2009 National West Nile Virus Conference-Savannah, GA
Conference Sessions

- Plenary
- Epidemiology
- Clinical
- Ecology
- Virology
- Prevention & Control
- Global Arboviral Threats

- Poster Sessions
- Work Groups

- A lot of emphasis on reviewing events of the last 10 years.
- Nothing earth shattering.
“...the United States has no comprehensive national system for detecting outbreaks of infectious disease. Outbreaks of any disease that is not on CDC's current list of notifiable illnesses may go undetected or may be detected only after an outbreak is well under way.”

“Although many local and regional vector-control programs can effectively combat small and even medium-size outbreaks of vector-borne disease, they are not equipped to deal with outbreaks that are national in scope.”

“The significance of zoonoses in the emergence of human infections cannot be overstated.”
…“West Nile virus was first isolated in 1937 from the blood of a febrile woman in the West Nile province of Uganda.”…
West Nile Virus Epidemics

• First recorded epidemic in Israel in 1950’s.
  – France – 1962
  – South Africa – 1974
  – Romania – 1996
  – Italy – 1998
West Nile Virus In New York - 1999
NYC Summary of Events

- **June/July**: dead birds (mostly crows). DVM reports nervous system sx in sick birds.
- **August**: Bronx Zoo start to see bird morbidity/mortality. Birds subm. for necropsy, etc. First human encephalitis cases reported to NY DOH. **NOTE: concurrent epidemic & epizootic, yet a complete disconnect between PH & veterinary communities.**
- **September**: Bronx Zoo birds tested at USGS & USDA. Virus isolated/unidentified. Virus isolate sent to CDC.
- **September**: human cases seropositive for flavivirus (presumed to be SLE).
- **September**: partial genetic sequencing of virus shows interpreted as WNV-like / Kunjin-like. Complete sequencing confirms WNV.
Buzz City
by
Barry Blitt

The New Yorker
Sept. 27, 2000
“I love the smell of malathion in the morning”
• Quote from Dr. Ali Kahn, CDC
• “Mother nature is the best bioterror agent out there.”
West Nile Virus Activity

Non-Human WNV Activity
Human Disease Cases

National Center for Infectious Diseases

Cumulative results for 2004 calendar year reported as of June 21, 2005

2004
West Nile Virus Activity

Non-Human WNV Activity
Human Disease Cases

2006
West Nile Virus Activity
Cumulative results for 2006 calendar year
National Center for Infectious Diseases
CDC
West Nile Virus Activity

- Non-human WNV activity
- Human Disease Cases

National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2008 calendar year reported as of November 03, 2008
West Nile Virus Activity: 1999-2008

West Nile Virus Activity
- Non-human WNV activity
- Human Disease Cases

CDC
What happened in 2002?

- NY 99 virus – mutation – substitution of alanine in place of valine
- WN 02 – more efficient replication in mid-gut of the mosquitoes
- Shorter extrinsic incubation period – mosquitoes became infectious in 5 days instead of 8+ days.
- Also, ↑ temps seemed to ↑ infectivity.
- WN 02 completely displaced NY 99 from coast-to-coast.
West Nile Virus Neuroinvasive Disease Cases in United States

Regional epidemics

Avg = 1295/year

(*As of 11/18/2008)
Reported WNV Human Disease Cases U.S., 1999-2008

- 28,943 cases from 1,824 counties in 47 states and DC
  - WNND 11,807 (41%)
  - WNF 16,463 (57%)
  - Other clinical illness 673 (2%)

- 1,130 (4%) fatal cases
Estimated Number of WNV Infections and Fever Cases, U.S., 1999-2008

- Diagnoses and reporting of WNV fever varies by year and location. Reporting of WNV fever is ↓.
- WNND most reliable indicator of WNV disease activity in humans
- Based on serosurveys
  - 140 WNV infections per 1 WNND case
    140 x 11,807 WNND = ~1.65 million infections
  - 28 WNV fever cases per 1 WNND case
    28 x 11,807 WNND = ~331,000 WNV fever
Average Annual Incidence of WNND.
Transmission of WNV Without Mosquitoes
Other Modes of Transmission

- Blood transfusion
- Organ Transplant – 7 cases
- In utero transmission – 1 confirmed, 3 suspected
- Breast feeding – Mich. 2002
- Bird exposure - laboratory
Transfusion Transmission

• Blood transfusion – 23 transfusion cases occurred in 2002.
• WNV blood screening by NAT – 2003.
• Last documented transfusion case – 2006.
• ARC data: 2,800 WNV+ blood products interdicted, preventing ~ 8,400 infections.
ARC Donor Interview Studies

