

West Nile Virus

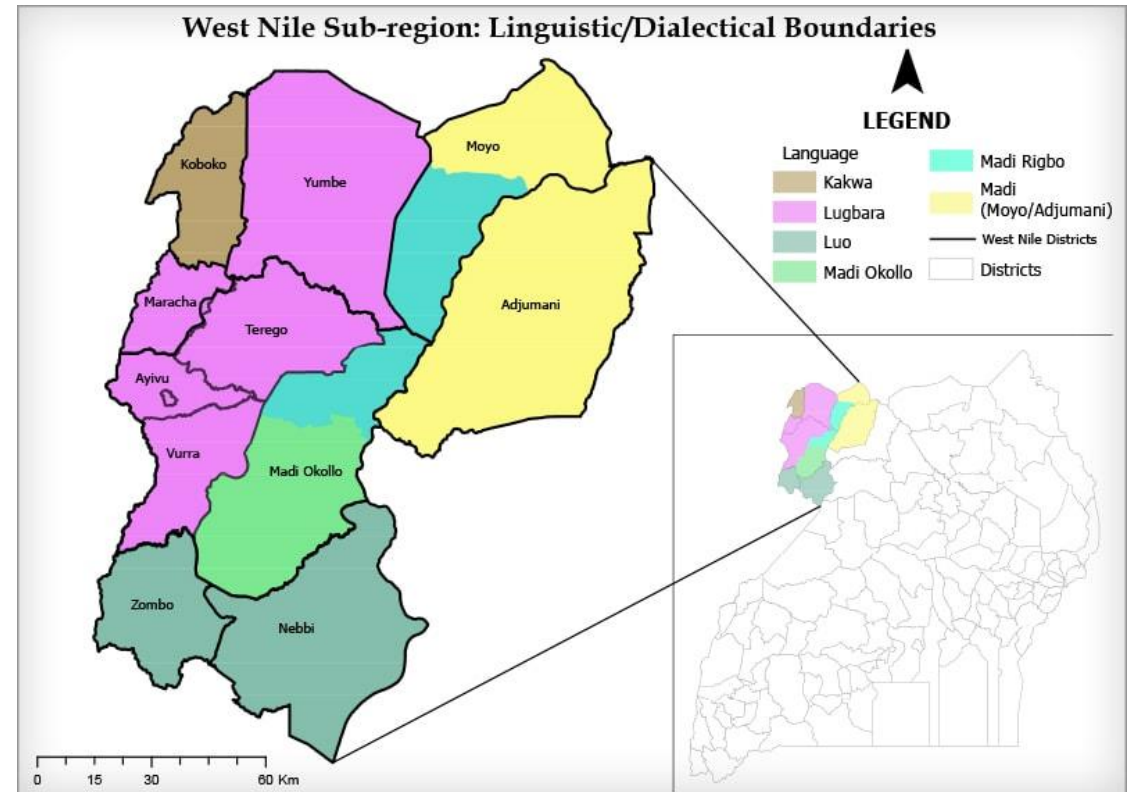
A Virus With Wings

Katharine McIver, DVM
MPH Capstone Project



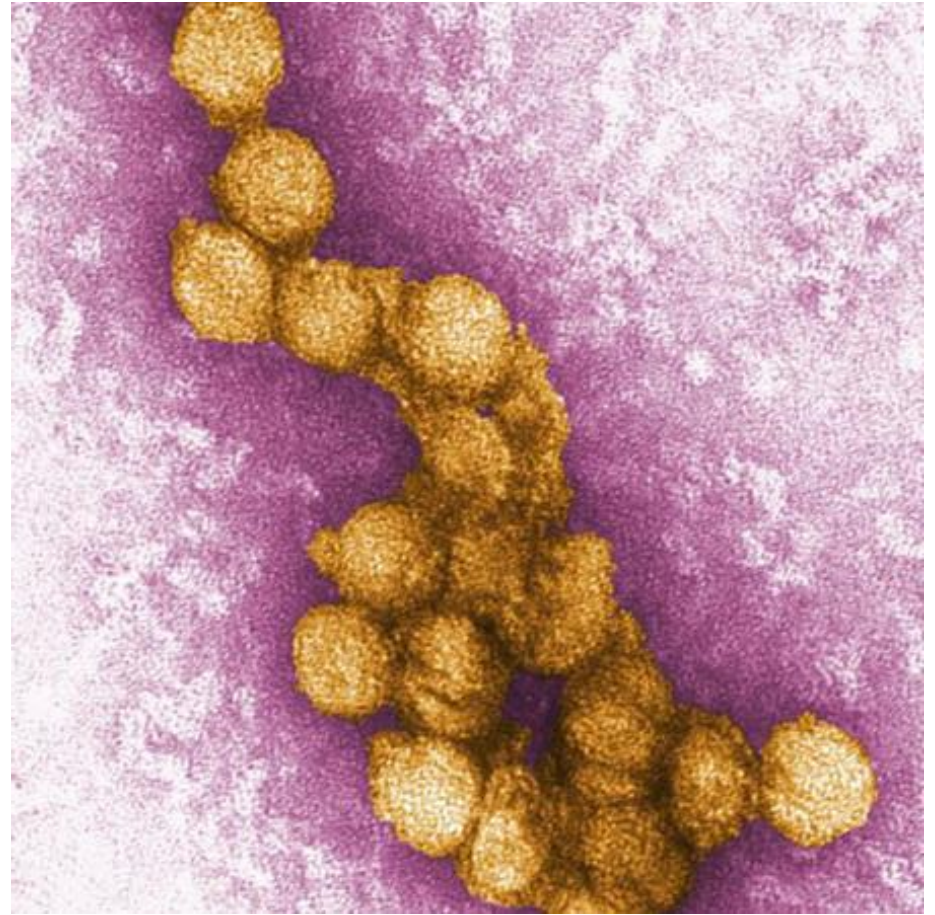
Background

- First isolated in 1937 in the West Nile Province of Uganda
- Six Lineages have been Identified
- Lineage 1
 - Central and north Africa
 - Europe
 - Australia
 - Responsible for 1999 United States outbreak
- Lineage 2
 - Endemic to southern Africa
 - Emerged in Europe in 2005



Agent

- Family: Flaviviridae
 - Found in arthropods
 - Includes Yellow fever, Dengue, Zika Virus, and Japanese Encephalitis Virus
