NO], reactive oxygen species [ROS], matrix metalloproteinases [MMPs])
  - Chemokines → Recruitment of white blood cells (WBCs) to the site of infection
  - Cytotoxic events

- Damage to CNS
  - By direct invasion
  - By inflammatory cascade
- Inflammatory mediators:
  - Direct neurotoxicity
  - Increase vascular permeability
  - Increase cerebral blood flow
- Physiologic events
  - Cerebral edema
    - Vasogenic edema: loss of blood-brain barrier
    - Cytotoxic edema: from cellular swelling and destruction
    - Obstruction to CSF outflow at arachnoid villi
  - Cerebral hypoperfusion from local vascular inflammation and/or thrombosis
  - Loss of autoregulation
- ENCEPHALITIS
  - Involvement of the tissue itself
  - Ischemic lesions associated with vasculitides



# The Good Ole' Mosquito

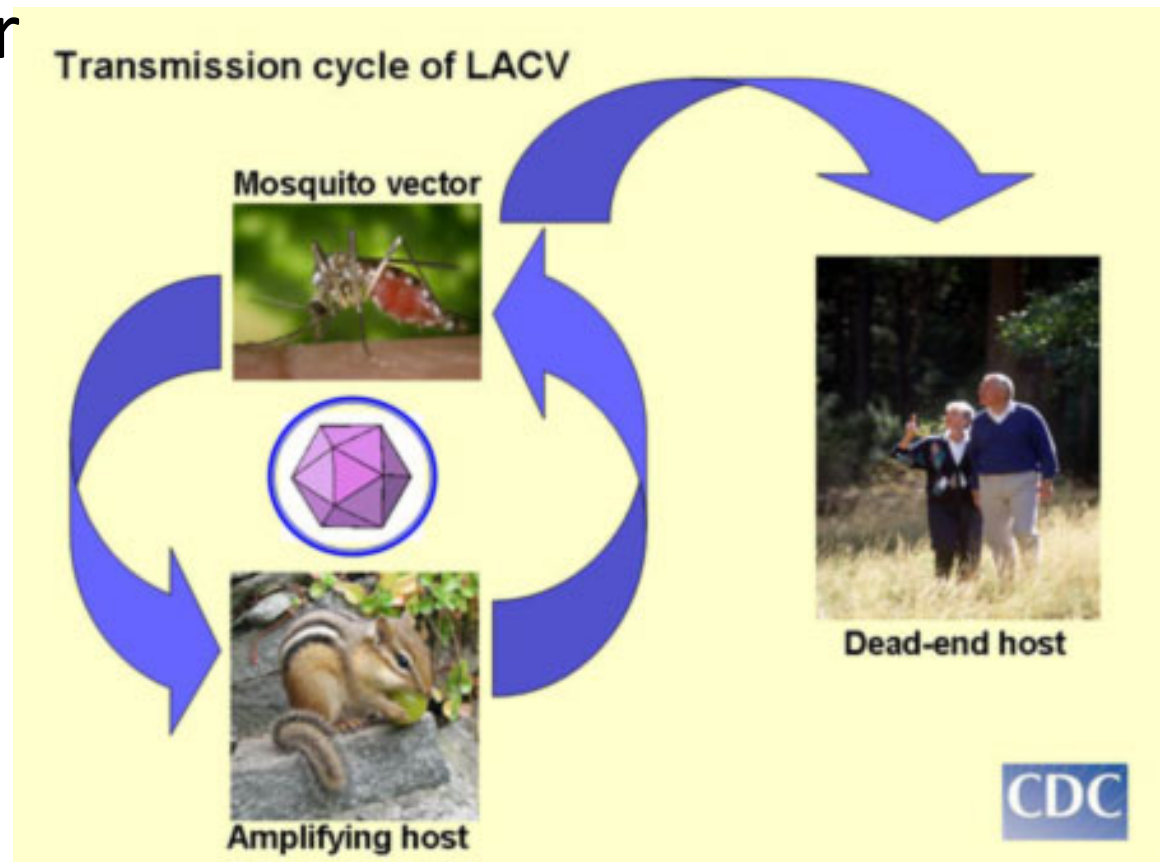


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# Summer is Arriving

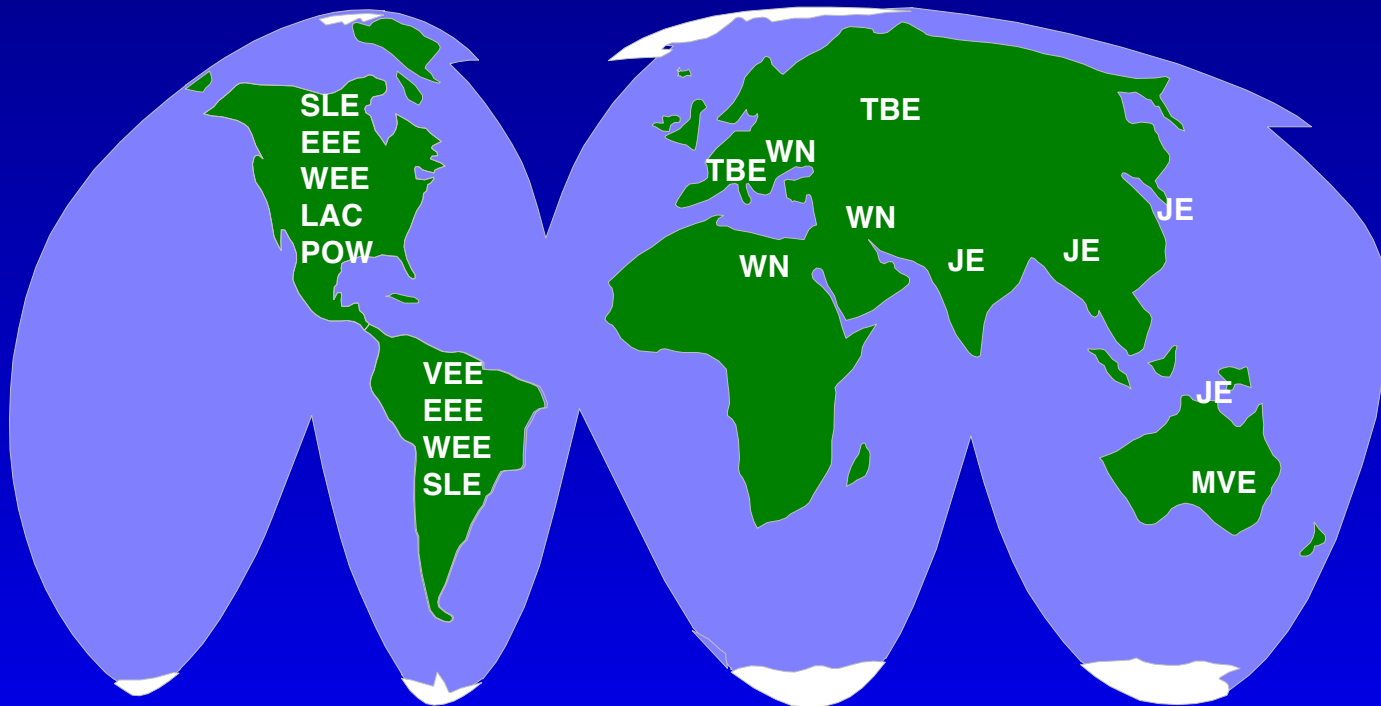
- Muggy weather
- Standstill water
- Birds, rodents
- Vacation



# Arbovirus

- Eastern Equine Virus
- Western Equine Virus
- St Louis Virus
- La Crosse Encephalitis
- West Nile Virus
- Dengue fever
- Powassan Encephalitis
- Chikungunya
- Yellow Fever
- Nipah Virus

# Worldwide Distribution of Major Arboviral Encephalitides

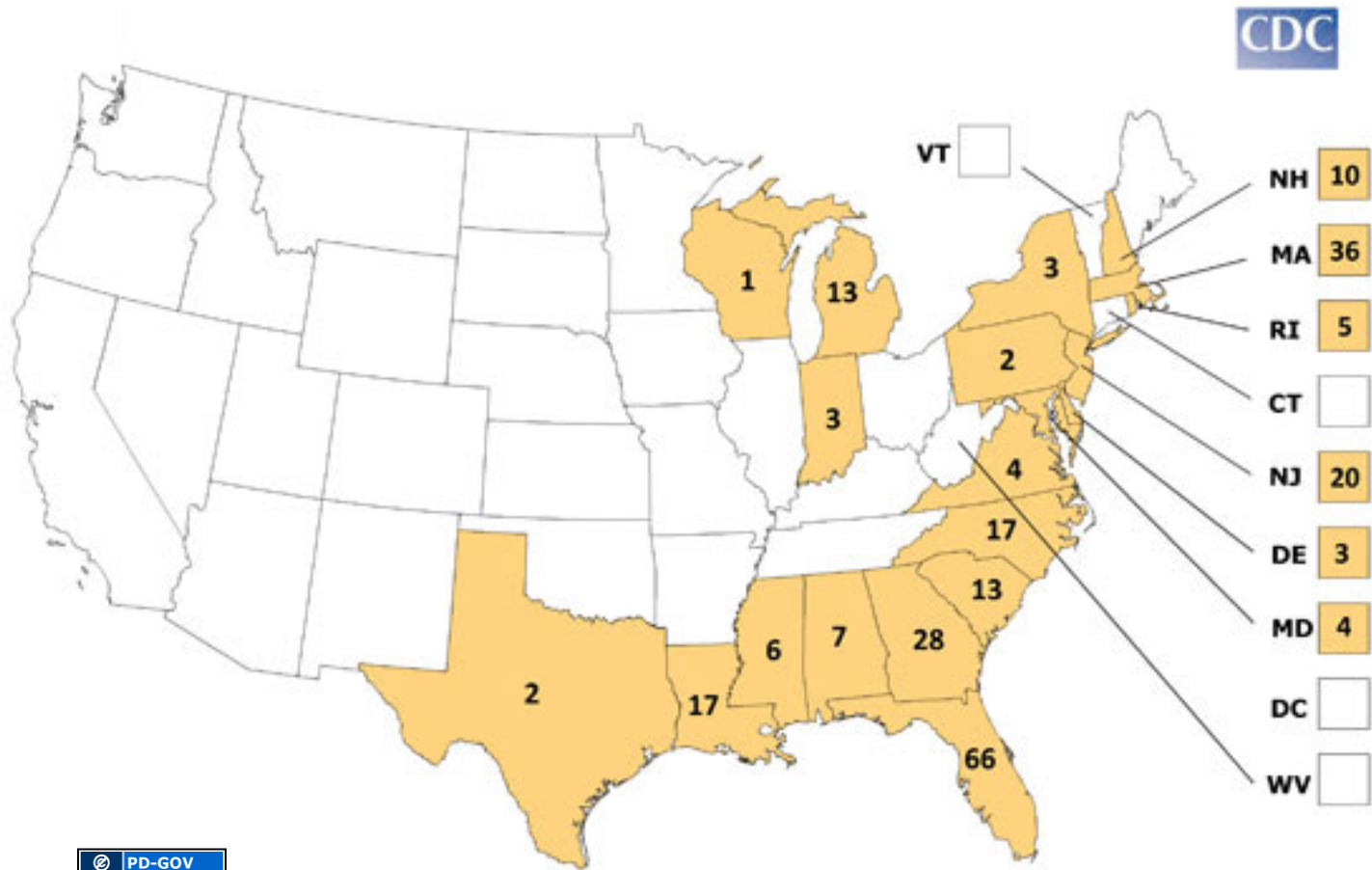


EEE: Eastern equine encephalitis  
JE: Japanese encephalitis  
LAC: LaCrosse encephalitis  
MVE: Murray Valley encephalitis  
POW: Powassan encephalitis

SLE: St. Louis encephalitis  
TBE: Tick-borne encephalitis  
WEE: Western equine encephalitis  
WN: West Nile encephalitis  
VEE: Venezuelan equine encephalitis

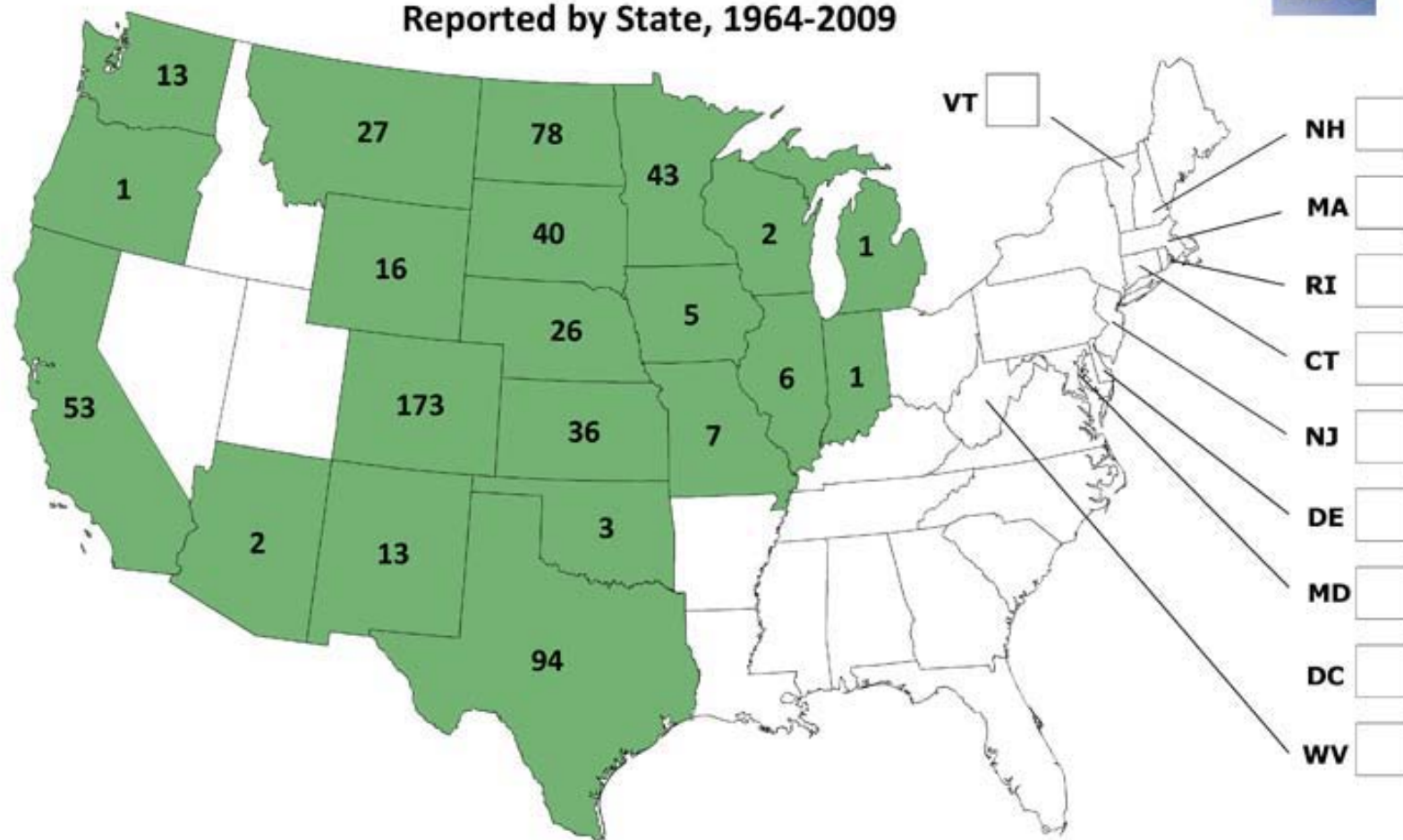
**CDC**  
Centers for Disease Control  
and Prevention

EEEV by STATE  
1964 – 2009  
182 cases



Centers for Disease Control

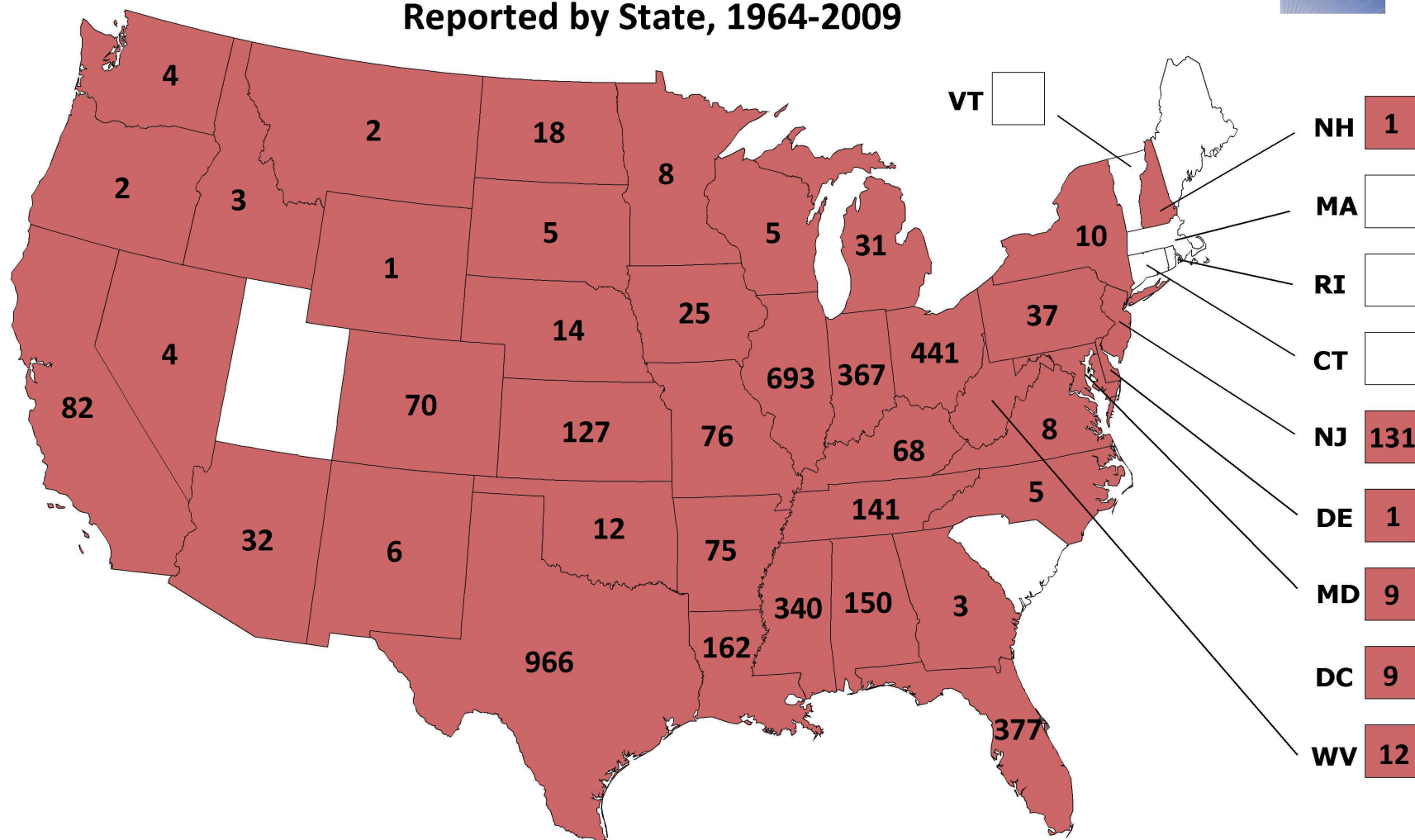
# Western Equine Encephalitis Virus Neuroinvasive Disease Cases Reported by State, 1964-2009



Centers for Disease Control

640 cases

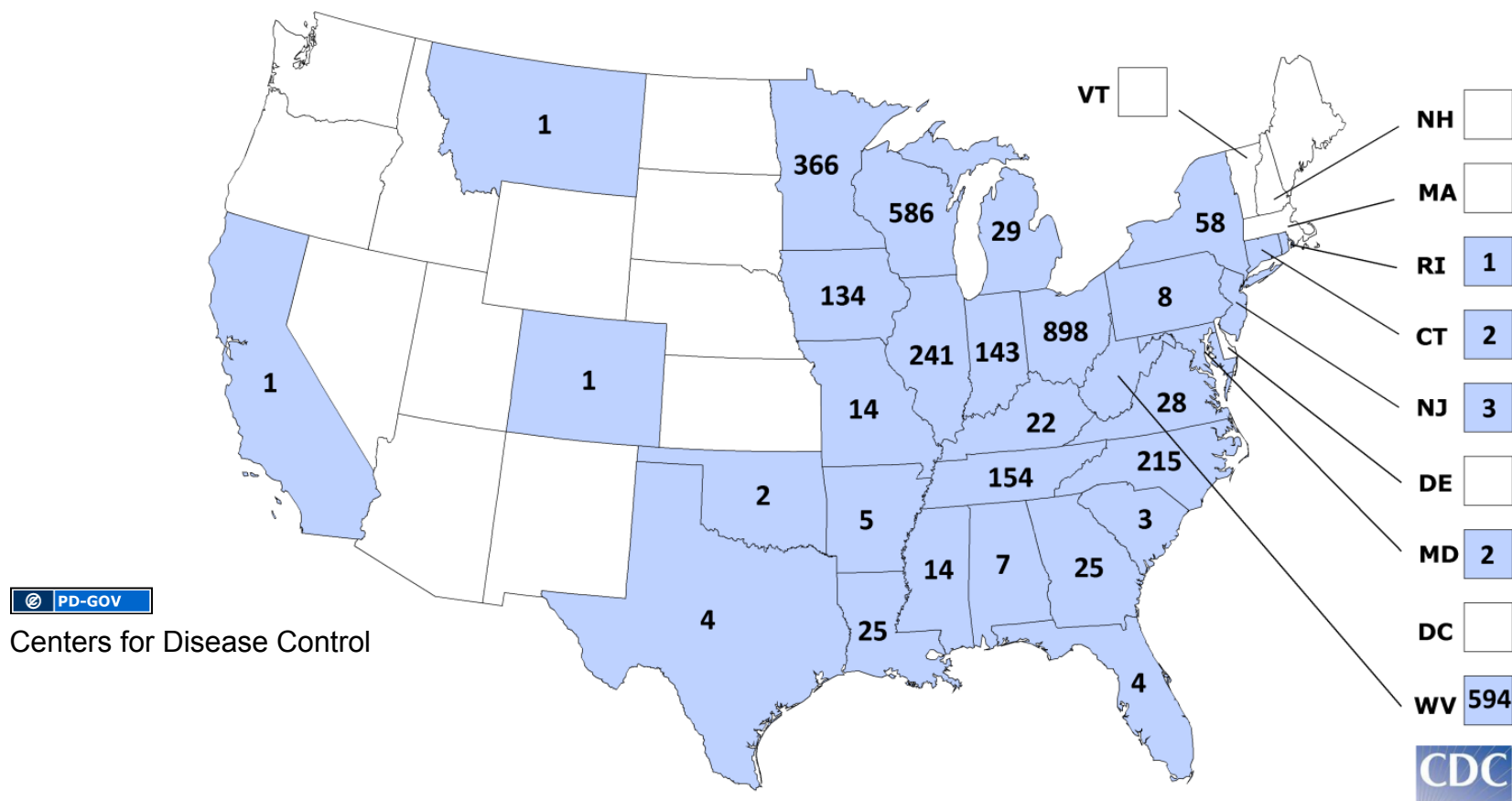
# St. Louis Encephalitis Virus Neuroinvasive Disease Cases Reported by State, 1964-2009



Centers for Disease Control

4482 cases

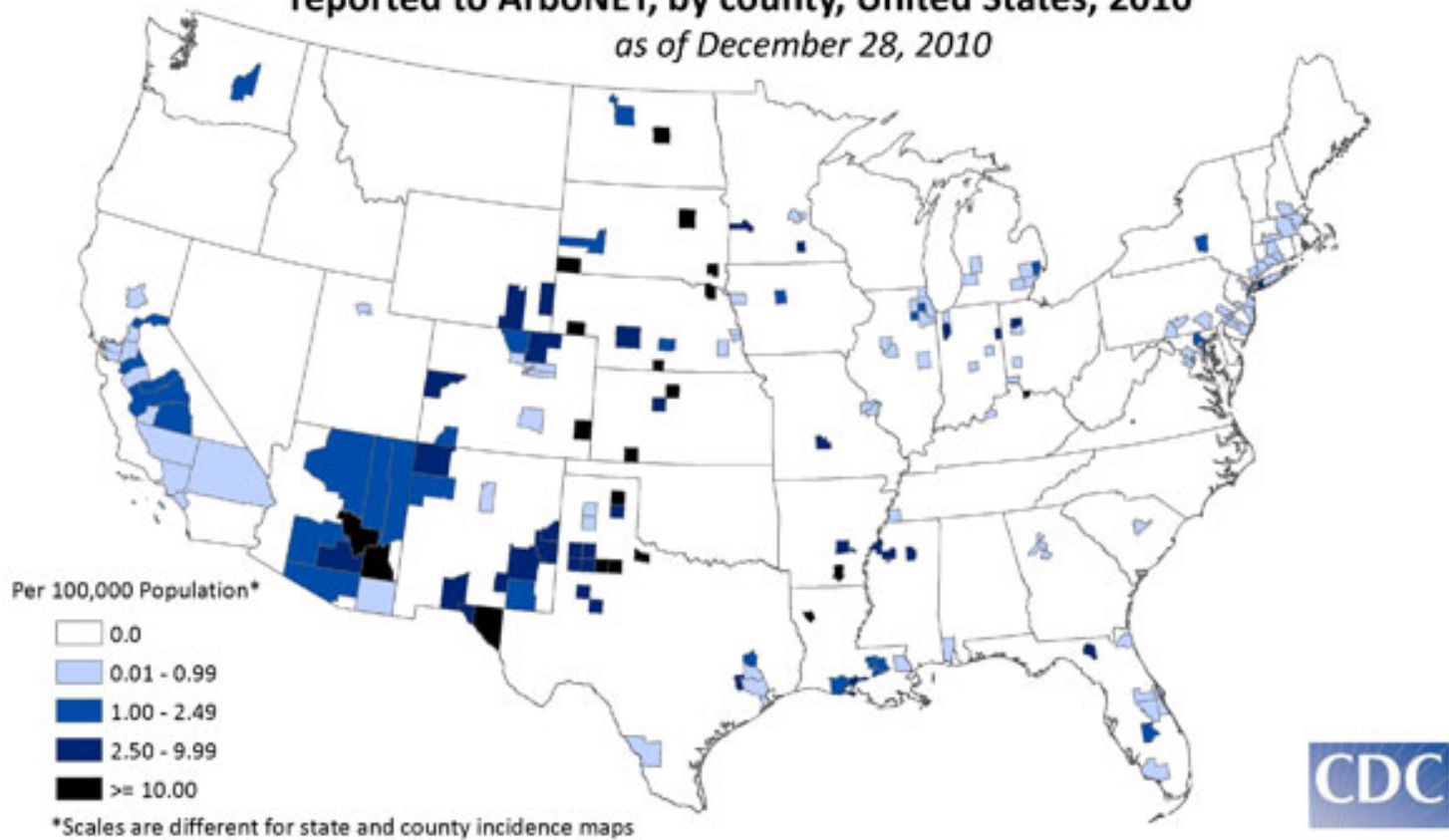
# California Serogroup Virus Neuroinvasive Disease Cases\* Reported by State, 1964-2009





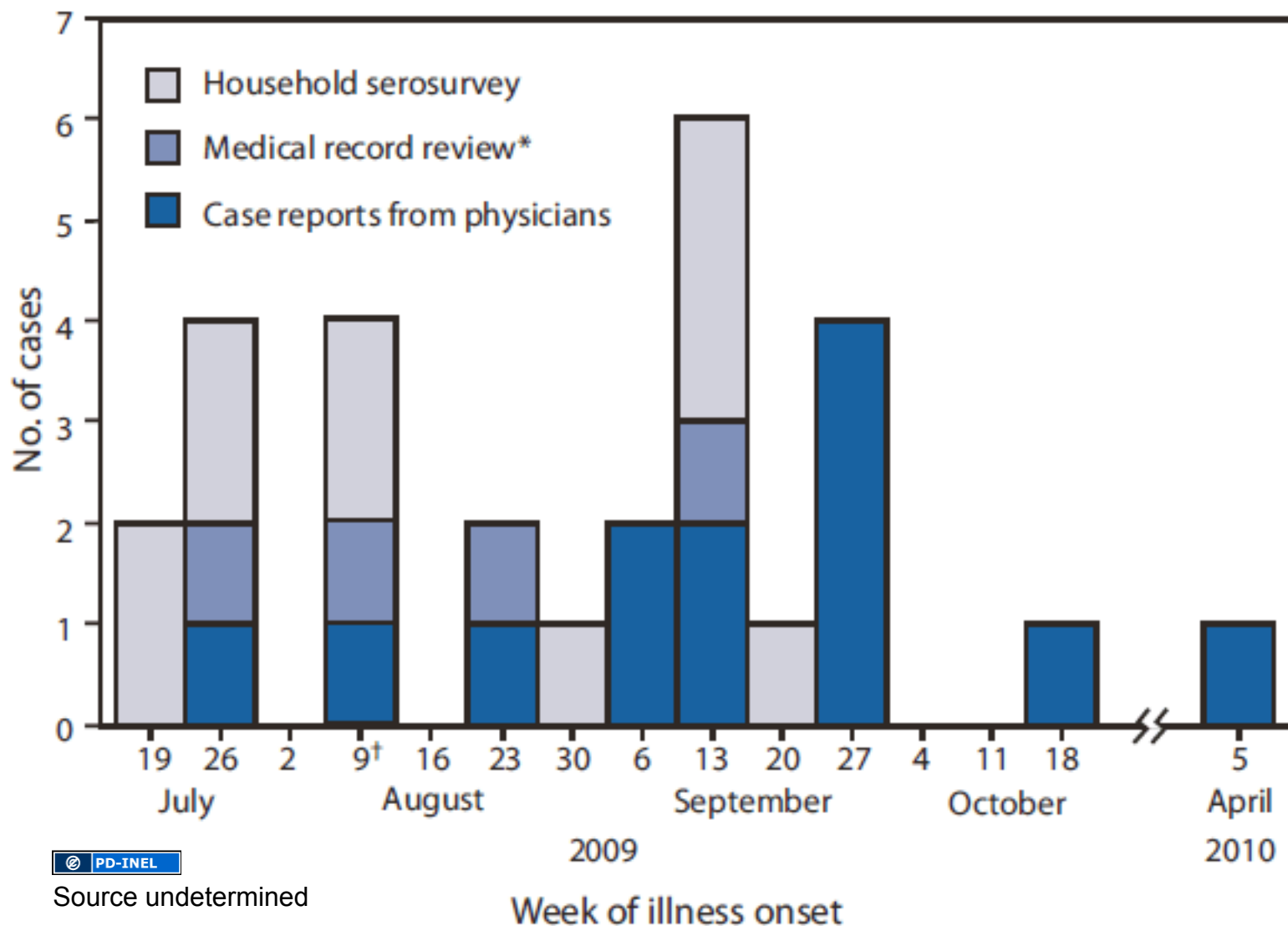
**West Nile virus (WNV) neuroinvasive disease incidence  
reported to ArboNET, by county, United States, 2010**

*as of December 28, 2010*





# Dengue Encephalitis in Key West



# Dengue Symptoms

<b>Symptoms</b>	<b>number</b>	<b>percentage</b>
Fever	28	(100)
Headache	22	(79)
Myalgia	23	(82)
Arthralgia	18	(64)
Eye pain	14	(50)
Rash	15	(54)
Bleeding	6	(21)

\* Percentages might not add to 100% because of rounding.

# Arboreal Encephalitis

- Case per year: 150- 3000
- Sequele
  - Greatest with EEE
- Annual Cost
  - \$150 million including vector control and surveillance

- History
  - Geographic and seasonal factors.
  - Foreign travel or migration history.
  - Contact with animals (for example, farm house) or insect bites.
  - Immune status.
  - Occupation.

## Are there specific clinical features to be considered for Encephalitis ?

Signs and symptoms "at presentation"\* for all hospitalised adult encephalitis cases in three Hunter New England hospitals, Australia, July 1998-December 2007

Symptoms at presentation		Cases, n = 74 (%)	
Fever	57 (77.0%)	Focal neurological signs	23 (31.1%)
Altered Consciousness State (ACS) including irritability and/or coma	51 (68.9%)	Seizures	19 (25.7%)
Headache	46 (62.1%)	Photophobia	13 (17.6%)
Encephalitis "triad"(headache, fever, ACS)	26 (35.1%)	Neck stiffness	11 (14.9%)
Lethargy	24 (32.4%)	Abnormal behaviour	9 (12.1%)
		Rash	7 (9.5%)
		Myalgia and/or arthralgia	2 (2.7%)

\*a sign/symptom was considered to be present "at presentation" if the patient/next of kin reported to have had the sign/symptom in the 24 hours prior to presentation or if it was documented in the patient record during the first 48 hours of their admission.

- CBC, Chemistry, LFT, ESR, CRP, U/A, CXR
- CT Brain
- LP
  - Specific serology ELISA, PCR

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- MRI
- EEG
- PET scan
- PCR studies

# Serum

- In general
  - Relative lymphocytosis
- WNV: anemia, leukopenia, thrombocytopenia
- Rickettsial and hemorrhagic viral infections
  - Leukopenia and thrombocytopenia
- IgM Arbovirus testing
  - Results can take 2 weeks

# Is CT required before LP?

- It is preferred
  - CT scan of the head is used to identify patients at higher risk for herniation with intracranial pathology such as hydrocephalus, mass lesions, cerebral edema, and midline brain shift.
  - Herniation from LP requires both increased ICP and obstruction to free CSF flow and equilibration
- Hasbun R, Abrahams J, Jekel J, et al. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med 2001;345(24): 1727–33.
    - 234 patients....
      - Age greater than 60,
      - seizure in the past 1 week,
      - immunocompromise,
      - history of CNS disease,
      - altered mental status, gaze or facial palsy, abnormal language
      - inability to answer two questions or follow two commands,
      - visual field abnormalities, and
      - arm or leg drift
    - 96 patients (41 %) did not have these features and the CT was abnormal 3%- 9% of the time
      - 1 out of 11 patients can have an abnormal CT



# LP and the needle

- Atraumatic needles significantly reduced the incidence of moderate to severe headache and the need for medical interventions after diagnostic lumbar punctures, but they were associated with a higher failure rate than standard needles
  - **Randomised controlled trial of atraumatic versus standard needles for diagnostic lumbar puncture.**  
**Thomas SR - *BMJ* - 21-OCT-2000; 321(7267): 986-90**
- A noncutting needle should be used for patients at high risk for PDPH, and the smallest gauge needle available should be used for all patients.
  - **Postdural puncture headache and spinal needle design. Metaanalyses.**  
**Halpern S - *Anesthesiology* - 01-DEC-1994; 81(6): 1376-83**

# CSF results

- Bacterial vs Viral
  - > 1000 WBC
  - Low glucose
  - High protein
  - EEEV pleocytosis with predominant neutrophils
  - HSV has high RBC
- Nigrovic LE, Kuppermann N, Macias CG, et al. Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. JAMA 2007;297(1):52–60.
  - 2093 children (serum WBC, CSF WBC, CSF protein, seizure, gram stain)
  - 4% of patients with bacterial meningitis had non of these criteria

# EEG/MRI/ EMG

- MRI
  - WNV: anterior horn cells
  - HSV, LaCrosse virus: temporal horns
- EEG
  - HSV and LaCrosse similar

# Questions from patients

- I found a dead bird what should I do?
- My friend has a mosquito virus?
- Can I nurse with my infection?
- Am I contagious?
- Should I buy the fancy mosquito catcher?
- What should I do when I go outside?
- What are my chances of getting encephalitis?
- I have flu like symptoms with fever and headache...

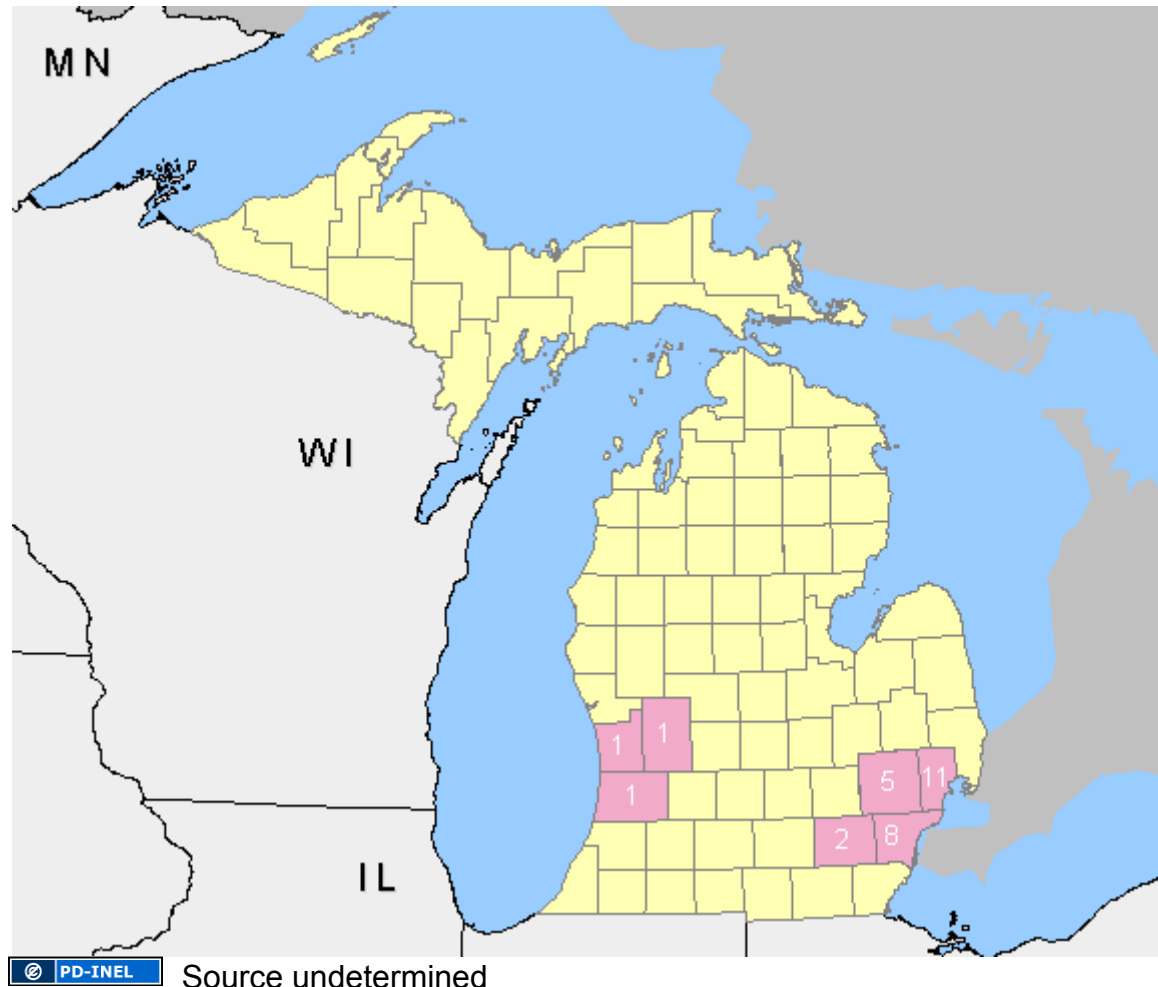
# West Nile Virus

- First isolated in West Nile region of Uganda in 1937
- Arrived in the US in 1999
- Crows, ravens, blue jays
- Symptoms
  - Flu like mild
  - 1 out of 150 develop encephalitis
- 2000/2001
  - News media
  - Dead birds
- 2002
  - 4100 cases –largest epidemic
    - 3000 with meningoencephalitis
    - 246 deaths
  - 13 cases via blood transfusion
- Likely life long immunity
- Transmitted through placenta, breast milk, organ transplants
- Long-term
  - Fatigue
  - Memory impairment
  - Weakness
  - Headache
  - Balance problems

# WNV 2010

## 29 patients

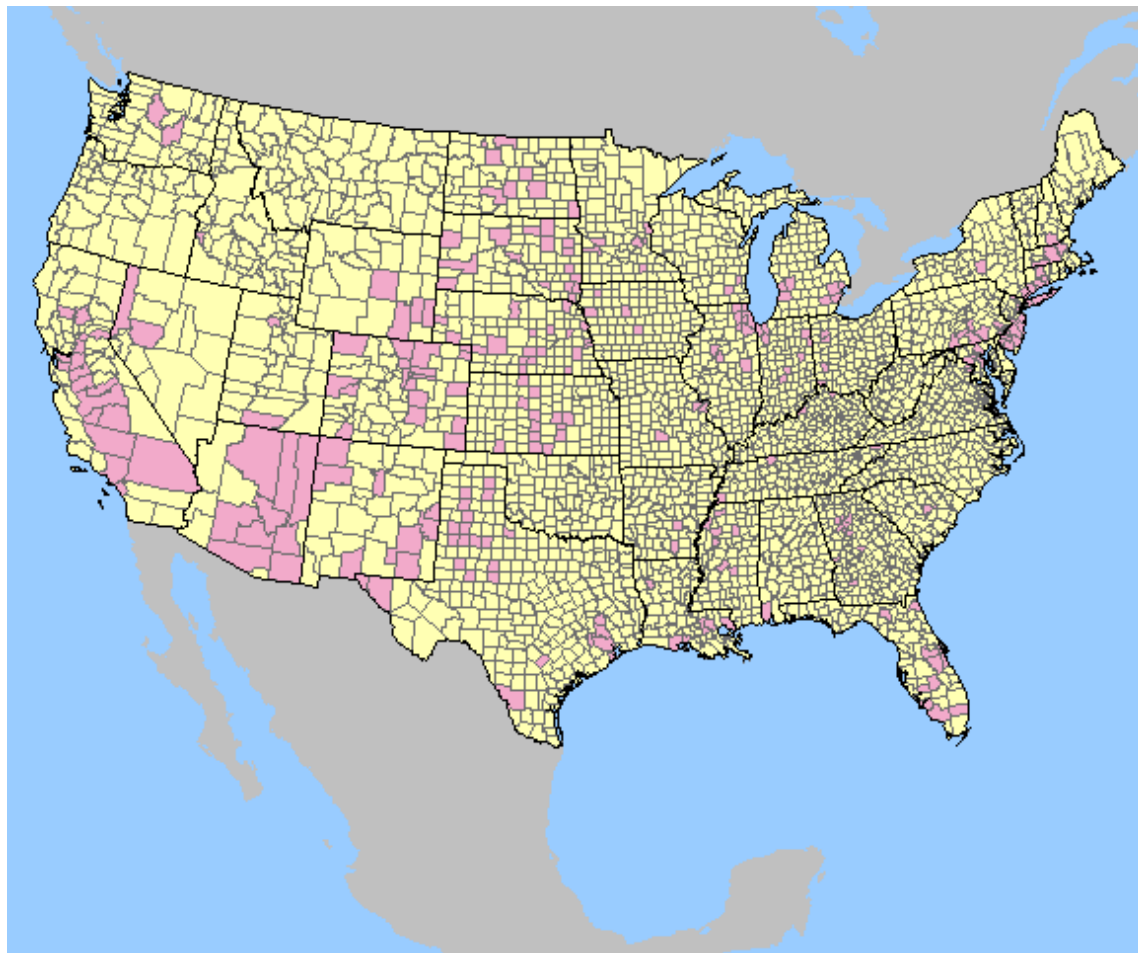
25 neuroinvasive



# US WNV 2010

## 981 patients

601 neuroinvasive, 45 deaths



# Clinical presentation

- 20-40 % patients
- Incubation 2-14 days
- Typical 3-10 days.....median 60 days
  - Patnaik et al, Emergency Infectious Disease
    - 531 patients....54 percent symptoms for 30 days
    - 79 percent missed work for 16 days
- Similar to dengue fever
- 3-6 days
  - Fever eye pain
  - Headache pharyngitis
  - Malaise N/V/D
  - Backpain abdominal pain
  - Myalgia rash ( maculopapular)





© PD-INEL

Canadian Medical Association Journal

West Nile Fever Rash

# Neuroinvasive WNV

- Meningitis, Encephalitis, Flaccid Paralysis
- Most Susceptible
  - Elderly, alcoholics, diabetics
    - Bode, *WNV disease, a descriptive study of 221 patients hospitalized in 4 county region in Colorado*, Clinics of Infectious Disease 2003, 2006
- Presentation
  - EPS, tremor, myoclonus, instability, bradykinesia, seizure, encephalopathy, confusion, coma, death
  - Flaccid paralysis (Guillain – Barre)
    - Need to confirm neuropathy before initiating symptoms

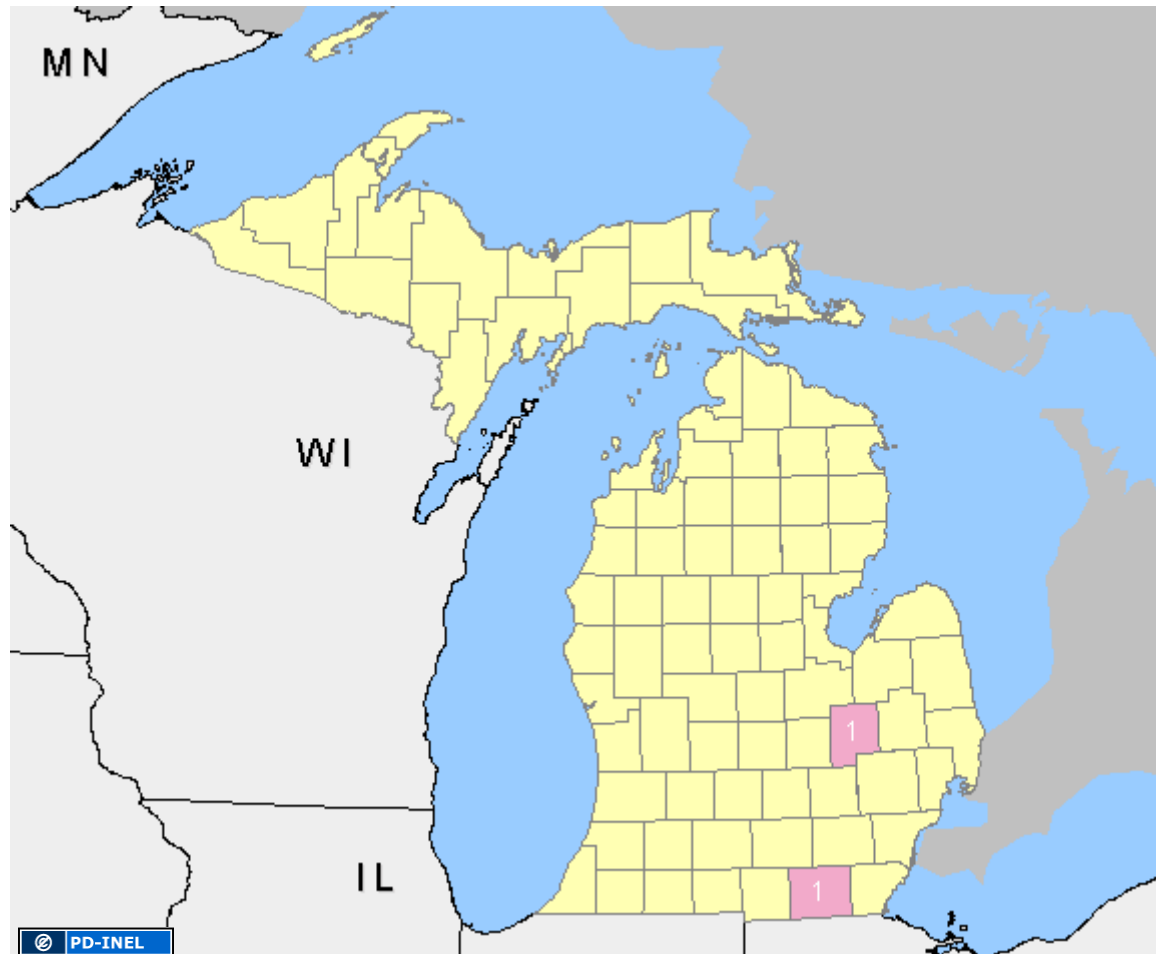
# Diagnosis/Treatment

- Serologic testing with EIA for IgM Ab
  - Within first 8 days of symptoms
- LP if neuro or mental status changes
  - EIA of IgM Ab
- Nucleic Acid testing in immunocompromised
- Supportive

# LaCrosse Virus/ California serovirus

- Similar to WNV...no flaccid paralysis
- 80-100 encephalitis cases
- Incubation 5-15 days
- Fever for 2-3 days
- Neuroinvasive cases usually under 16 yo
- Usually full recovery
  - Rare: seizure, hemiparesis, behavior or cognitive d/o
  - Mortality <1%
- CSF best way to dx with IgM Ab

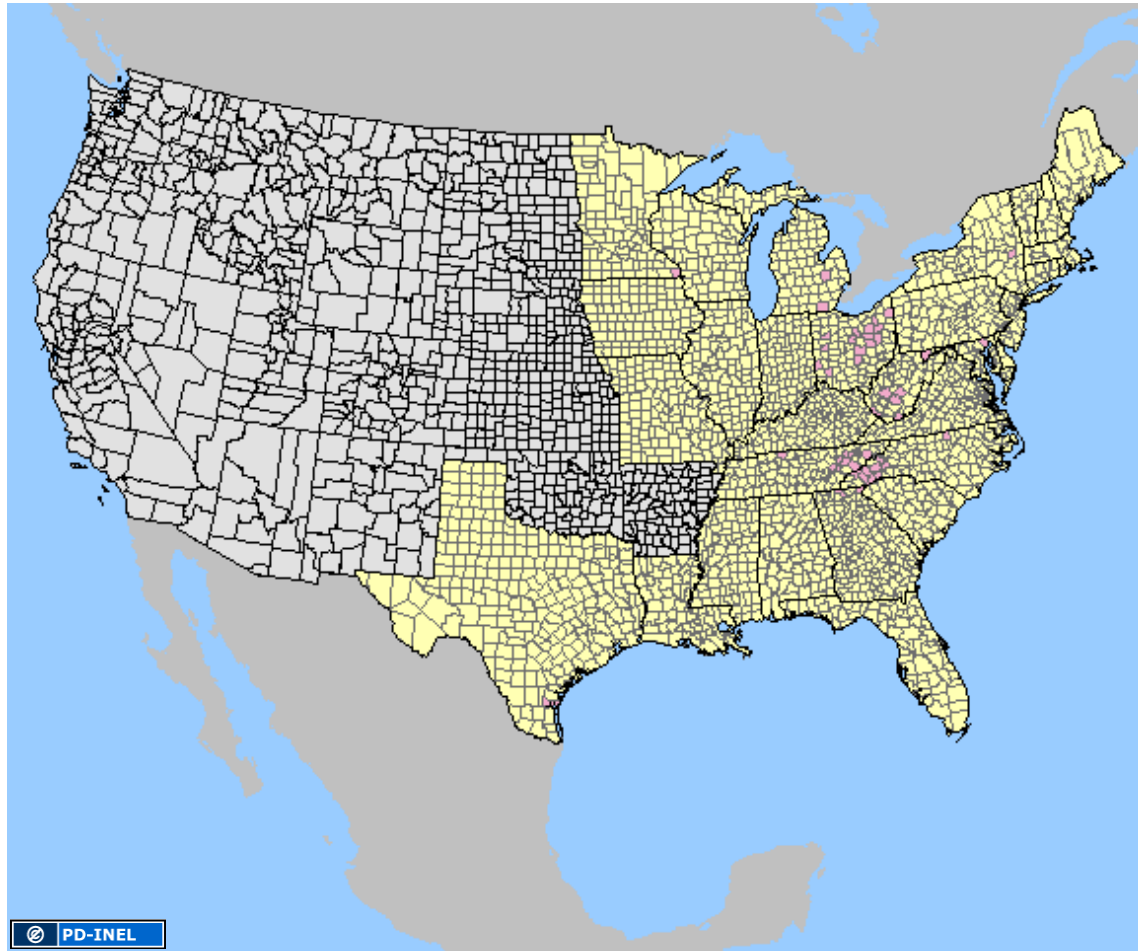
# LAC 2010



Source undetermined

# LAC 2010

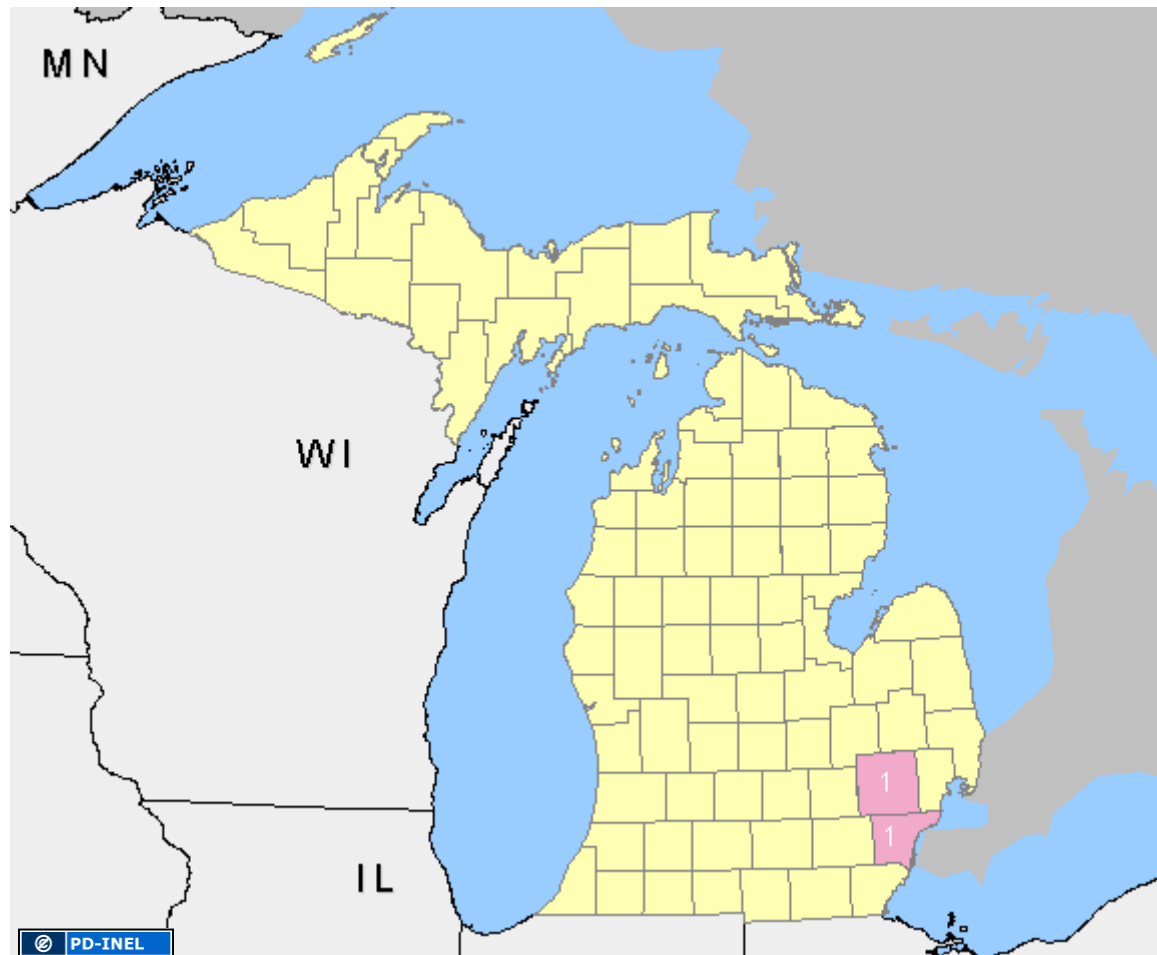
## 70 patients



# St. Louis virus encephalitis

- Symptoms similar to all arboviral infections
  - <1% patients have symptoms
    - 40% have HA and fever
    - 90% elderly develop encephalitis
- Incubation 5-15 days
- Fatality 5-10%
- 1975
  - 2000 cases in Ohio-Mississippi River Basin

# SLE 2010

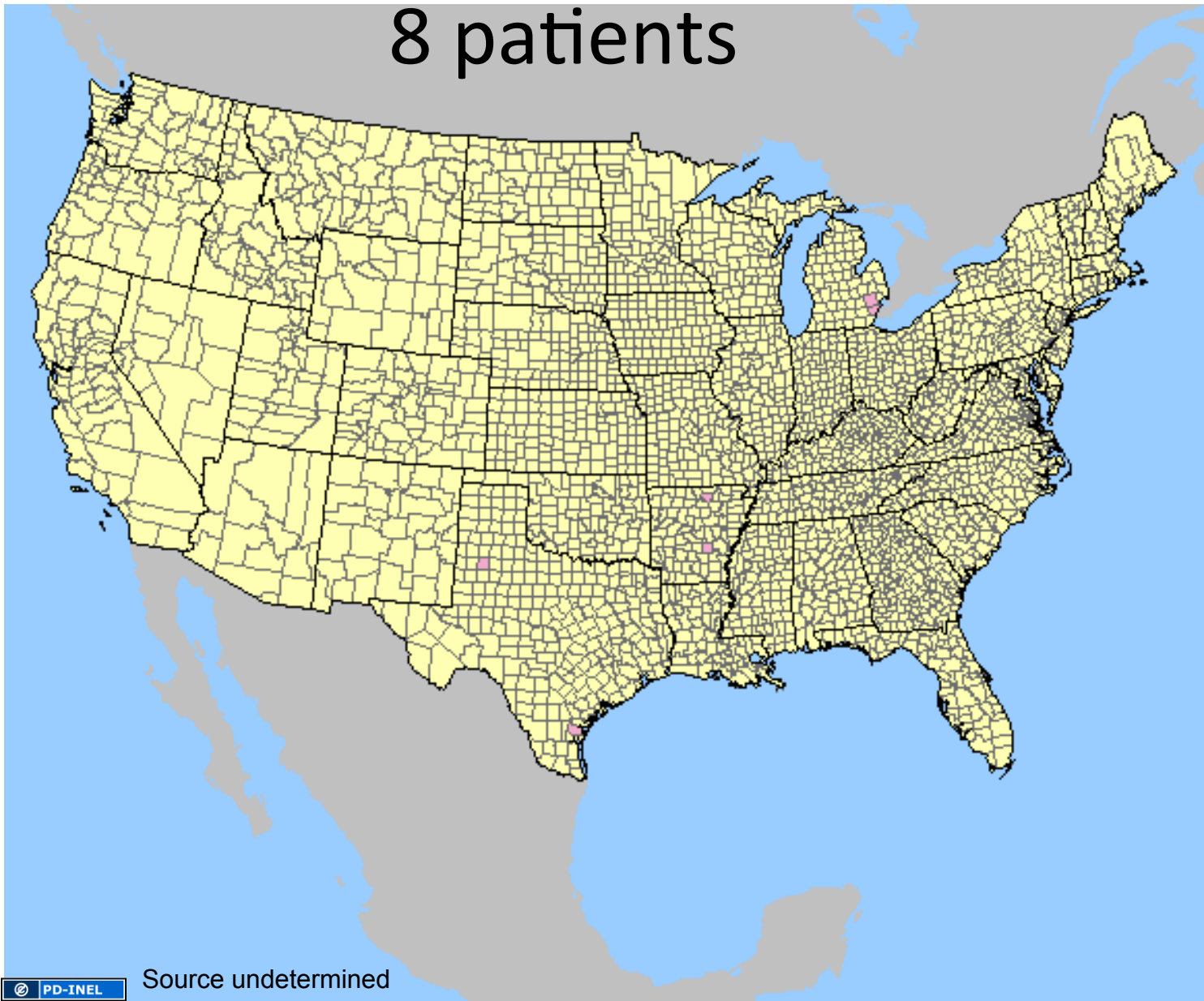


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# SLE 2010

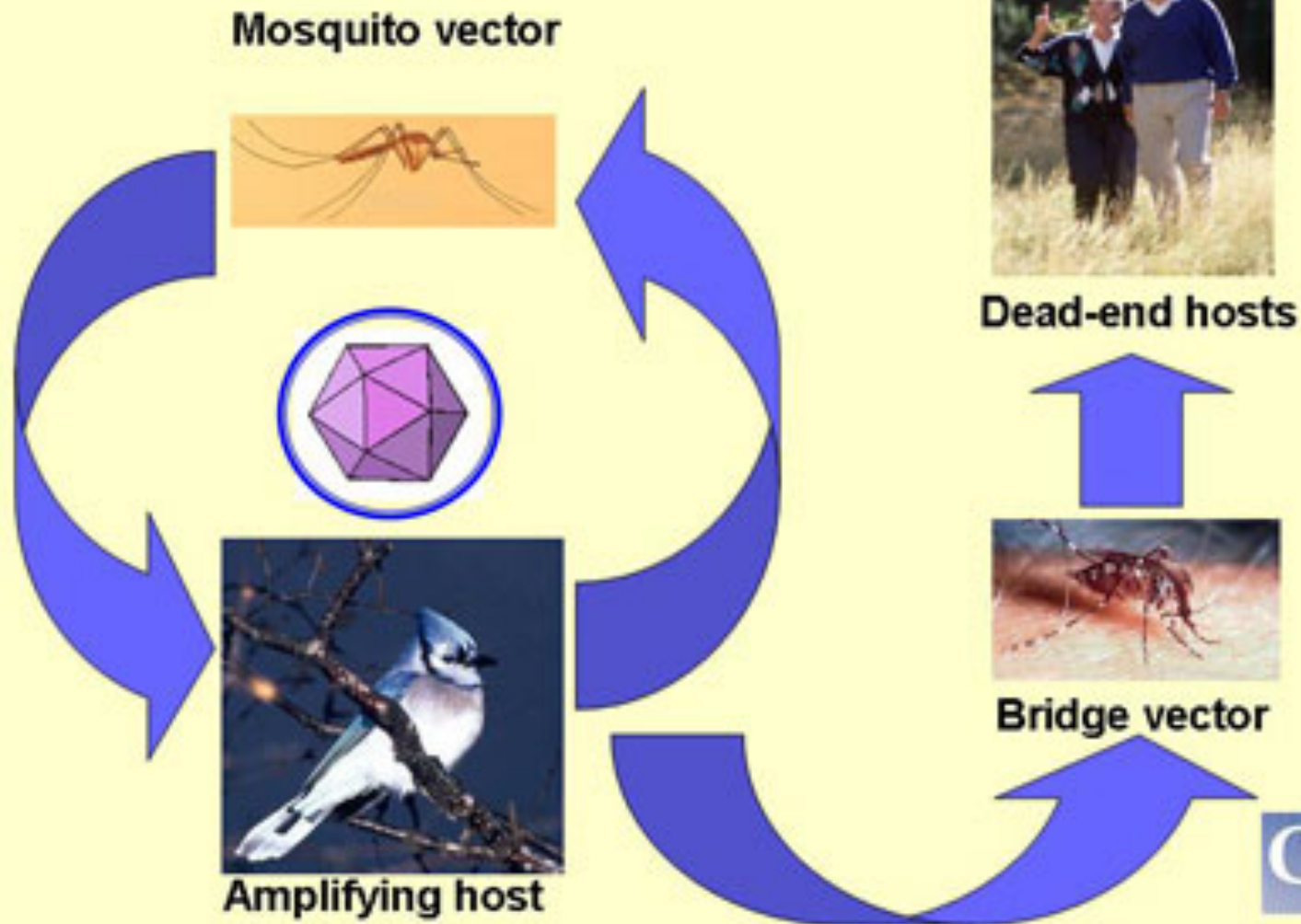
## 8 patients



# Eastern Equine Encephalitis

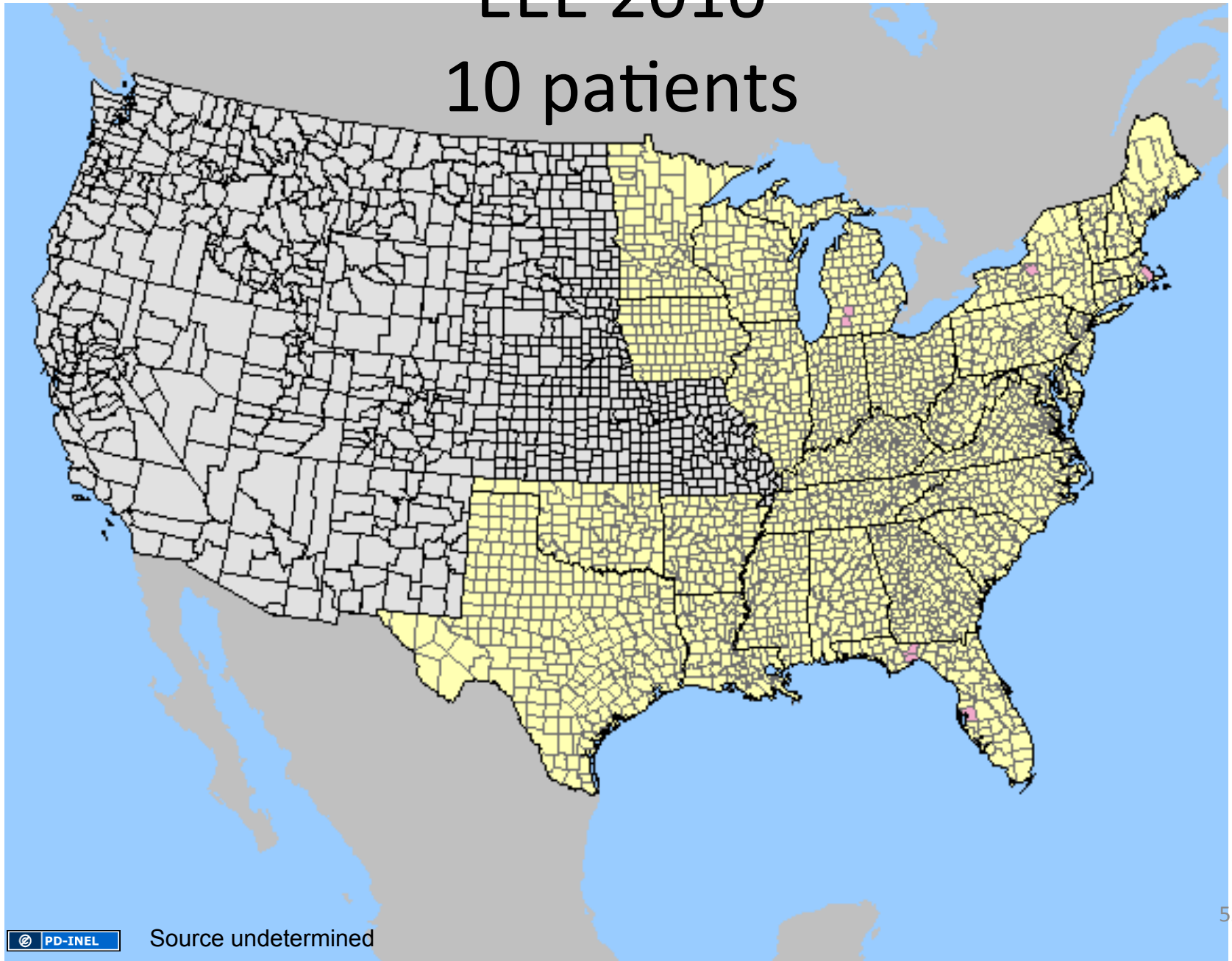
- Rarely symptomatic
- Incubation 4-10 days
- Systemic infection last 1-2 weeks
- In neuroinvasive forms (4-5% of infections)
  - **35% mortality**, death at day 2-10 of symptoms
  - Sudden high fever, HA, seizure, disorientation, vomiting, restless, drowsy, anorexia
  - Survivors with SIGNIFICANT brain damage
    - Intelligence                      seizure                      CNS dysfunction
    - Personality disorder              paralysis                      death

# Transmission cycle of EEEV

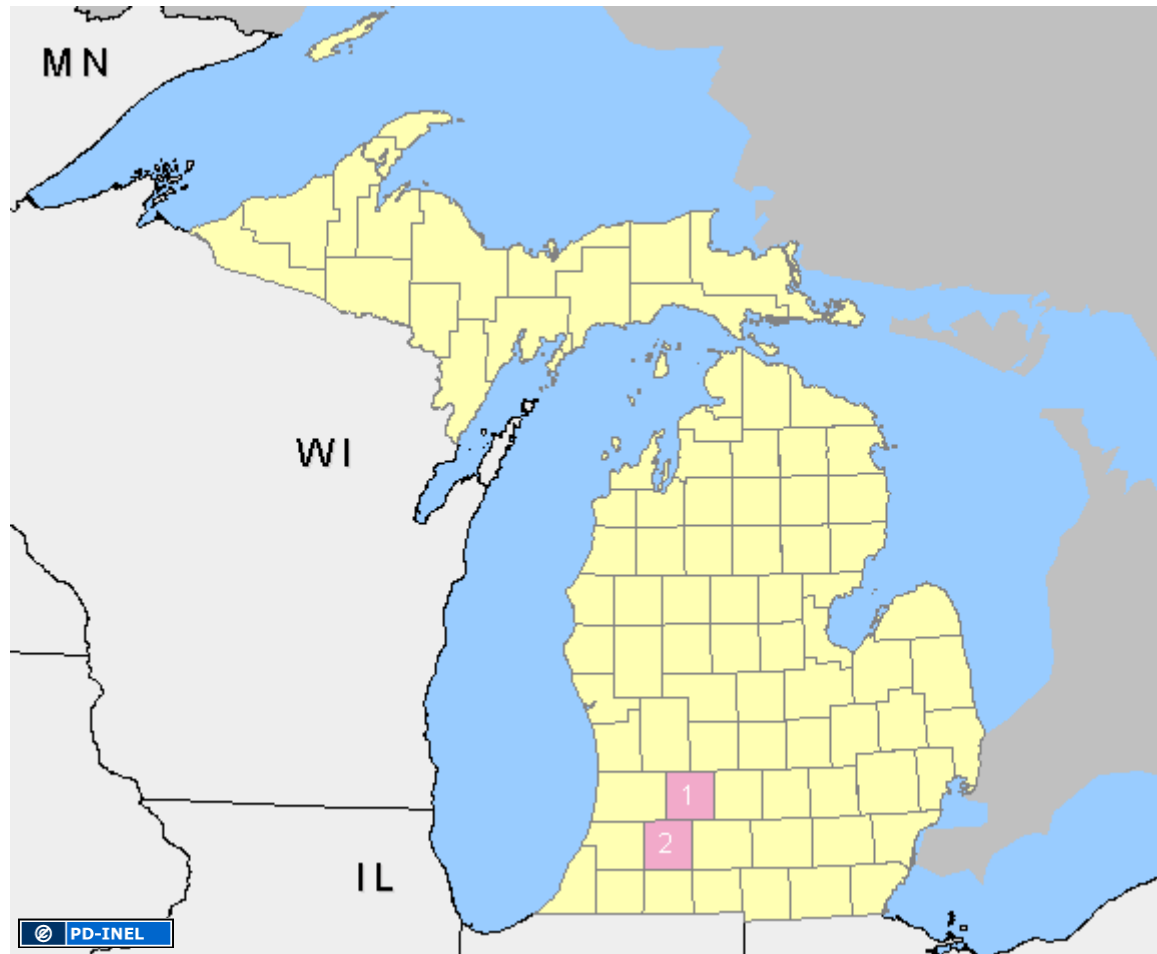


# EEE 2010

## 10 patients



# EEE 2010



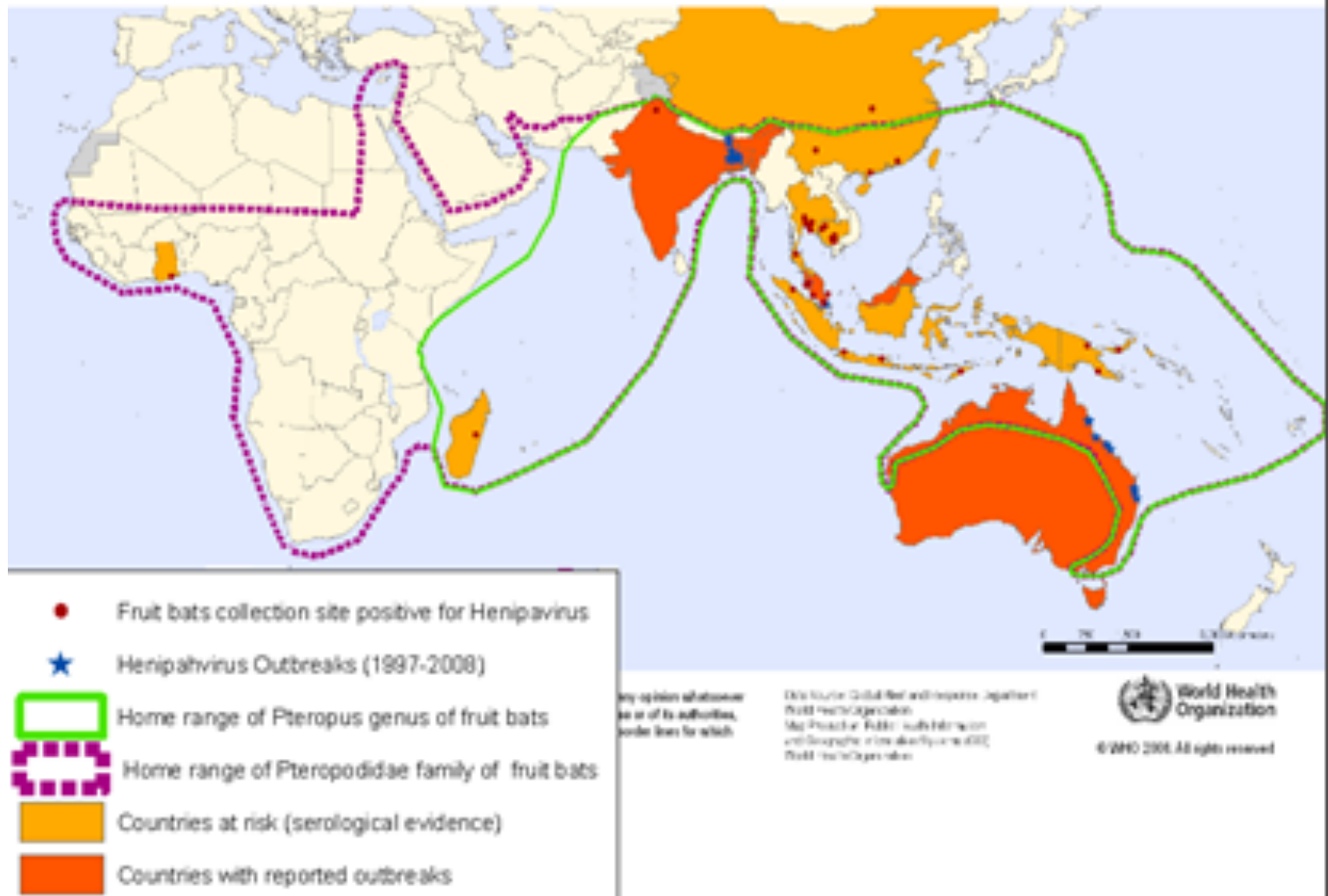
Source undetermined

# Henipah(Nipah) Virus Encephalitis

- 1998- 1999
- Malaysian pig farmers and health care workers
- 200 cases
- Transmission
  - Secretions from pigs, fruit bats
  - Human to human?
  - CDC
- Bangladesh Bans Sale of Palm Sap After an Unusually Lethal Outbreak
  - New York Times

[DONALD G. McNEIL Jr. Published: March 21, 2011](#)

## Geographic distribution of Henipavirus outbreaks and fruit bats of Pteropodidae Family





# Clinical Features

## Clinical Features of Nipah Virus in Humans

### Characteristics:

- Fever
- Migraine
- Vomiting
- Emphysema
- Myalgia
- Encephalitis (may relapse after recovery)
- Meningitis
- Disorientation
- Neurologic deficits (may persist after recovery)
- Coma
- Death

Case-fatality rate: 40%\*

*\*From APHIS Center for Emerging Issues 1999 (see References).*



# Bottom Line

- Altered mental status
  - Encephalopathy
  - Consider infection
  - Summer months in Michigan think arbovirus
  - Supportive treatment
  - CT and LP ....a MUST....admit abnormalities
- CLOSE FOLLOW UP
- Case: Lawsuit filed in 2001, Verdict for defense 2003, Appeal closed 2009

- 
- HSV :acyclovir
  - Influenza: oseltamavir, zanamivir
  - Arbovirus: no medication