- 389 WNV+ blood donors
  - 15% - fever
  - 23% - HA
- 387 Controls
  - 3% - fever
  - 5% - HA
ARC Studies

**WNV+ donors**
- IgM – detected in 3-9 days
- IgG – detected in 7+ days
- Viral loads were already declining in WNV+ donors before any Ab was detected.
- Asymptomatic donors typically had a more robust T-cell response.
WNV—Novel Modes of Transmission

• Solid organ transplant-associated transmission
  – Total of 7 cases
    
    Kidney (3)  Liver (2)
    Lung (1)    Heart (1)

  – Included 1 cluster in which donor was WNV-IgM / IgG antibody + / nucleic acid PCR –

• Implications for organ donor screening

*Iwamoto et al, NEJM 2003
# CDC, MMWR 2005
WNV And Pregnancy

• One confirmed intrauterine transmission (2002)*
  – 20-year old female with WNND 2 months before delivery
  – Infant with subsequent retinitis, lissencephaly
  – Birth tissues WNV PCR +, infant serum & CSF WNV IgM +

• Subsequent surveillance, 2003 – 2005#
  – 0 / 79 intrauterine transmissions
  – 3 / 79 with infection shortly after birth (transplacental transmission?)

# O’Leary et al. Pediatrics 2006
WNV: The Other “Iceberg”

- Acute WNV Illness

- WNV Long-term effects
WNV: Long-Term Outcomes

• West Nile Fever:
  – Persistent symptoms commonly reported
  – Chicago Study of 2002 cases: 63% of WNF patients had persistent symptoms at 30 days; median duration of symptoms 60 days*
  – Sx: fatigue, weakness, concentration/memory & cognitive abilities ↓, persistent pain, etc.

• West Nile Encephalitis:
  – Persistent disabling neurologic sequelae
  – Tremors, movement disorders, subjective cognitive problems in >50%#
  – >3 years after acute illness
  – Higher all-cause mortality rates >1 year post-infection^
WNV: Long-Term Outcomes

- West Nile Poliomyelitis
  - High acute mortality
  - Prolonged ventilatory support, institutionalization among those with respiratory weakness
  - Severe long-term weakness
    - Recovery in only 1/3 of 23 patients by 4 years*
  - Young, healthy people frequently affected
    - Loss of productive years

*Sejvar et al, EID 2006
Treatment Trials

- Interferon
- Hyperimmune Globulin
- Monoclonal Ab
- Ribavirin
- Steroids

*Note: treatment have been largely unsuccessful. None of the treatment trials / drugs have shown efficacy in WNV rx. Treatment is still mgmt of symptoms.*
Treatment Trials - Barriers

- Insufficient enrollment / small N-size
- Delays in patient enrollment. For most, treatment needs to start w/in 72 hours.
- Geographic separation of patients.
- Impossible to predict which areas, and which hospitals to enroll.
- Some drugs (e.g. interferon) are already commercially available. MDs will simply treat their patients w/ antivirals rather than enroll them in a drug/placebo trial.
- Difficulty in getting timely IRB approvals.
WNV Vaccine Development

• Live attenuated vaccine
• DNA vaccine
• Chemically inactivated vaccine (derived from NY 99 – equine isolate)
• Viral vectored vaccine – (e.g. canary pox, or vesicular stomatitis).
• Subunit protein based vaccine
• Note: currently there are 4 licensed equine vaccines and 1 vaccine for geese.
WNV Vaccine Development

Three vaccines now in clinical trials

• YF 17D Chimera (ChimeraVax-WN) – Phase I & II
• PrMe VLP expressed DNA vaccine – Phase I
• WNV DEN 4’ Δ30 - Phase I

Two vaccines subm. as IND – planned for future clinical trials.

• Most vaccines may be 3 dose; 0M,1M,3M
## PVD Data from ArboNET

<table>
<thead>
<tr>
<th>Year</th>
<th>WNND</th>
<th>PVDs</th>
<th>WNND:PVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>2866</td>
<td>714</td>
<td>4.0</td>
</tr>
<tr>
<td>2004</td>
<td>1148</td>
<td>224</td>
<td>5.1</td>
</tr>
<tr>
<td>2005</td>
<td>1309</td>
<td>417</td>
<td>3.1</td>
</tr>
<tr>
<td>2006</td>
<td>1495</td>
<td>361</td>
<td>4.1</td>
</tr>
<tr>
<td>2007</td>
<td>1227</td>
<td>352</td>
<td>3.5</td>
</tr>
<tr>
<td>2008</td>
<td>674</td>
<td>178</td>
<td>3.8</td>
</tr>
<tr>
<td>Total</td>
<td>8719</td>
<td>2246</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Pathogenesis of WNV Infection