- Genus: Flavivirus
 - Nucleic acid: (+) sense single stranded RNA
 - Capsid: icosahedral
 - Enveloped
 - 50 nm

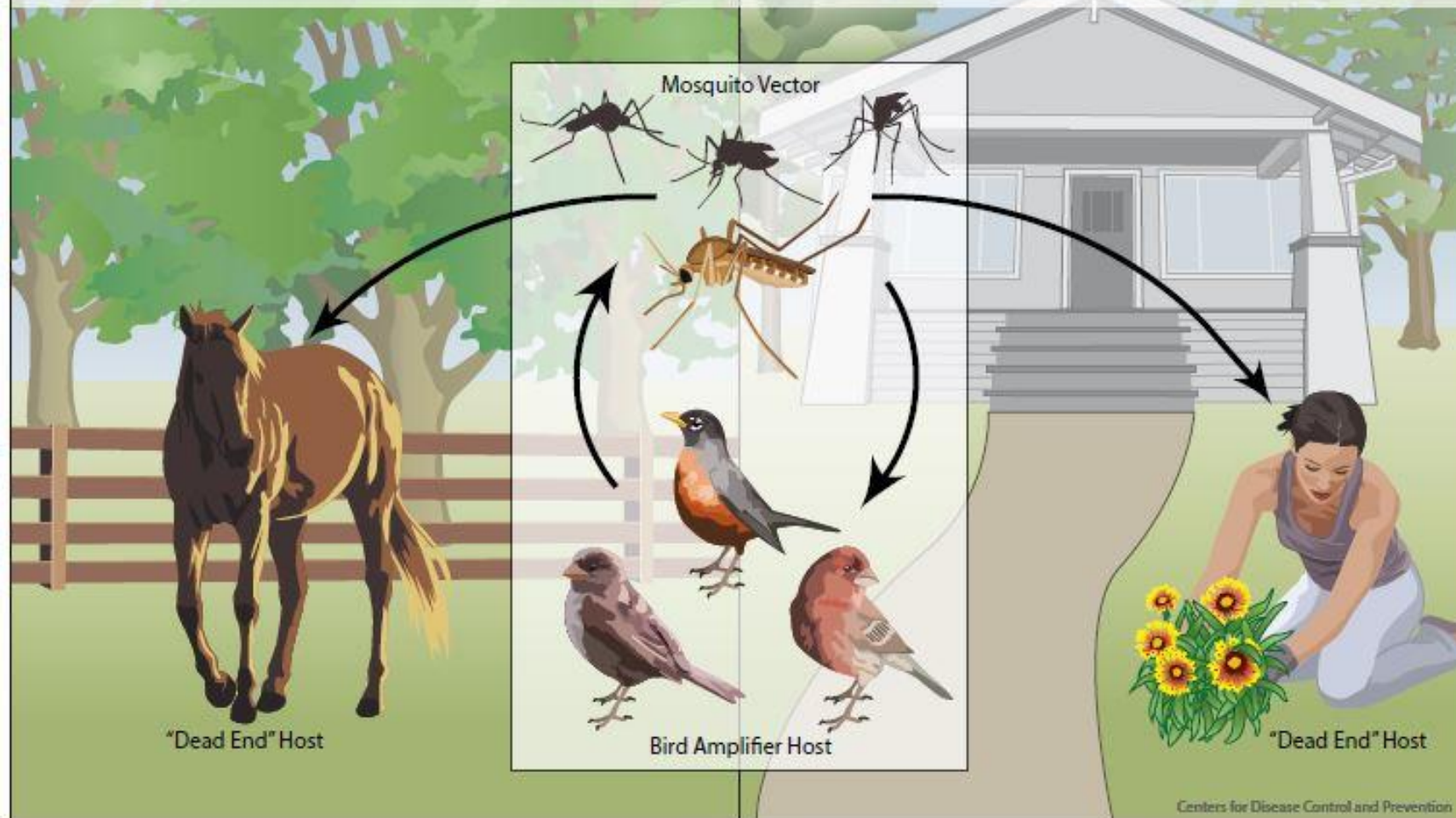


Transmission

West Nile Virus Transmission Cycle

In nature, West Nile virus cycles between mosquitoes (especially *Culex* species) and birds. Some infected birds, can develop high levels of the virus in their bloodstream and mosquitoes can become infected by biting these infected birds. After about a week, infected mosquitoes can pass the virus to more birds when they bite.

Mosquitoes with West Nile virus also bite and infect people, horses and other mammals. However, humans, horses and other mammals are 'dead end' hosts. This means that they do not develop high levels of virus in their bloodstream, and cannot pass the virus on to other biting mosquitoes.



<https://www.cdc.gov/westnile/transmission/index.html>



Vectors

45 species and 8 genera

Culex pipiens

*the northern
house mosquito*



*Culex
quinquefasciatus*

*the southern house
mosquito*

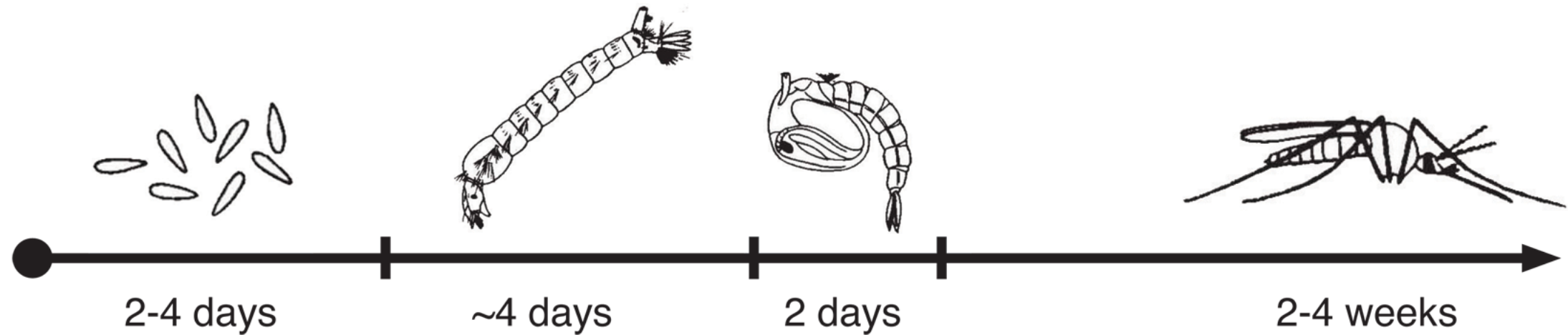


Culex tarsalis

*the western encephalitis
mosquito*



Mosquito Life Cycle



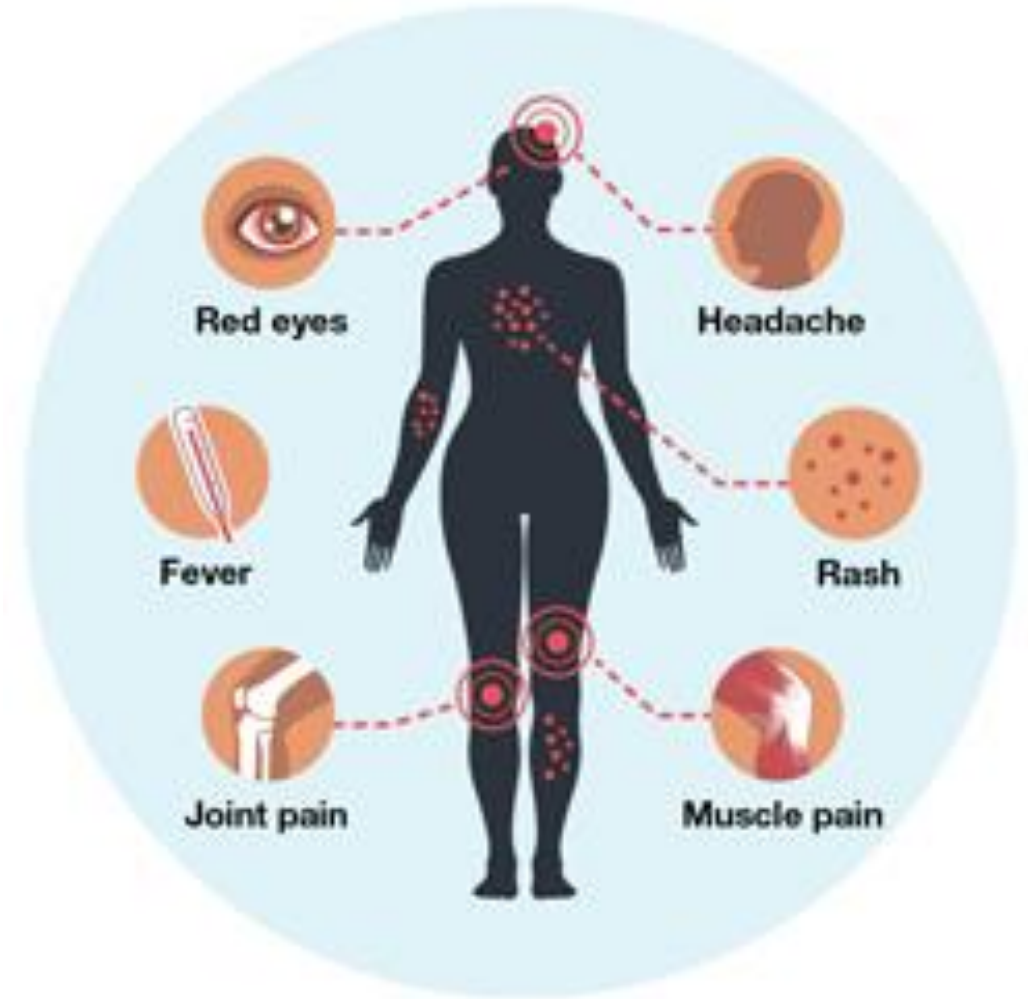
Environment

- Locations near standing water
- *Culex sp.* lays eggs in rafts in standing water
 - Eggs require water to hatch
 - *Culex* eggs are susceptible to dessication



Signs and Symptoms

- Incubation – 2-15 days
- Duration – 1-3 weeks
 - Fever/Chills
 - Vomiting
 - Diarrhea
 - Skin rashes
 - Muscle/joint pain
 - Malaise
 - Headache



Equine Specific Signs

- Head tilt
- Limb dragging
- Inability to eat
- Muscle fasciculations
 - Muzzle
 - Eyelids
 - Head
 - Neck
 - Trunk
- Mentation Change
 - Increased aggression



Diagnosis

- Confirmatory diagnosis is through laboratory testing
- Specimens include
 - Whole blood (including serum and plasma)
 - Cerebral Spinal Fluid
- Tests run
 - Nucleic Acid Testing – Real Time - PCR
 - Serology - IgM detection



Treatment in People

There is no vaccine or specific antiviral for treatment

- Little to no treatment is necessary in mild or asymptomatic cases
- Hospitalization and supportive care may be needed in cases that progress to encephalitis
 - Treatment with antivirals such as Interferon alpha-2b (INFa-2b)
- Expected recovery and seroconversion in about a week



Treatment in Horses

- A treatment protocol consists of three elements: antiviral medication, systemic anti-inflammatories, and supportive care.
- The goal is to decrease pain and discomfort while resolving the viral infection.
 1. Antiviral medication → Interferon alpha, hyper-immune equine WNV plasma
 2. Systemic analgesia → Banamine
 3. Supportive care → IV fluids, limb bandages, prophylactic antibiotics



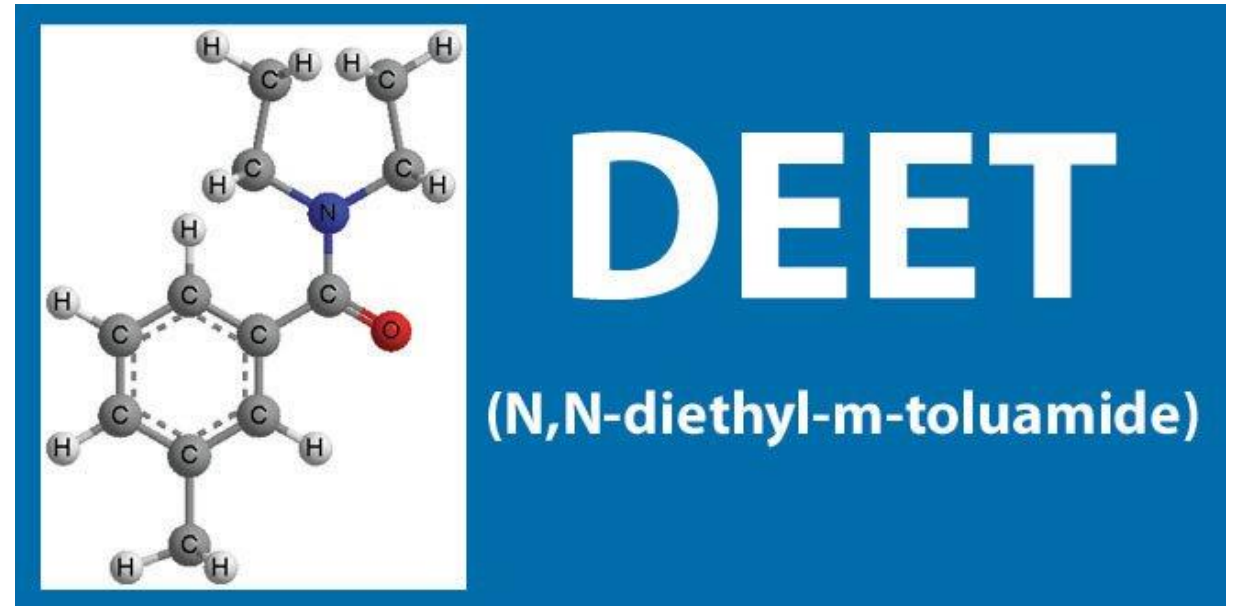
Prognosis

- Equine Mortality
 - Ranges from 22 to 30%
 - Once a horse becomes laterally recumbent, the mortality risk increases to 71% (Delph, 2018).
- Human morbidity
 - Only 20% of infected individuals will have clinical symptoms
 - Less than 1% of those individuals will progress to encephalitis (Philpott, 2019).
 - Mortality from viral encephalitis ranges from 3-15% (Green, 2005).



Prevention

- Limit mosquito bites
 - Apply repellent
 - Mosquito nets

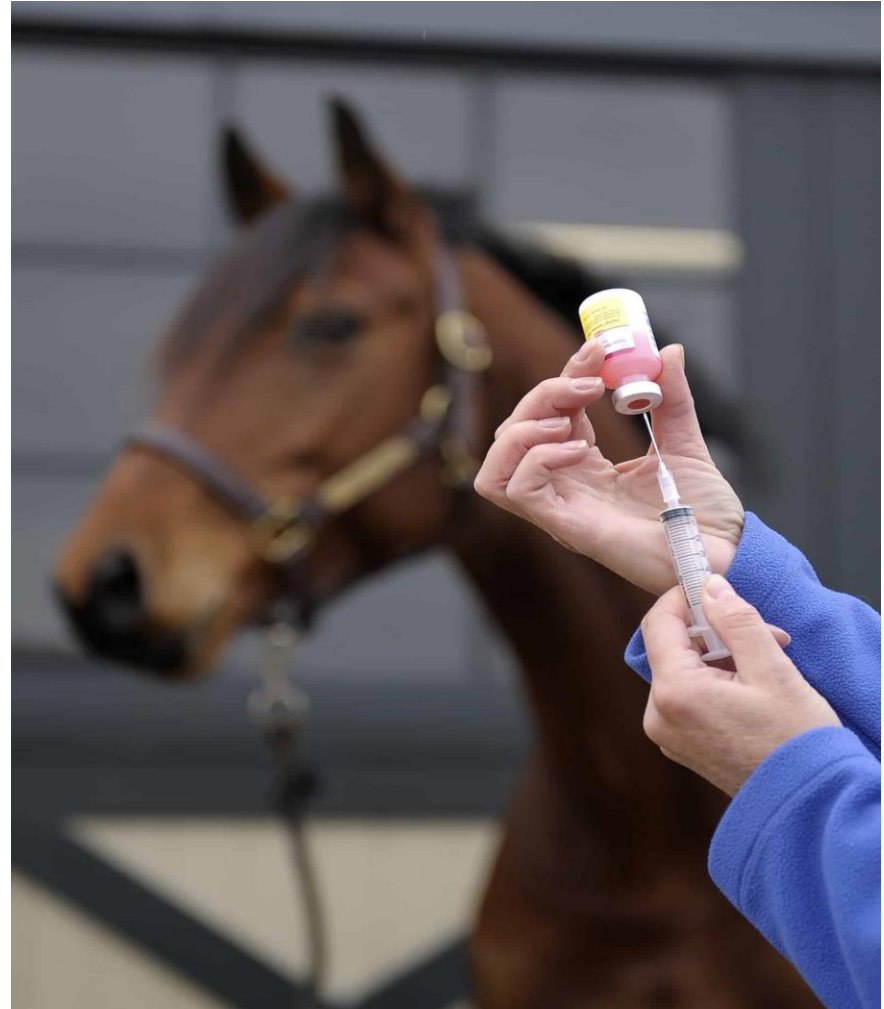


No available human vaccine for WNV



Prevention – Equine Vaccination

- Implementation of a vaccination protocol with a WNV vaccine before fly season will boost immunity.
- This may be annual or bi-annual based on location.



Prevention – Mosquito Control

- Integrated Mosquito Management

- Reduce mosquito populations by attacking all life stages

1. Eggs, Larvae and Pupae

- Reduce mosquito breeding sites by eliminating standing water
- Use larvicides to treat areas where water accumulates
 - e.g. Fountains, septic tanks, pool covers

2. Adults

- Adulticide sprayers
- Release sterile male mosquitoes



Epidemiology – The First Outbreak

- New York City, NY (1999)
 - 62 reported cases
 - 59 progressed to West Nile Neuroinvasive Disease (WNND)
 - 7 deaths
- New Jersey and Connecticut (2000)
 - 21 reported cases
 - 19 progressed to WNND
 - 2 deaths



20 0 20 40 Miles

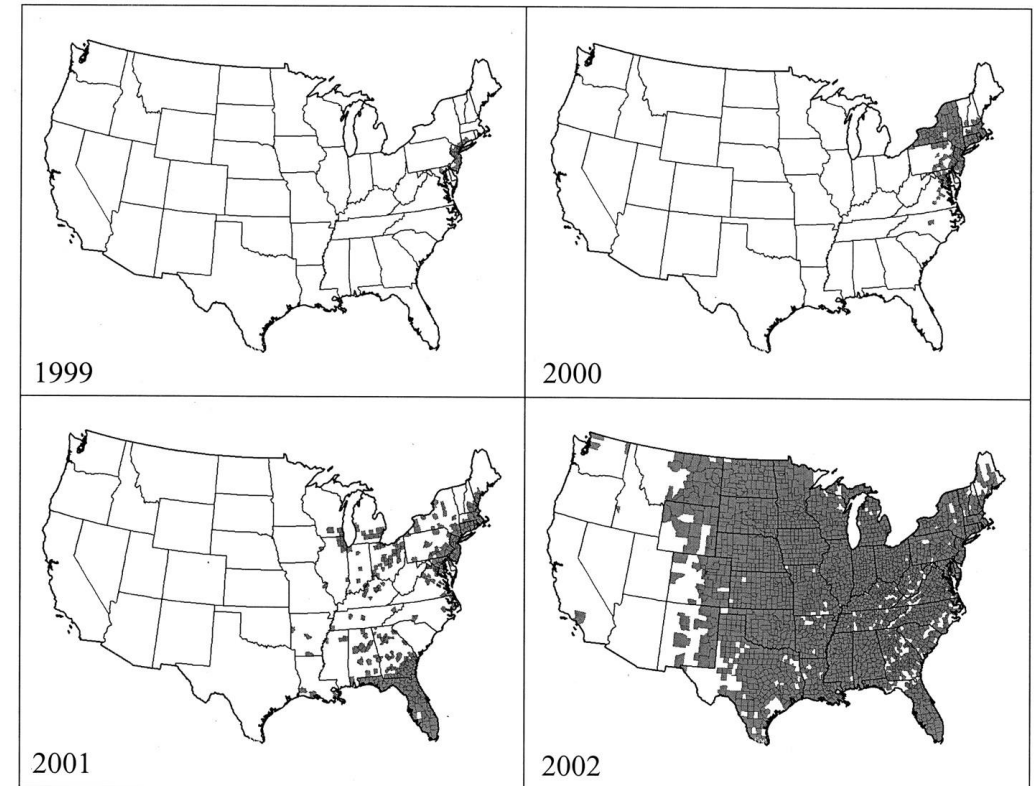
● 1999 West Nile cases

▲ 2000 West Nile cases



Epidemiology – The March West

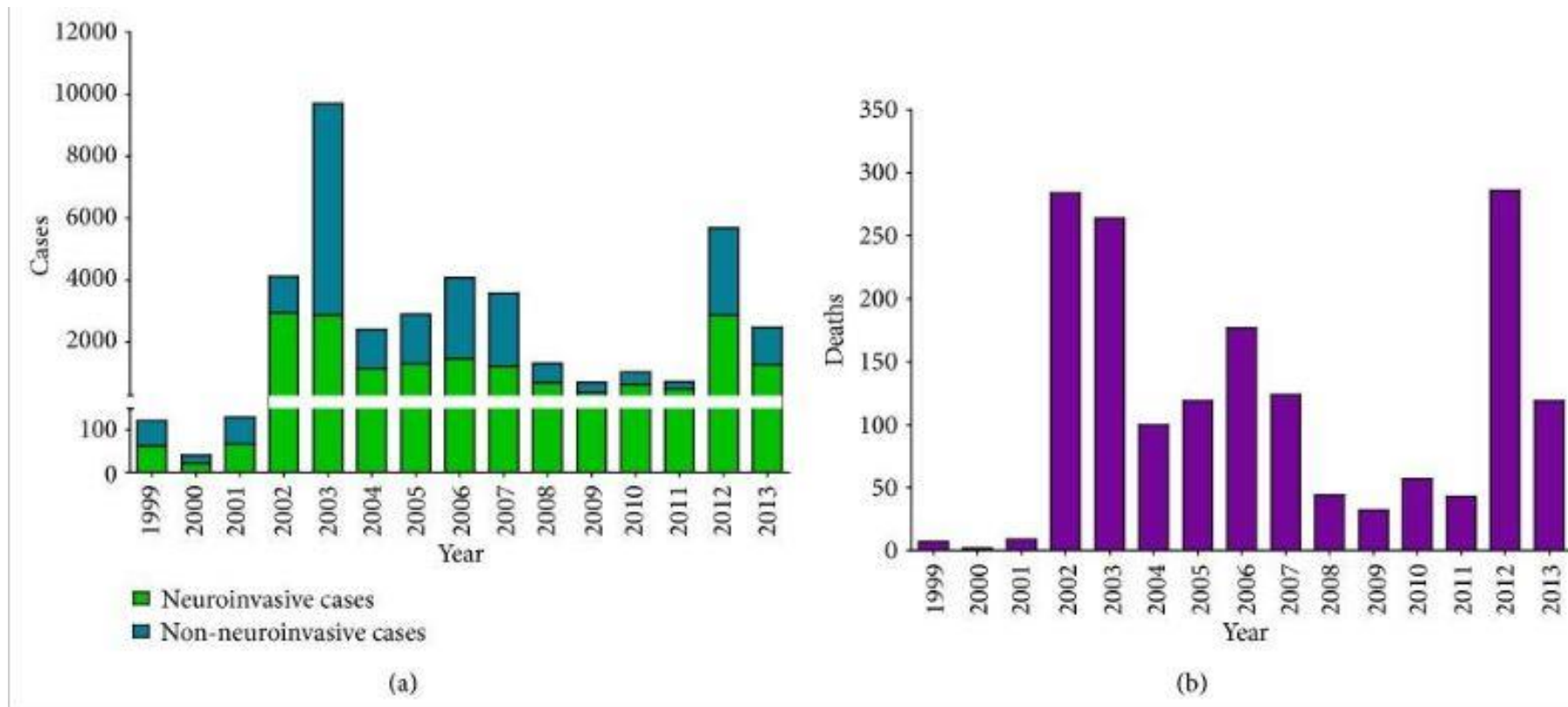
- 2001
 - 66 cases were reported in 10 states
- 2002
 - 4,156 cases reported in 40 states
 - approximately 70% of those cases resulted in WNND
 - 284 deaths
- 2004 – WNV is considered endemic
 - Cases reported in all 48 continental United States



Epidemiology – The Endemic

1999-2013: A total of 39,557 cases → 17,381 resulted in WNND → 1,667 deaths

= average of 111 deaths per year



Case Report

Signalment: 1-year-old QH Stallion

- Presented to KSU Equine Medicine Service for 1 day history of colic
- On presentation he was recumbent and notably ataxic with difficulty standing and walking
- Two days after presentation progressed to lateral recumbency with an inability to stand



Case Report – Diagnostics

- Cervical vertebral radiographs – unremarkable
- Cerebrospinal fluid (CSF) analysis
 - mononuclear pleocytosis consistent with a viral infection
- Submission of the CSF for
 - WNV ELISA – positive
 - Eastern Equine Encephalomyelitis IgM capture ELISA – negative
 - Western Equine Encephalomyelitis IgM capture ELISA - negative



Case Report - Therapy

- INFa-2b
 - 3 million units administered subcutaneously once daily
- Supportive Therapy
 - IV fluid administration, Doxycycline, Flunixin meglumine, Gabapentin, Sucralfate, Reserpine, Omeprazole, and vitamin E supplementation



Case Report – Complications

- Superficial skin ulcers
 - treated with topic gentamicin and routine bandage changes
- Superficial corneal ulcer OS
 - resolved after treatment with Ofloxacin and Atropine administered through a subpalpebral line
- Prolonged recumbency
 - A sling was employed to help support standing for short periods of time 3 to 4 times daily



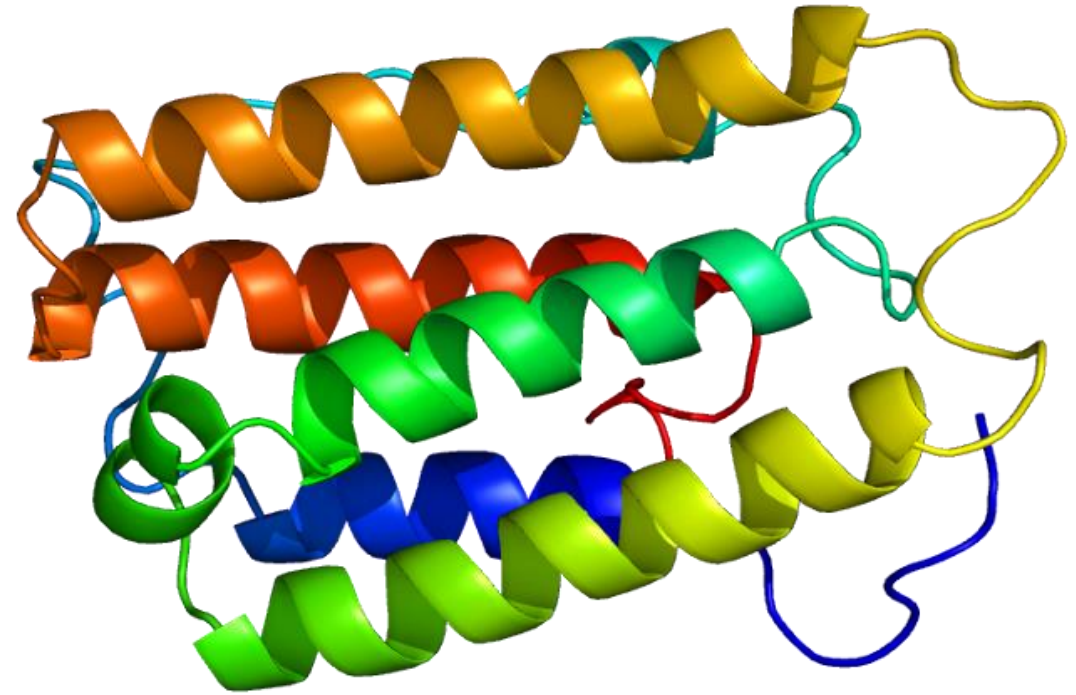
Case Report – Discharge

- After 14 days of aggressive therapy the stallion could stand without assistance
- He was discharged 35 days after admission



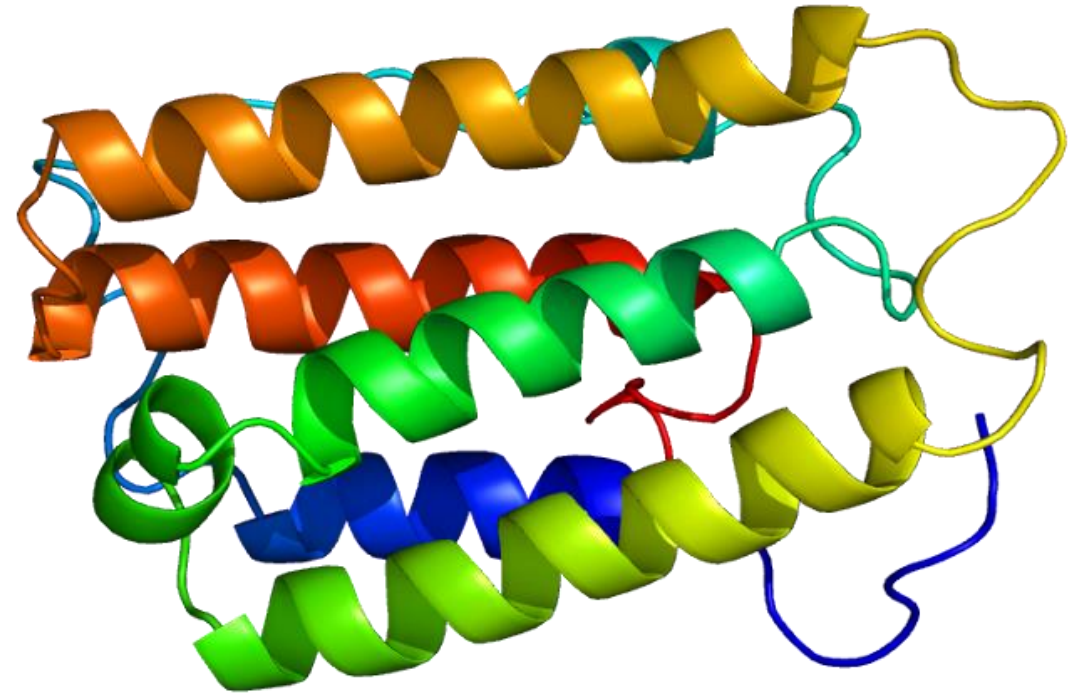
INFa-2b

- Glycoprotein - 166 amino acids in length
- Activates the Janus activated kinase/signal transducer activation of transcription (JAK-STAT) pathway through phosphorylation
- Pathway plays a key role in cell growth regulation, apoptosis, and cell differentiation



INFa-2b – Historical Uses

- Approved by FDA as therapy for
 - melanoma, leukemia, follicular lymphoma, and renal cell carcinoma, and Hepatitis C
- Upregulates p53 response rate to stress signaling
- Can initiate apoptosis through the tumor necrosis factor alpha (TNFa) signal transduction pathway



INFa-2b – WNV Studies

“Alpha/Beta Interferon Protects against Lethal West Nile Virus Infection by Restricting Cellular Tropism and Enhancing Neuronal Survival”(Samuel, 2005)

- INFa/b knockout mice (KO) vs Wild Type (WT) mice in response to WNV challenge
 - INFa-2b increased the innate immune response to the virus and decreased viral replication
 - KO mice showed a higher viremia with increased viral burden in peripheral tissues
 - KO mice showed higher titers to WNV in neural tissues
 - KO mice had increased neuronal cell death when compared to the WT mice



INFa-2b – WNV Studies

“Use of Interferon- α in Patients with West Nile Encephalitis: Report of 2 Cases” (Kalil, 2005)

- Two obtunded patients affected with WNND
 - 3 million units of INFa-2b administered subcutaneously three days after clinical presentation
 - After the second day of administration, both patients' mental status was greatly improved.
 - INFa-2b therapy continued for 14 days
 - Serial follow-up appointments showed continued improvement and complete resolution of symptoms at 1 year



INFa-2b – WNV Studies

“Interferon-alpha in a patient with West Nile Virus myelitis: A case-report” (Fateh 2015)

- 26-year-old female presented with paraparesis and urine/fecal retention
 - 3 million units of INFa-2b administered subcutaneously seven days after clinical presentation
 - INFa-2b therapy continued for 14 days
 - At 4 weeks urine/fecal retention as well as lower limb sensation improved
- Limited response to therapy may suggest there is a critical window for INFa-2b therapy



INFa-2b – Further investigation needed

- Hypothesis: timely administration of exogenous INFa-2b may help mediate the detrimental effects of the virus
 - WNV indirectly inhibits the INF signaling pathways
 - leads to activation of the cell-mediated immune response

Since both people and horses have similar biologic responses to WNV, further study into the use of INFa-2b as a first-line therapy, at early onset of neurologic signs, is warranted.



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Summary of Portfolio Products with MPH Foundation Competencies

Portfolio products completed at KDA under the supervision of Dr. Lake.

1. WNV Pamphlet: Educational brochure to be given to clients of WNV positive horses by hospital staff at diagnosis/discharge.
 - 18. Select communication strategies for different audiences and sectors
2. WNV PowerPoint: Online presentation on the KSU Vet School website for education on the disease (specifically transmission and prevention).
 - 21. Performs effectively on inter-professional teams



Summary of Portfolio Products with MPH Foundation Competencies

Portfolio products completed at KDA under the supervision of Drs. Pohlman, Larson, and Delph.

3. West Nile Virus – An Epidemiological Review

- 4. Interpret results of data analysis for public health research, policy, or practice
- 22. Apply systems thinking tools to a public health issue

4. Recovery from a severe West Nile Virus infection in a one-year-old stallion following interferon alpha-2b treatment: an equine model for human therapy

5. Oral Presentation on WNV

- 19. Communicate audience- appropriate public health content, both in writing and through oral presentation



Summary of MPH Emphasis Area Competencies

<i>IDZ Emphasis Area Competency</i>	<i>Description of Competency</i>
1 <i>Pathogens/pathogenic mechanisms</i>	Evaluate modes of disease causation of West Nile Virus – obtained through epidemiology review report
2 <i>Host response to pathogens/immunology</i>	Investigate the host immune response to West Nile Virus – obtained through case study report
3 <i>Environmental/ecological influences</i>	Examine the influence of environmental and ecological forces on West Nile Virus – obtained through epidemiology review report
4 <i>Disease surveillance</i>	Analyze West Nile Virus risk factors and select appropriate surveillance – obtained through epidemiology review report
5 <i>Disease vectors</i>	Investigate the role of vectors in WNV– obtained through epidemiology review report



Questions?



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