West Nile Fever
West Nile Virus
What is West Nile Fever?

- West Nile Virus (WNV)
  First isolated from a woman in the West Nile district of Uganda in 1937
  Mosquito-borne viral infection of people

- West Nile Fever (WNF)
  Viral disease (encephalitis) in people caused by the West Nile Virus

- Equine West Nile Virus Encephalomyelitis
Family of *flaviviruses* - arbovirus

- St. Louis encephalitis
- Rocío and St. Louis (Brazil)
- West Nile virus
- Japanese encephalitis
- West Nile and Japanese encephalitis
- Japanese and Murray Valley encephalitis
- Murray Valley and Kunii
West Nile Virus
1999 - 2007

- Human Cases
  - 1999 – 62
  - 2000 – 18
  - 2001 – 56
  - 2002 – 4,008
  - 2003 – 9,122
  - 2004 – 2,470
  - 2005 – 2,949
  - 2006 – 4,219
  - 2007 – 3,576

- Horse cases
  - 1999 – 25 horses
  - 2000 – 60 horses
  - 2001 – 738 horses
  - 2002 – 15,257 horses
  - 2003 – 4,636 horses
  - 2004 - 1,341 horses
  - 2005 – 1,088 horses
  - 2006 – 1,061 horses
  - 2007 – 484 horses
West Nile Virus Transmission Cycle

Mosquito vector

West Nile virus

West Nile virus

Bird reservoir hosts

Incidental infections

Incidental infections
West Nile Virus Disease in birds

- Europe – only subclinical infections
- North American outbreak
  - First indication – dead crows
  - Neurologic disease – circling, ataxia, seizures
  - Disease of other organ systems
  - Sudden death
  - Fatal in many species of birds
West Nile Virus

Clinical signs in birds

- Weakness, sternal recumbency
- Ataxia
- Tremors
- Anisocoria
- Abnormal head posture
- Circling
- Convulsions
Found in at least 138 bird species

- American crow
- Ring-billed gull
- Yellow-billed cuckoo
- Rock dove
- American robin
- Blue jay
- Fish crow
- Red-tailed hawk
- Broad-winged hawk
- Cooper's hawk
- Belted kingfisher
- American kestrel
- Herring gull
- Laughing gull*
- Bald eagle*
- Black-crowned night-heron*
- Mallard*
- Sandhill crane*

* Captive bird
Other Domestic Animal Hosts

- Horses
- Humans
- Sheep
- Chickens
- Pigs
- Cows
- Dogs
- Cats
West Nile Virus

Other WNV-Positive Mammals

2002 Outbreak
- 3 dogs
- 8 squirrels
- 2 unspecified species

2003 Outbreak
- Camelids
Can West Nile Virus Cause Illness in Dogs or Cats?

Dogs - South Africa
- 37% of dogs seropositive (138/377)
- Virus isolated from 1 dog
- Experimental induction – mild recurrent myopathy
- Low level viremia

Cats
- No published reports
- WNV isolated from dead cats (3) New York

Serosurvey NY 1999 epidemic low infection rate
Equine West Nile Virus Encephalomyelitis World Wide

- 1962-1965 France
- 1963 Egypt
- 1990 Portugal
- 1996 Morocco
- 1998 Italy, Israel
- 1999 Long Island (NY)
- 2000 Northeastern USA, France, Israel
- 2001 Eastern USA
- 2002 – 2006 USA
West Nile Virus
1999 equine outbreak

• Serology from 83/146 resident horses
  Convalescing horses
  Contact horses
    Commingled with a case
    Co-owned or managed by an owner of a case animal

• 83 horses sampled
  15 had a recent clinical illness – all positive
  68 horses no history of clinical illness
    21 (31%) were serologically positive
West Nile Virus
Serology

- Nigeria – 71% of horses seropositive
- Greece
  20% of horses
  9% of sheep, 9% of goats, 4% of cattle, 1% of pigs
  25% of birds, 29% of humans
- Russia
  67% of horses, 24% of wild animals
  7% of camels, 9% of sheep, 35% of cattle
- France
  5% of cattle, 2% of sheep, 3% pigs, 5% of humans
- USA – 1999
  31% of horses on outbreak farms
West Nile Virus
Equine disease in the old world

14 horses from Tuscany, Italy
- Ataxia, weakness, paresis of the hind limbs
- Paraparesis progressing to tetraplegia, recumbency (2 - 9 days).

94 equids (horses, mules, donkeys) in Morocco
- Influenza-like syndrome
- Hind limb paresis progressing to paralysis
- Death in 5 – 10 days in 45% of cases

France
- Incubation period about 6 days
- Biphasic fever (6-10 days then 18 days with CNS signs)
- Ascending meningoencephalitis
- Staggering gait progressing to hind leg paralysis
- Death in 14 – 21 days
West Nile Virus
Epidemiology

- Exposure geographically clustered
  - Exposure chance event
- Blackbird roosts/waterfowl within 0.5 mile
- Pleasure horses at higher risk
  - More likely exposed to vector? - trail riding activities
- Insect control methods - farm or horse level
  - Not associative with likelihood of infection
  - Primarily aimed at fly control
- Increased risk when not housed in stalls at night
- Mosquito species
  - *Culex spp* primarily identified
  - Transmission to horses ??
West Nile Equine Encephalitis Cases:
Trend Comparisons for 2002, 2003, and 2004

Number of Horses

Date

5/9 6/28 8/17 10/6 11/25 1/14

2002 2003 2004
Equine West Nile Virus Encephalomyelitis

Clinical Signs

- Fever (< 50%)
- Acute onset of ataxia of all limbs
- Marked hypermetria
- Recumbency
- Single foreleg lameness
  - Progressing to bilateral forelimb lameness/ataxia
  - Monoparesis, paraparesis,
    tetraparesis progressing to recumbency
- Radial nerve paralysis
Equine West Nile Virus Encephalomyelitis

Clinical Signs

- Hypersensitivity to touch and sound
- Somnolent - periodically falling to knees
- Anisocoria and a slow pupillary light response
- Tremors and lip twitching
- Muscle fasciculations
  Most pronounced in the neck and triceps region
- Difficulty swallowing
- Facial nerve paralysis
- Central blindness
- Seizure activity
Equine West Nile Virus Encephalomyelitis
Laboratory Findings

- CBC – normal
- Fibrinogen – normal
- CSF – usually normal
  - Increase CSF protein and xanthochromia
- Blood chemistry normal
Equine West Nile Virus Encephalomyelitis Diagnosis

- Serology
  - Fluorescent antibody
  - Virus neutralizing antibodies (3 wks PI to years)
  - IgM capture ELISA (10-12 days PI to weeks?)
- RT-PCR
  - Blood – negative
  - CSF – negative
  - Brain/cord - positive
- Virus isolation
  - Blood – negative
  - Brain/cord
Experimental infection WNV in horses

Joubert et al. Bull Acad Vét Fr, 1971
Multifocal Hemorrhages
Severe inflammation of the gray matter (poliomyelitis)
Inflammation and necrosis of the neural cells
West Nile virus antigen – cytoplasm of neuron
Equine West Nile Virus Encephalomyelitis
Differential Diagnosis

- Eastern, Western, Venezuelan Equine Encephalomyelitis
- Equine herpes virus 1
- Rabies
- Equine protozoal myelitis
- Leukoencephalomalacia
- Stenotic cervical myelopathy
- Hepatic, intestinal or renal encephalopathies
Equine West Nile Virus Encephalomyelitis

Treatment

- Supportive, Preventing self-inflicted injury
- Fluids
- Treat for other differential diagnoses
  - Herpes virus suspect status
  - Rabies suspect status
- Hyperimmune plasma?
- Interferon therapy?
Equine West Nile Virus Encephalomyelitis
Clinical Course and Outcome

Recovery
- 80% patients recover fully
- Course averages 22 days

Reported fatality rates
- World wide 30 – 64%
- USA 50 - 33%
  - Presented with the most severe signs (recumbency)
  - Rapid progression of neurologic signs leading to recumbency
  - Recumbent horses 78 times more likely to die
  - Female 2.9 times more likely to die
  - > 3 years old more likely to die

Prognosis good if continued ability to rise
Course before death average 2 days (0 – 6 days)
Equine West Nile Virus Encephalomyelitis
Fort Dodge vaccine

• Fully licensed
  Vaccine tested with challenge studies
  • No vaccinates or controls developed signs
  • Vaccinates did not develop viremia

• Millions of doses sold
  Few adverse reactions
  Lay horsemen fear reproductive problems
  • Internet web site
Equine West Nile Virus Encephalomyelitis

Fort Dodge vaccine

• Efficacy unknown
  Weeks after 2nd dose before a measurable antibody response.
  Horses may develop WNV soon after 1st dose of vaccine
  • Suggesting that one dose is not protective

• The manufacturer’s recommendations
  2 doses 3-6 weeks apart
  Yearly booster

• Epidemiology
  Unvaccinated horses > 2 X more likely to die
Equine West Nile Virus Encephalomyelitis

Merial vaccine

• Recombitek
  Recombinant canarypox vaccine
  Vectored recombinant DNA vaccine
• Stimulates both arms of the immune system
• Challenge studies
  Prevents viremia up to 1 year later
  Need 2 vaccinations
• Appears safe in small field studies
  Not labeled for use in pregnant mares
• Efficacy unknown
Equine West Nile Virus Encephalomyelitis Prevention

- Other arbovirus encephalitis vaccines
  - EEE, WEE, VEE
  - *Do not cross protect*
- Mosquito control very important
Equine West Nile Virus Encephalomyelitis Prevention

• Stop the bird – mosquito infection cycle

• Mosquito control
  
  Primary *Culex spp*
  
  Equine vector?

Range < 1000 yards

Local problem – local control
Larval habitat destruction

*Culex spp*

- Any puddle that lasts more than 4 days - habitat
- Reduce the amount of standing water available
  - Water troughs, water buckets
  - Swimming pools, plastic wading pools
  - Bird baths, wheelbarrows
  - Clogged roof gutters
  - Recycling containers
  - Discarded tires
  - Tin cans, plastic containers, ceramic pots
  - Any water-holding container
Prevention
Mosquito Control

• Practice mosquito control on farms
  Identify and destroy larval habitats
  Larvicides - BTI - *Bacillus thuringiensis var. israelensis*
• Stable horses during peak mosquito feeding times
  Dusk, Dawn
  Stable at night
• Adult mosquito control – last resort
  Use insect repellents
What is the risk of transmission from a mosquito bite?
Risk of Transmission by a Mosquito Bite in an Endemic Area

- Area where birds have West Nile virus
- Area where mosquitoes carry the virus
- Very few mosquitoes carry the virus
  1 less than out of 500
  Chance that one mosquito bite will be from an infected mosquito is very small
- If bitten by an infected mosquito
  Chance of developing illness are roughly 1 in 300
Can I Get Infected with West Nile Virus by Caring for an Infected Horse?

• West Nile virus is mosquito transmitted

• No evidence of animal-to-person transmission
Can a Horse Infected with West Nile Virus Infect Other Horses?

- No documented evidence that West Nile virus is transmitted from horse-to-horse.
- New evidence – possible transplacental infection

Abortion
Are Horses a Source of West Nile Virus?

- Are horses terminal hosts?
- Historic evidence
  - No virus in blood when clinically ill
  - 2 experimental induction studies
- USDA & CSU/CDC
  - 3 exp inoculation/transmission studies since 1999
  - 16 horses max viremia $10^3$/ml (most < $10^2$/ml)
  - 8 horses infected via mosquito (*Aedes albopictus*)
    - 1 hrs developed clinical signs
    - > 600 mosquitoes fed on viremic horses – all negative
- Virus in nervous tissue
- Very little virus in tissues
Should a Horse Infected with West Nile Virus be Destroyed?

- There is no reason to destroy an infected horse
- At least half of the horses recover from the infection
- Treatment is supportive and not specific
Equine West Nile Virus Encephalomyelitis

I. Definitions

A) West Nile Virus (WNV) - Flavivirus in the Japanese Encephalitis Antigenic Complex; arbovirus.
B) West Nile Fever (WNF) – viral encephalitis in people caused by the West Nile Virus

II. Background

A) West Nile virus has emerged in regions of Europe and North America. WNV causes fatal encephalitis in humans and horses, as well as causing mortality in certain domestic and wild birds.
B) WNV was first isolated from a febrile woman in the West Nile District of Uganda in 1937. Equine disease was first noted in Egypt and France in the early 1960s.
D) Human cases
III. Transmission

A) Arbovirus transmitted primarily by *Culex spp* mosquitoes
   1) The virus has been isolated from 43 mosquito species, predominantly of the genus *Culex*.
   2) Transovarial transmission has been demonstrated though at low rates.
   3) Requires 6-10 days incubation after feeding on infected bird before mosquito is infectious.
   4) Virus isolations have occasionally been reported from other hematophagous arthropods (e.g., bird-feeding argasid [soft] or amblyommine [hard] ticks), and experimental transmission has been successful.

B) Not thought to be transmitted by direct contact with birds
   1) In North America, infected birds have been found to have an abundance of virus in many tissues and to excrete virus in feces.
   2) It is possible, when handling dead birds or when carnivores eat birds infected with WNV, that exposure may occur.
   3) Preliminary reports suggest possible direct bird to bird transmission.
      (a) Raptors can acquire the virus by eating infected prey
      (b) Birds may transmit virus in feces
      (c) Transovarial transmission may occur
   4) Caution should be taken when handling live or dead birds in a WNV endemic area.

C) All mammals, with the possible exception of Lemurs, are thought to be dead end hosts.
   1) WNV has been isolated from mice and hamsters, camels, camalids, cattle, horses, dogs, humans, lemurs, and frogs.

D) Transmission does not occur by direct mammal-to-mammal contact.

IV. Disease in birds

A) In Europe – only subclinical infections

B) North American outbreak
   1) First indication that the virus is in an area is often the finding of dead corvids, especially crows.
   2) The birds show signs of neurologic disease
      (a) Weakness, sternal recumbency
      (b) Ataxia
      (c) Tremors
      (d) Anisocoria
      (e) Abnormal head posture
      (f) Circling
      (g) Convulsions
3) Disease of other organ systems - virus can be found in the heart, kidney, liver and gastrointestinal tract with abundant virus in the lumen of the GI tract.
4) Sudden death from systemic infection is common.
5) Has been identified in at least 138 species of birds in North America.

V. Equine West Nile Virus Encephalomyelitis World Wide

A) 1962-1965 - Camargue (France) – 50 cases
B) 1963 – Egypt
C) 1990 – Portugal
D) 1996 – Morocco - 42 of 94 affected horses died
E) 1998 – Italy - 14 cases in 1998, 6 died or were euthanized
F) 1998 – Israel
G) 1999 – Long Island (NY) – 13 of 25 cases fatal
H) 2000 – Northeastern USA - 23 of 65 cases fatal
   1) New Jersey (27 horses), New York (24 horses), Connecticut (7 horses), Delaware (4 horses), RI (1 horses), Massachusetts (1 horses), Pennsylvania (1 horses).
I) 2000 – France – highly fatal outbreak
J) 2001 – Eastern USA – 738 equine cases in 20 states.
   1) 33 % fatality rate (156/470).
K) 2002 – USA - 14,717 equine cases in 40 states.
L) 2003 – USA – 4,426 equine cases in 48 states.
M) USA - 2004 – 1,341 equine cases; 2005 – 1,075 equine cases; 2006 – 1061 equine cases; 2007 – 466 equine cases ; 2008 – 218 equine cases
N) Seroepidemiology (high rate subclinical infections): 31% in the Long Island outbreak, 20-70% of normal horses seropositive in endemic areas Europe. France 8% of horses in outbreak IgG titers; 4% had IgM titers.

2006 – 1061 EQUINE CASES
VI. Epidemiology -- USDA case control study 2000

A) 1487 equids on 49 case farms and 101 control farms
   1) Farms located in Connecticut, Delaware, Massachusetts, New Jersey, New York, Pennsylvania and Rhode Island.

B) Findings
   1) Marginally significant association between case farms and presence of Blackbird roosts and waterfowl congregations within 1/2 mile.
   2) Insect control methods -- farm or horse level
      (a) Not associative with likelihood of infection
      (b) lack of association may be due to
         (1) Heterogeneous approach from farm to farm
         (2) Control methods targeted flies

3) Pleasure horses at higher risk
   (a) More likely expose the vector? -- trail riding activities
4) Increased risk when not housed in stalls at night
5) Occurrence of cases associated with horse demographics and geographic distribution of dead birds
   (a) Endemic focus in bird roosts results in virus amplification
   (b) Proceed spillover to horses
6) Exposure of horses is geographically clustered
   (a) But within regions of virus activity, exposure of horses appears to be a chance event
   (b) This type of pattern may respond to effective vaccination
7) Mosquito species responsible for transmission to horses
   (a) Has not been identified
   (b) Control measures should be directed towards appropriate mosquito species

VII. Clinical disease - North American experience

A) Clinical signs
   1) Fever – in less than half the cases
   2) Acute onset of ataxia of all limbs
   3) Marked hypermetria
   4) Early recumbency
   5) Single foreleg lameness progressing to bilateral forelimb lameness/ataxia, monoparesis, paraparesis, tetraparesis progressing to recumbency
   6) Radial nerve paralysis
   7) Hypersensitivity to touch and sound – frequently present
   8) Somnolent – periodically falling to knees
   9) Anisocoria and a slow pupillary light response
10) Tremors and lip twitching
11) Muscle fasciculations
12) Most pronounced in the neck and triceps region
13) Difficulty swallowing
14) Facial nerve paralysis
15) Central blindness
16) Seizure activity

B) Estimated incubation period 5 – 15 days
C) Fatality rate – 40 - 33%
D) Course before death average 2 days (0 – 6 days)

VIII. Laboratory Findings

A) CBC – normal
B) Fibrinogen – normal
C) CSF – normal 3 of 4 cases
   1) Abnormal case had increase CSF protein and xanthochromia (N=1)
D) Blood chemistry normal

IX. Diagnosis

A) Serology
   1) Fluorescent antibody
   2) Virus neutralizing antibodies
   3) IgM capture ELISA
B) RT-PCR
   1) Blood – negative?
   2) CSF – negative?
   3) Brain/cord - positive
C) Virus isolation
   1) Blood – negative?
   2) Brain/cord – positive

X. Differential Diagnosis

A) Eastern, Western, Venezuelan Equine Encephalomyelitis
B) Equine herpes virus 1
C) Rabies
D) Equine Protozoal myelitis
E) Leukoencephalomacia
F) Stenotic cervical myelopathy
G) Hepatic, intestinal or renal encephalopathies
XI. **Outcome**

A) 1999 outbreak Long Island (NY) – 50% fatal  
B) 2000 outbreak Northeastern USA – 40% fatal  
C) 2001 outbreak Northeastern USA – 33% fatal  
D) Reported mortality rates 30 – 64%

XII. **Post Mortem**

A) Only nervous tissue involvement  
   1) Few gross lesions within the brain – occasional hemorrhages  
B) Prominent rhombencephalic lesions  
   1) Multifocal perivascular lymphocytic rhombencephalitis  
   2) Ring hemorrhages, neutrophils and multifocal microgliosis  
C) Peroxidase immunohistochemical staining  
   1) West Nile virus antigen in cytoplasm  
   2) Few neurons, nerve fibers, glial cells, neutrophils  
D) Virus isolation  
E) RT-PCR

XIII. **Treatment**

A) Supportive  
B) Preventing self-inflicted injury  
C) Fluids  
D) Treat for other differential diagnoses  
E) Herpes virus suspect status  
F) Rabies suspect status  
G) Plasma transfusion – passive antibody transfer  
H) Interferon therapy

XIV. **Prevention**

A) Available vaccine  
   1) Fort Dodge  
      (a) Vaccine tested with challenge studies  
         (1) No vaccinates or controls developed signs  
         (2) Vaccinates did not develop viremia  
   2) Millions of doses sold  
   3) Few adverse reactions  
      (a) Internet stories of abortion with congenital malformations  
      (b) Appear to have no basis – for numbers vaccinated, few reported adverse reactions  
      (c) Killed vaccine unlikely source of congenital malformations
(d) Isolation of wild virus from some aborted fetuses in Kentucky
   (1) Wild virus
   (2) Undefined role in abortion
   (3) Isolated in small percent of aborted fetuses
4) Efficacy unknown
   (a) It may take several weeks after the second dose before a measurable
       antibody response.
   (b) Horses may develop WNV soon after receiving the first dose of vaccine
       (1) Suggesting that one dose is not protective
   (c) The manufacturer’s recommendations
       (1) 2 doses 3-6 weeks apart
       (2) Yearly booster
   (d) Vaccinated horses may develop disease
       (1) Frequency this occurs is under investigation
       (2) The percent of vaccinates which are not fully protected unknown
   (e) Unvaccinated horses > 2X more likely to die

B) Recombitek® - Merial vaccine
   1) Recombinant canarypox vaccine
   2) Prevents viremia up to 1 year

C) Other arbovirus encephalitis vaccines
   1) EEE, WEE, VEE
   2) Do not cross protect

D) Mosquito control very important
   1) Stop the bird – mosquito infection cycle
      (a) Mosquito control
         (1) Primary infected mosquito is Culex spp
         (2) Control tailored to this species
         (3) Vector for horse could be another, less commonly infected, species
   2) Culex spp control
      (a) Range < 1000 yards
      (b) Local problem – local control
   3) Larval habitat destruction for Culex spp
      (a) Any puddle that lasts more than 4 days - habitat
      (b) Reduce the amount of standing water available
         (1) Water troughs, water buckets
         (2) Swimming pools, plastic wading pools
         (3) Bird baths, wheelbarrows
         (4) Clogged roof gutters
         (5) Recycling containers
         (6) Discarded tires
         (7) Tin cans, plastic containers, ceramic pots
         (8) Any water-holding container
      (c) Larvicides - BTI - Bacillus thuringiensis var. israelensis
4) Stable horses during peak mosquito feeding times  
   (a) *Culex* spp - dusk, dawn  
5) Adult mosquito control – last resort  
   (a) Use insect repellents  
      (1) Pyrethroid-based  
      (2) Containing DEET? – only equine approved products

XV. **Control**

A) What is the threat to caregivers?  
   1) No evidence of animal-to-person transmission  
B) Can a horse infected with West Nile virus infect other horses?  
   1) No documented evidence that WNV is transmitted from horse-to-horse.  
C) Are horses a source of West Nile virus? Are horses terminal hosts?  
   1) Historic evidence  
      (a) No virus in blood when clinically ill – dead-end host  
   2) 2 historic experimental induction studies  
      (a) Showed low level or no viremia – dead-end host  
   3) 3 experimental inoculation/transmission studies since 1999 in US  
      (a) USDA & CSU/CDC  
      (b) 16 horses studied - maximum viremia $10^3$ /ml (most < $10^2$/ml)  
      (c) Below number needed to infect feeding mosquitoes – dead-end host  
4) 8 horses infected via mosquitoes (*Aedes albopictus*)  
   (a) 1 hrs developed clinical signs  
   (b) 600 mosquitoes fed on horses during viremia – all negative  
5) Virus  
   (a) In nervous tissue – very low numbers  
   (b) No virus seen in other tissues – dead-end host  
D) Should a horse infected with West Nile virus be destroyed?  
   1) There is no reason to destroy an infected horse  
   2) Half of the horses recover from the infection