- Mosquito bite / inoculation of virus
- Virus spreads to local lymph nodes
- Virus replication → viremia
- Spread to visceral organs
- Hematogenous / retrograde spread → CNS
  - Retrograde axonal transport →
  - Spinal cord
  - Hippocampus/brain stem
WNV Human Infection “Iceberg”

- ~80% Asymptomatic Infection
  - ~80% of infections
  - Generation of lifelong immunity (presumed)

- <1% CNS disease
- ~20% “West Nile Fever”
West Nile Fever

- 10-30% of infections
- Fever, headache, rash, fatigue

Approximately 80% are asymptomatic.

Approximately 20% develop West Nile Fever.

Less than 1% develop CNS disease.
Asymptomatic ~80%

“West Nile Fever” ~20%

CNS disease <1%

WNV Human Infection “Iceberg”

WNV Neuroinvasive Disease (WNND)

• <1% of all infections
• Meningitis, encephalitis, poliomyelitis
• Survivors of WNND had increased odds of dying of something else.
West Nile Neuroinvasive Disease (WNND)

- “Meningitis”: Inflammation of the covering of the brain
- “Encephalitis”: Inflammation of the brain itself
- “Meningoencephalitis”
- “(Polio)Myelitis”: Inflammation of the spinal cord
Clinical Spectrum of WNV illness

WN Fever

WN Meningitis

WN Encephalitis

WN “Acute Flaccid Paralysis”
Clinical Spectrum of WNV Illness: Revised

- WN Fever
- WN Meningitis
- WN Encephalitis
- WN “Poliomyelitis”
  - Inflamatory Neuropathy
  - Radiculopathy / plexopathy
West Nile Fever

- Majority of symptomatic infections
- Abrupt fever, headache, myalgias, fatigue
- Nausea, vomiting, diarrhea (~25%)—may lead to dehydration
- Transient macular rash
- “Mild” febrile illness? Resolution in ~1 week?
WNV Rash

Rash more prevalent in: *
--mild disease (Fever>Meningitis>Encephalitis)
--younger patients (under age 65 > over age 65)

## WNV “Poliomyelitis”

- Often in younger age, previously healthy
- **Clinical hallmarks**
  - Absence of meningitis, encephalitis, fever, HA
  - CSF pleocytosis and protein elevation
  - Asymmetric weakness; often monoplegia
- Neuromuscular respiratory failure may occur
  - “Iron lung”
  - CFR ~50%
- Acute facial weakness in ~30% (generally transient)

*Samuel M et al. PNAS 2007;104(43): 17140-17145*
WNV and Movement Disorders

- **Tremor**
  - Coarse; postural / kinetic
  - Occasionally functionally impairing

- **Myoclonus**
  - Upper extremities, face
  - Nocturnal

- **Parkinsonism**
  - “Cogwheel” rigidity, bradykinesia
  - Postural instability

- **Cerebellar ataxia**
# Syndromes Reported as Associated with WNV Infection

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Non-Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Febrile Illness</td>
</tr>
<tr>
<td>Radiculitis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Myoclonus</td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Plexopathy</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Stiff-person syndrome</td>
<td></td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Chorioretinitis</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>Vitritis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>Rash Illness</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Myocarditis</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td></td>
</tr>
<tr>
<td>Guillain-Barre-like syndrome</td>
<td>Congenital defects</td>
</tr>
<tr>
<td>Tremor</td>
<td>Orchitis</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus</td>
<td></td>
</tr>
</tbody>
</table>

*Leadership for a Healthy Arizona*
WNV and Ocular Disease

• Absolute incidence unclear, but frequently reported

• Most frequent manifestations:
  – Chorioretinitis
  – Retinal hemorrhage
  – Vitritis
  – Optic atrophy, optic neuritis also described

• Course generally benign; permanent visual impairment uncommon
Non-human Epidemiology

United States
# WNV Surveillance Totals, U.S., 1999-2008*

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Tested</th>
<th>No. Positive</th>
<th>No. States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>NA</td>
<td>29,121</td>
<td>47</td>
</tr>
<tr>
<td>Mosquito</td>
<td>23 million</td>
<td>65,135</td>
<td>48</td>
</tr>
<tr>
<td>Dead bird</td>
<td>170,961</td>
<td>62,694</td>
<td>48</td>
</tr>
<tr>
<td>Veterinary</td>
<td>NA</td>
<td>25,293</td>
<td>47</td>
</tr>
<tr>
<td>Sentinel animals</td>
<td>NA</td>
<td>9,708</td>
<td>30</td>
</tr>
</tbody>
</table>

* Provisional Data as of February 13, 2009

* Leadership for a Healthy Arizona*

- **Culex species**
  - Cx. quinquefasciatus
  - Cx. pipiens
  - Cx. tarsalis
  - Cx. restuans
  - Cx. salinarius

- **Aedes species**
  - Ae. albopictus
  - Ae. vexans

- 64 mosquitoes species have tested positive for WNV in the U.S. from 1999-2008
Bird Immunity Studies

• Evidence of competitive displacement of SLE by WNV. Since the arrival of WNV, SLE has declined (in spite of increased surveillance).

• House finches – WNV infection provided cross immunity against SLE infection.

• WNV specific Ab prevented SLE infection.

• Prior SLE infection in finches did NOT provide immunity against WNV infection. Finches still developed WNV infection. But, it did increase the survival of WNV infected birds.
Mexico & Central American Studies

- Mystery continues.
- Surveillance shows ample evidence of WNV activity in Mexico & C.A.
- In some areas of Mexico, 22% of horses are WNV+
- Similar results seen in bird serology studies.
- Yet, morbidity & mortality is rarely seen in humans, equines, birds, etc.
- Reason is still unknown. Possibly - circulation of other flaviviruses creating some cross immunity?
Mosquito Blood Meal Analysis

• Mosquitoes are often feeding preferentially on specific bird species.
• Crow blood was rarely found in Culex blood meals. Crows were not the preferred entrée.
• Crows were contributing very little to Culex mosquito infection.
• Much of the crow mortality was crow-to-crow transmission.
• Viremic crows were often dying very acutely.
Equine Studies

- UC Davis study - monitored a herd of 40 unvaccinated horses for seroconversion.
- 30 horses seroconverted.
- Only 1 horse developed clinical sx.
- Vast majority (90%+) of WNV infections in horses are asymptomatic.
Green Pools - CA

• Increase in home foreclosures has resulted in record numbers of green pools.

• In CA, dipping surveys of green pools showed that 59% were breeding vector mosquitoes, primarily – *Cx. tarsalis*. 
Trends in Data Reporting

Dramatic reduction in USA counties reporting avian mortality surveillance data in last 6 years (see poster 27).
Percent of all U.S. counties reporting non-human WNV surveillance data to ArboNET by type and year, 2002-2007

From Lindsey, Poster # 27
ELC WNV Funds: Total Amount Distributed to States

Cumulative 2000-09 total: $188,290,161 distributed to states for WNV

Leadership for a Healthy Arizona
West Nile Virus

Just another Exotic - Invasive Species

Any species capable of propagating, that is not native to that ecosystem; and whose introduction does or is likely to cause economic or environmental harm or harm to human health.
West Nile Virus
Approximate Geographic Range in 1998
West Nile Virus - The most widespread of the flaviviruses
Global Arboviral Threats

• Yellow Fever – making a come back (S.A. 2007-2009)
• Chikungunya – Indonesia – 2004-2009
• Zika Fever – FSM 2007
• Rift Valley Fever
• Usutu
• Blue Tongue – Europe 2007
RESEARCH PRIORITIES

- Current and Future Geographic Distribution of WNV
- Bird Migration as a Mechanism of WNV Dispersal
- Vector and Vertebrate Host Relationships and Range
- Virus Persistence Mechanisms
- Mosquito Biology, Behavior, Vector Competence, Surveillance, and Control
- Development and Evaluation of Prevention Strategies
- Laboratory Diagnosis
- Clinical Spectrum of Disease and Long-Term Prognosis in Humans
- Risk Factor Studies
- Detailed Clinical Descriptions and Outcome in Human Cases
- Viral Pathogenesis
- Genetic Relationships and Molecular Basis of Virulence
- Vaccine Development for Animals and Humans
- Antiviral Therapy for West Nile Virus and Other Flaviviruses
- Economic Cost of the WNV Epidemic/Epizootic
- WNV Impact on Wildlife
- Investigate Alternate Modes of WNV Transmission to Humans
West Nile Virus Publications*

*PubMed Search 1/2/2009, West Nile Virus
• Joe Conlon – AMCA
• Prevention Education Campaign
• “I’m one!”
• Brief PSA – using WNV survivors “to put a face with the case.”
• Check the AMCA website at www.mosquito.org
Questions?

Power Points accessible at: