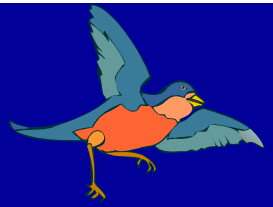
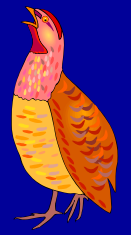



WEST NILE VIRUS INFECTION 2004 WESTWARD MIGRATION




Laurene Mascola, MD, MPH, FAAP
Chief, Acute Communicable Disease Control Program
County of Los Angeles Department of Health Services

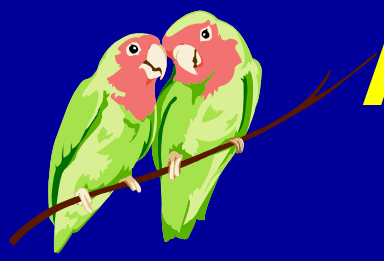
UCLA Grand Rounds

July 2, 2004

Contributor: Rachel Civen, MD, MPH and Carol Ann Glaser, DVM, et al.

OUTLINE

- West Nile Virus Overview
- West Nile Virus Outbreaks and entry to U.S. 1999
- Surveillance
- Epidemiology and Clinical Presentation
- Diagnosis
- New Modes of Transmission
- Prevention



ARTHROPOD-BORNE ENCEPHALITIS (1)

- Agents: Eastern equine, Western equine, St. Louis, La Crosse, California, West Nile viruses
- Incubation: 2-15 days
- Reservoir: Unknown, probably wild birds
- Transmission: Bite of infective mosquitoes

ARTHROPOD-BORNE ENCEPHALITIS (2)

- Presentation: Ranges from asymptomatic to aseptic meningitis to encephalitis
- Diagnosis: Serologic tests
- Treatment: Supportive
- Prevention: Mosquito avoidance, Mosquito abatement

WEST NILE VIRUS

- Single-stranded RNA enveloped virus of the familily Flaviviridae, genus *Flavivirus*
- Japanese encephalitis virus
  - ✓West Nile virus (WNV)
  - ✓Saint Louis encephalitis virus
  - ✓Japanese Equine encephalitis virus
  - ✓Murray Valley virus complex
  - ✓Kinjin virus

BACKGROUND: WNV INFECTIONS (1)

- 1937: First isolated in West Nile district of Uganda
- 1957: Israeli nursing home outbreak
  - ✓ Associated with severe neurologic disease and higher mortality rate
- 1990s: Frequency and severity of WNV outbreaks increased

BACKGROUND: WNV INFECTIONS (2)

- Outbreaks in:
  - ✓1994 Algeria
  - ✓1996 Romania: associated with severe neurologic illness
  - ✓1997 Czech Republic
  - ✓1998 Italy
  - ✓1999 Russia: associated with severe neurologic illness
  - ✓1999 USA: entry into US/NY outbreak

WEST NILE FEVER: BACKGROUND AND EPIDEMIOLOGY (1)

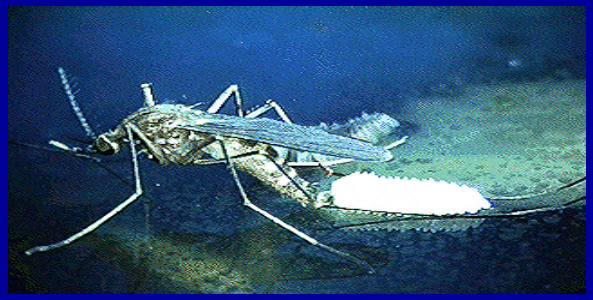
- Worldwide distribution
- Enzootic many parts of the world: Africa, Middle East, West Asia, Australia
- Caused primarily outbreaks of febrile illnesses: soldiers, children, and healthy adults

WEST NILE FEVER: BACKGROUND AND EPIDEMIOLOGY (2)

- Commonly found in humans and birds and other vertebrates
- Basic transmission cycle involves mosquitoes feeding on birds infected with the West Nile Virus
- Infected mosquitoes then transmit West Nile Virus to humans and animals when taking a blood meal

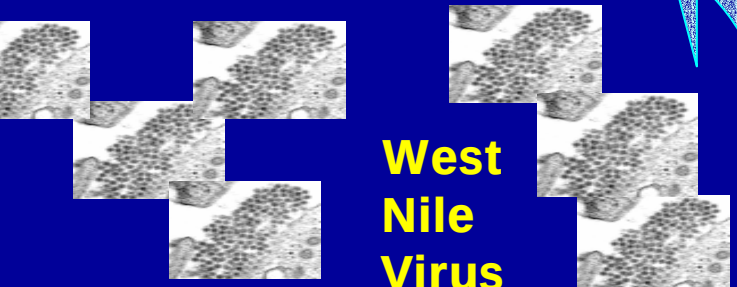
WEST NILE VIRUS (WNV) TRANSMISSION CYCLE

Mosquito Vector



Incidental Infections

West Nile Virus



Incidental Infections

Bird Reservoir Hosts

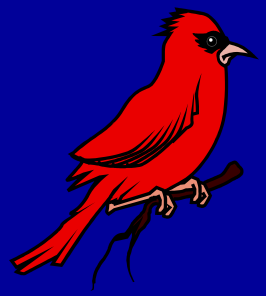
CDC

DHS

Acute Communicable Disease Control Unit

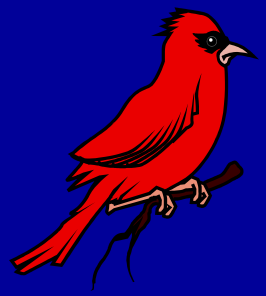
ECOLOGY

- Virus maintained bird—mosquito—bird cycle
- Small birds serve as 1°amplifying host
- Temperate climate cycle starts spring when mosquitoes 1st emerge and lasts until fall
- Like SLE, culex mosquitoes are 1°amplifying vectors. Other mosquitoes can act as bridge vectors biting both humans and birds



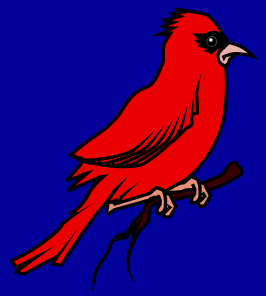
MYSTERY ILLNESS, NEW YORK CITY (1)

- August 1999, New York City (NYC)
- Infectious Disease physician reported 2 cases of encephalitis from northern Queens to NYC Dept of Health (NYCDOH)
  - ✓Fever, altered mental status, abnormal CSF
  - ✓One patient with severe muscle weakness
- NYCDOH initiated active case surveillance at nearby hospitals



MYSTERY ILLNESS, NEW YORK CITY (2)

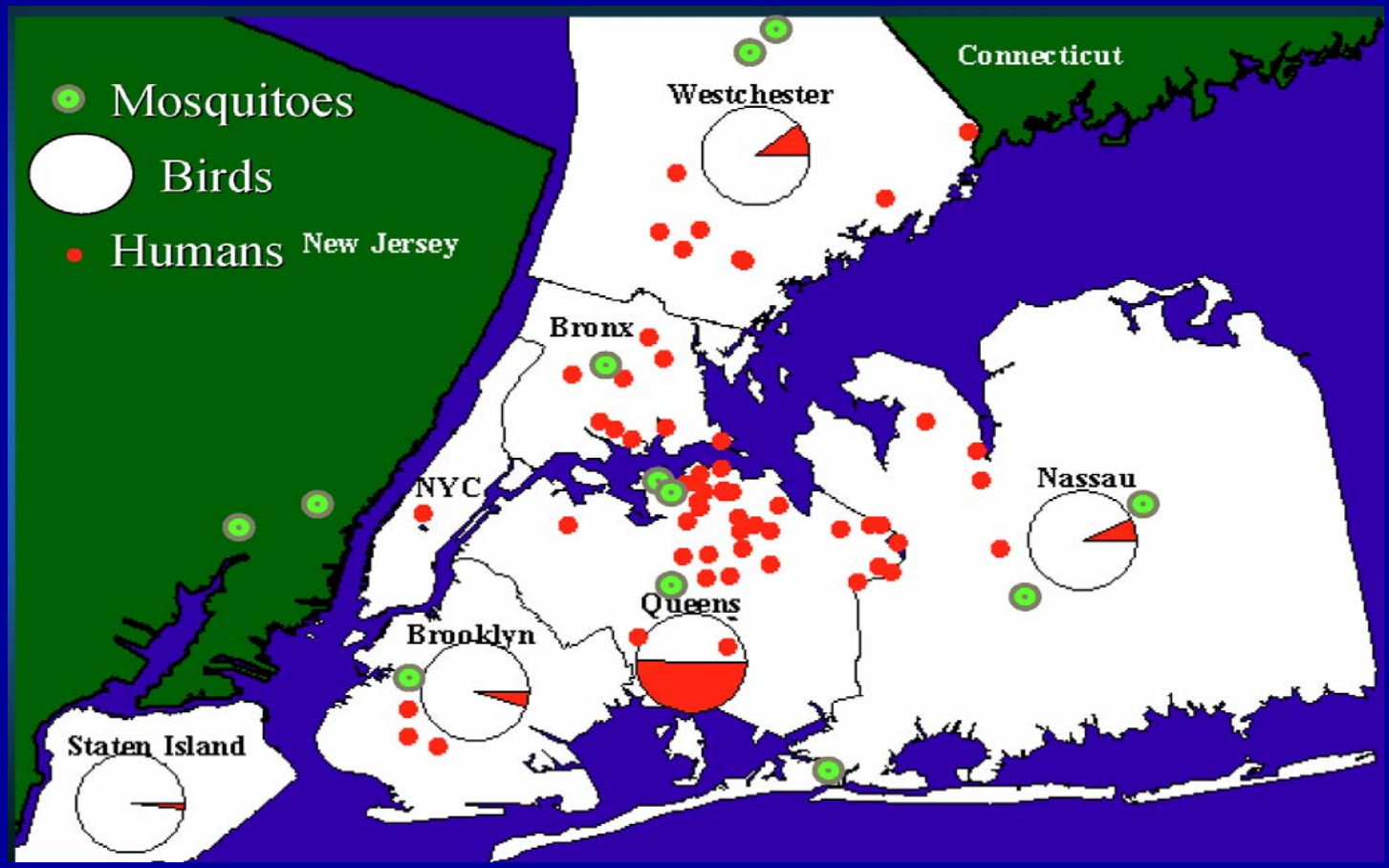
- At the same time...
- The Bronx zoo reported large numbers of zoo birds dying with encephalitis...
- Local residents reported large number of dead crows
- Zoo birds and dead crow work-up:
  - ✓ Molecular techniques identified WNV
- SLE does not normally kill avian reservoirs!



MYSTERY ILLNESS, NEW YORK CITY (3)

- Human case work-up:
  - ✓WNV identified by molecular, immunohistochemical, and serologic techniques
- First documented West Nile Virus in Western hemisphere
- First arboviral outbreak in NYC since the Yellow Fever epidemics of the 19th century

...THERE WAS WNV IN THE NYC AREA



WEST NILE VIRUS STRAIN

- 1999 NY WN strain from a flamingo "nearly identical" to 1998 Israel avian strain
- RT-PCR found > 99.8% similarity
- Avian strain isolated from a dead goose brain in 1998 similar to Israel epizootic outbreak
- Virus prior originated in Middle East

1999 VERIFIED WNV SURVEILLANCE REPORTS

Year	States	Humans/ Fatilities	Birds	Mosquito Pools	Horses
1999	4	62/6	?	16	25

- ✓Household-based human serosurvey in Queens determines 2.6% seroprevalence
- ✓WNV infected mosquitoes trapped in Ft. Totten, suggesting overwintering of WNV

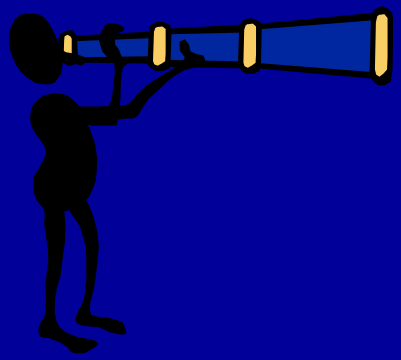
HOW DID WNV GET HERE ?

- No one knows...Some speculations
  - ✓Infected human host
  - ✓Bio-terrorism event
  - ✓Importation of infected birds or mosquitoes, larva
  - ✓Migration of infected birds
  - ✓Storm-transported vertebrae host (bird)

OUTCOME OF WEST NILE VIRUS INFECTION AMONG HOSPITALIZED PATIENTS

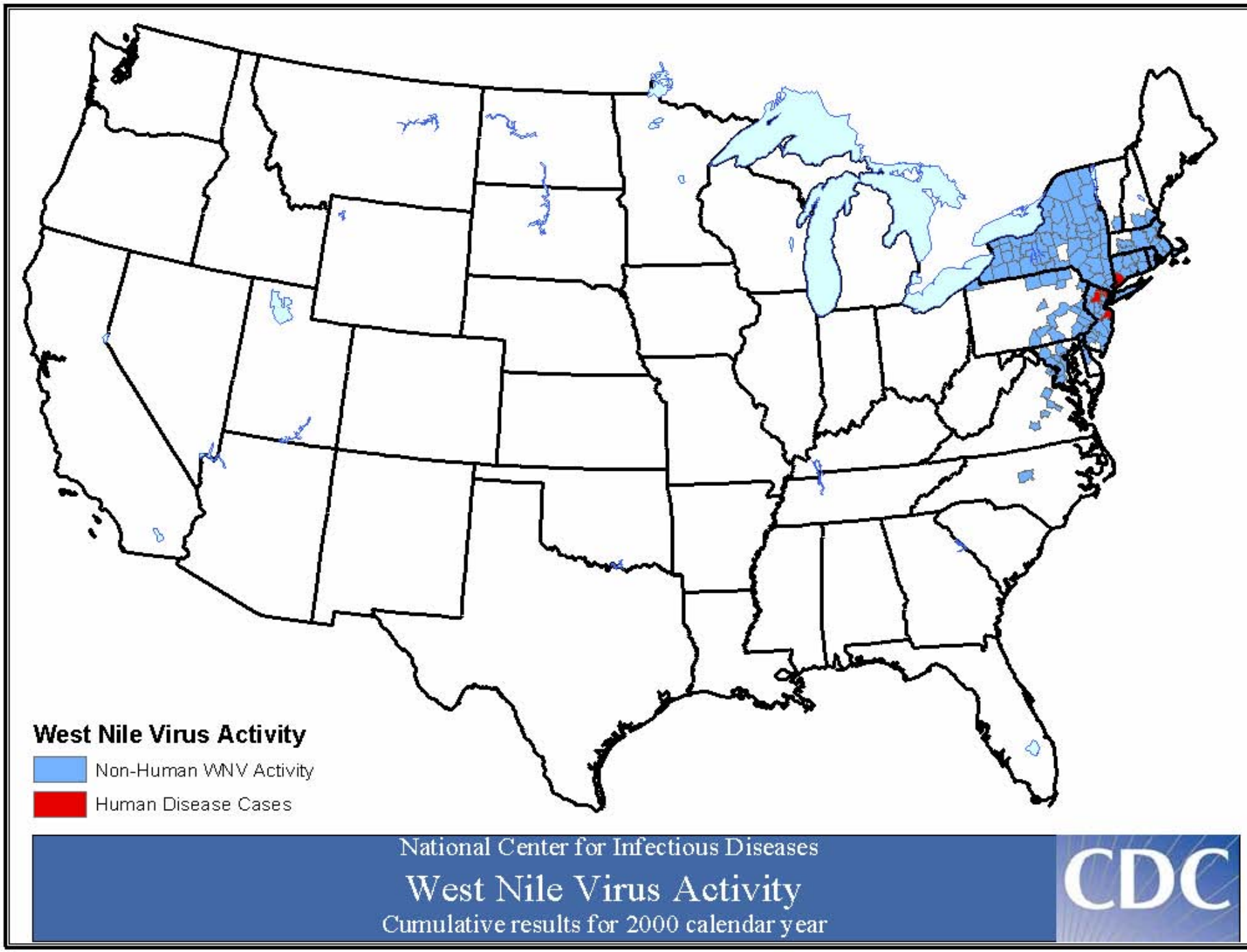
- At discharge (NY and NJ, 2000)
  - ✓More than half did not return to functional level
  - ✓Only one-third fully ambulatory
- At one year (NYC 1999 patients)
  - ✓Fatigue 67%, memory loss 50%, difficulty walking 49%, muscle weakness 44%, depression 38%
- Case fatality: 4–18%

SURVEILLANCE



2000!

Its Back or
The Year of the Corvid


West Nile Virus Activity
Non-Human WNV Activity
Human Disease Cases
National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2000 calendar year
CDC

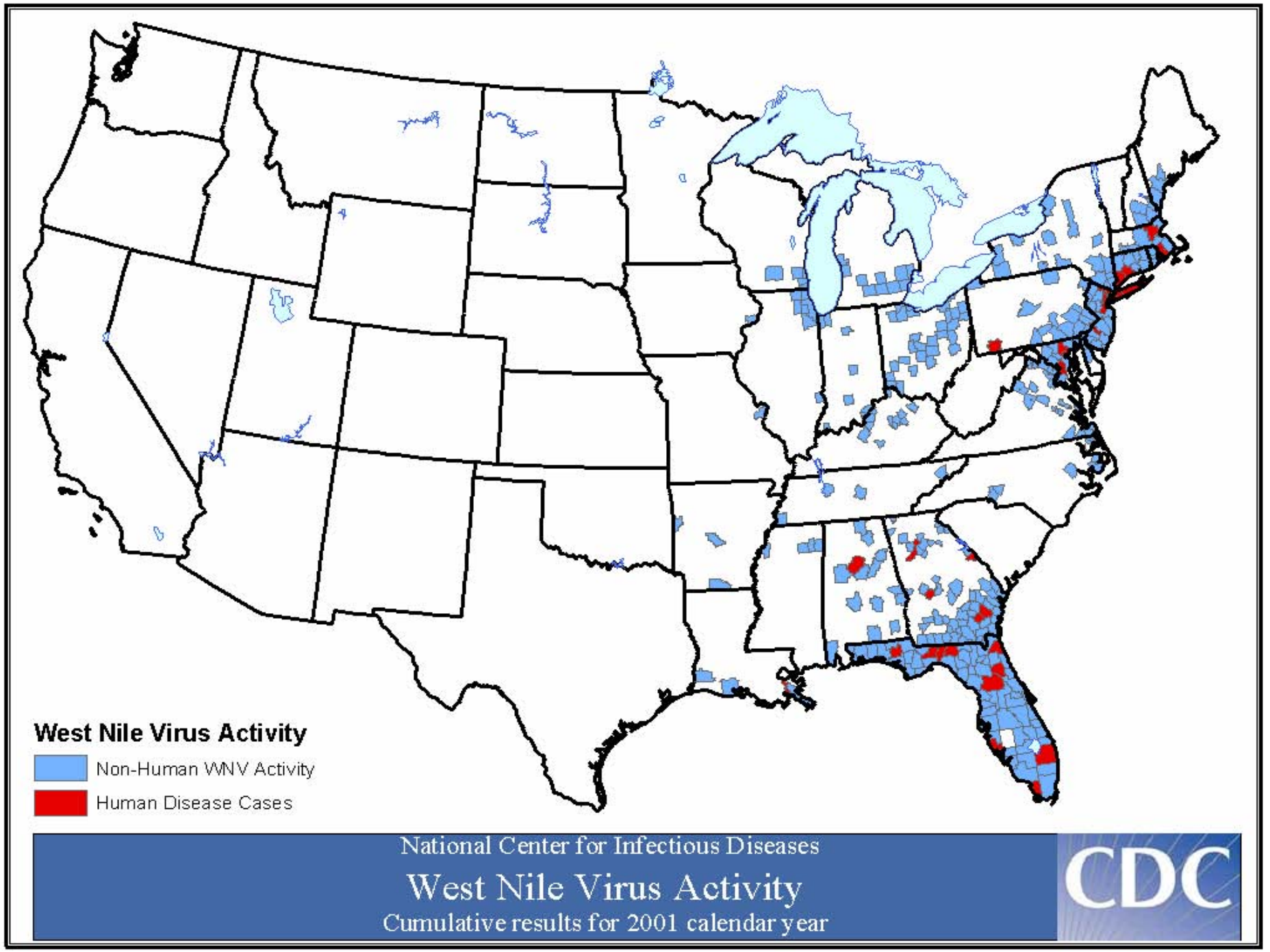
2000 VERIFIED WNV SURVEILLANCE REPORTS

Year	States	Humans/ Fatilities	Birds	Mosquito Pools	Horses
1999	4	62/6	?	16	25
2000	11 + DC	21/2	4,305	515	63

- ✓ Field-studies determine that dead crow = enzootic WNV foci
- ✓ Household-based serosurveys identify seroprevalence in Staten Island, Suffolk City, and Fairfield City, CT, to be lower than Queens in 1999

YEAR 2001

The Calm before the Storm!


West Nile Virus Activity
Non-Human WNV Activity
Human Disease Cases
National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2001 calendar year
CDC

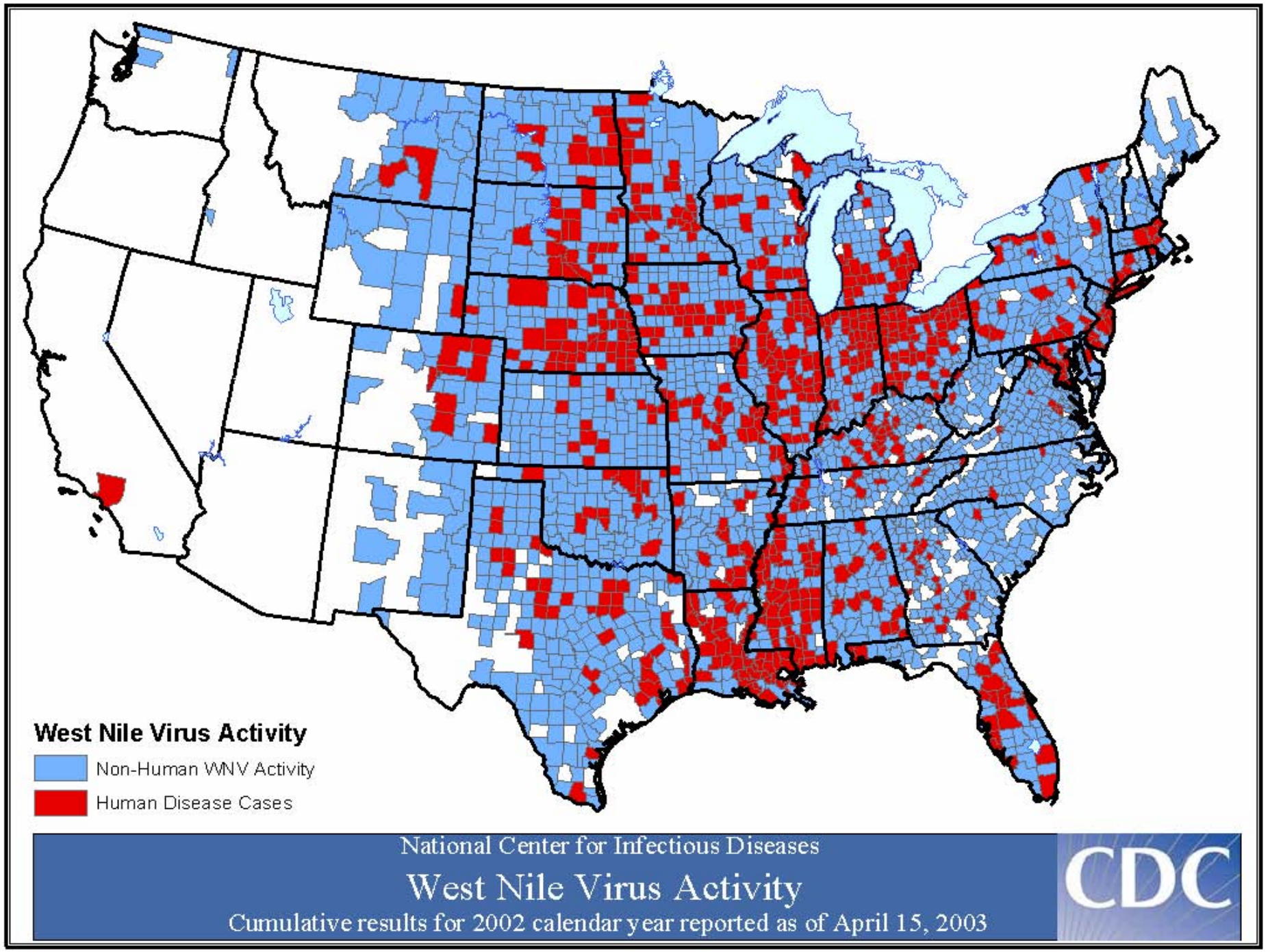
2001 VERIFIED WNV SURVEILLANCE REPORTS

Year	States	Humans/ Fatilities	Birds	Mosquito Pools	Horses
1999	4	62/6	?	16	25
2000	11 + DC	21/2	4,305	515	63
2001	27 + DC	66/9	7,332	919	731

- ✓ First major outbreaks in the South, GA and FL

YEAR 2002

- Largest arborviral epidemic ever documented in North America
- New modes of transmission documented!
  - ✓ Blood
  - ✓ Organ
  - ✓ Perinatal
  - ✓ Percutaneous
- New clinical syndromes documented
  - ✓ Acute Flaccid Paralysis Syndrome


West Nile Virus Activity
Non-Human WNV Activity
Human Disease Cases
National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2002 calendar year reported as of April 15, 2003
CDC

2002 VERIFIED WNV SURVEILLANCE REPORTS

Year	States	Humans/ Fatilities	Birds	Mosquito Pools	Horses
1999	4	62/6	?	16	25
2000	11 + DC	21/2	4,305	515	63
2001	27 + DC	66/9	7,332	919	731
2002	44 + DC	4,156/284	15,941	6,604	14,571

Horse vaccine became available

YEAR 2003

NIMBY:
"Not in My Backyard"

Now playing
Coast to Coast!

Welcome to Colorful Colorado!


FRIDAY
August 16, 2002

FORT COLLINS
COLORADOAN

Today's weather

Health board sends budget woes to county

Voters could decide fate of district's core programs

WHAT'S INSIDE
Life
Elvis

West Nile hits Colorado


FRIDAY
September 6, 2002

FORT COLLINS
COLORADOAN

Today's weather

Virus rears its head

West Nile cases in Colorado

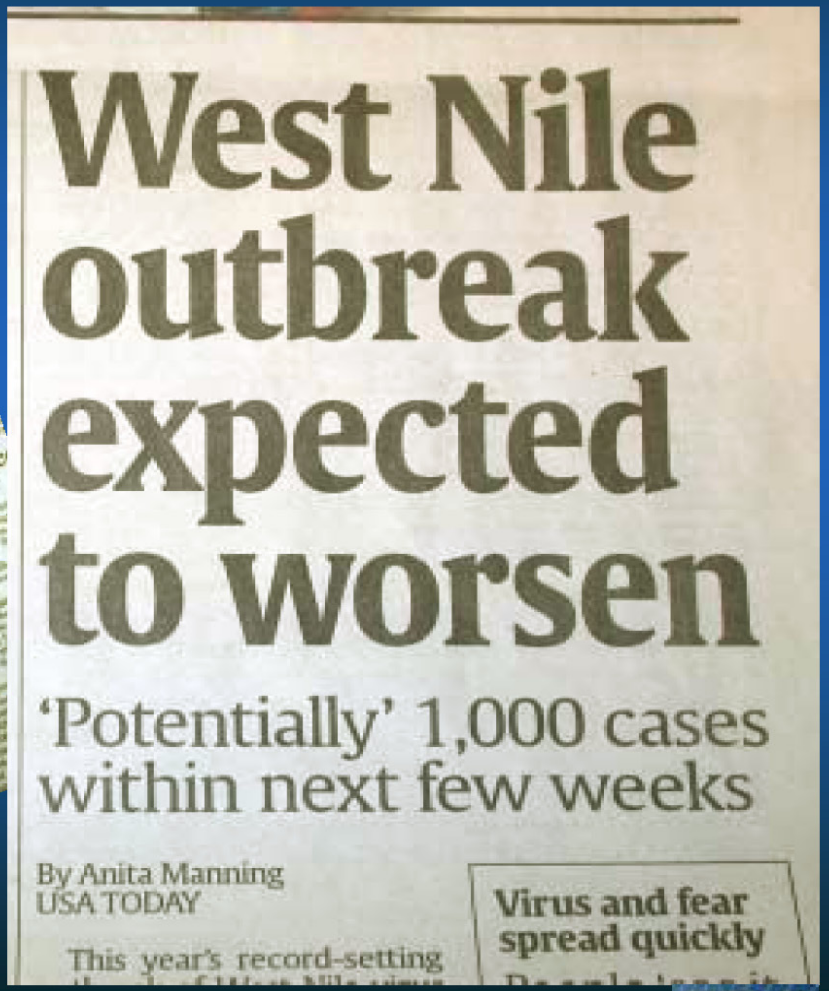
Controls on flights for 9/11 declared

Air traffic ove
NYC curtaile

Wellington horse positive for West Nile

WHAT'S INSIDE
Local
Spiffing up Lory's look
Page B1
Business
Rates on the rise
Page D1
Sports

The virus' westward spread


West Nile outbreak expected to worsen

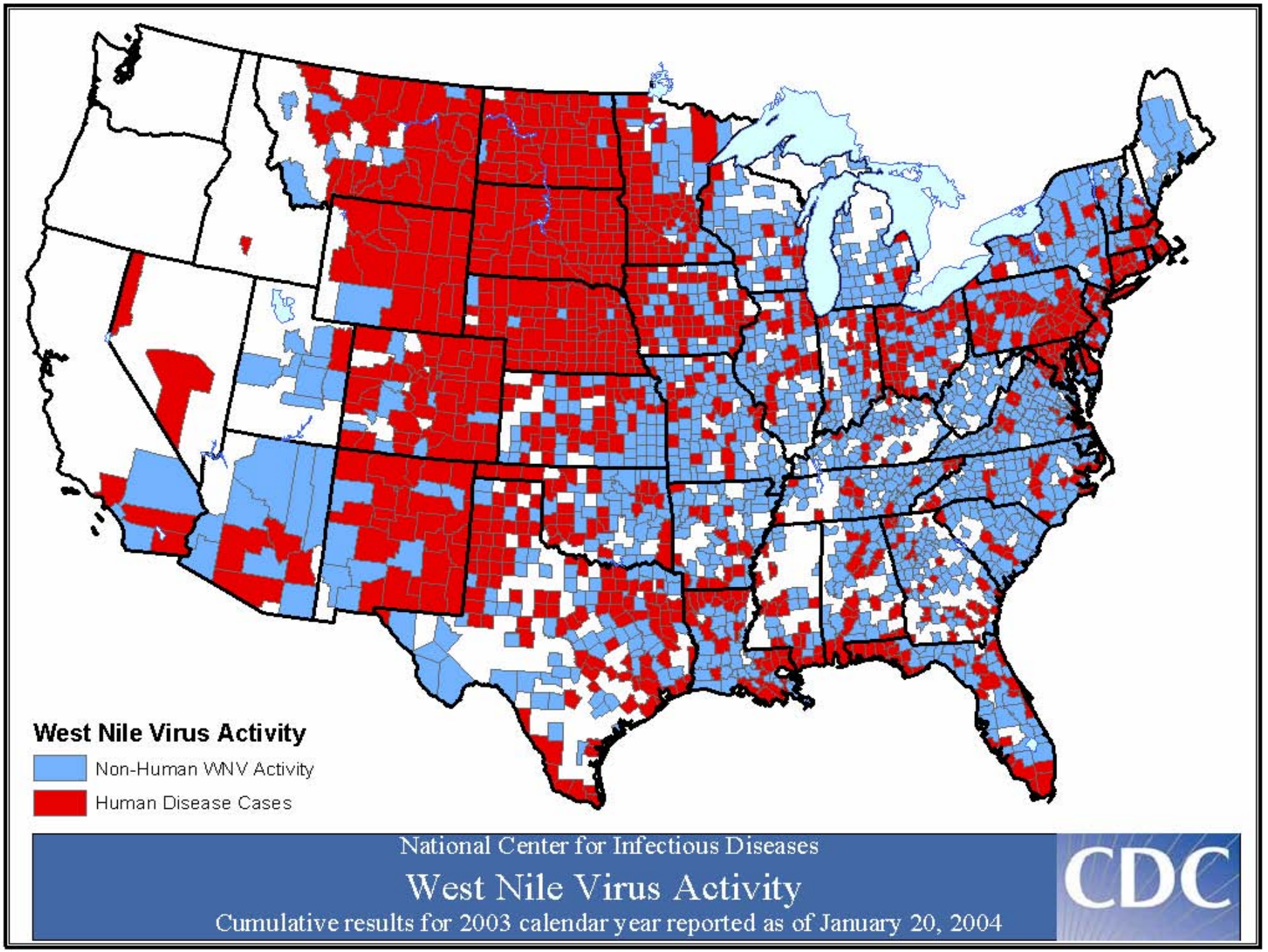
'Potentially' 1,000 cases within next few weeks

By Anita Manning
USA TODAY

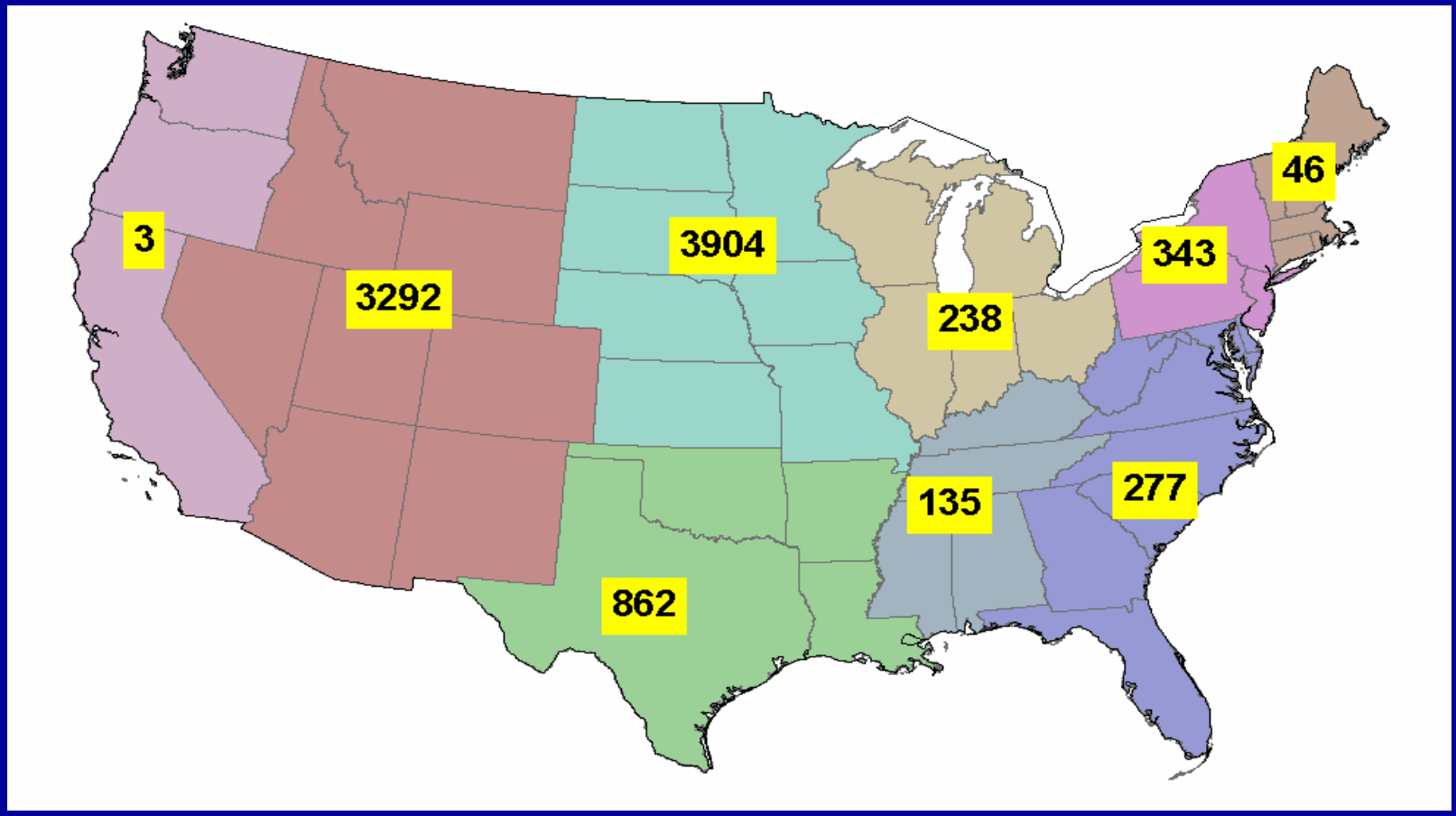
This year's record-setting

Virus and fear spread quickly

CDC


West Nile Virus Activity
Non-Human WNV Activity
Human Disease Cases
National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2003 calendar year reported as of January 20, 2004
CDC

HUMAN WNV DISEASE CASES, U.S., 2003*: REGIONAL DISTRIBUTION



CDC

* Reported as of 1/20/2004

DHS
Acute Communicable Disease Control Unit

WNV SURVEILLANCE ACTIVITY 2003

- 9,858 human cases confirmed in Arbonet from 47 states
  - ✓Colorado greatest number—2,477 cases
- 262 deaths nationwide
- Peak activity late July-Sept (~75%)
- WNV—fever 69% cases, 29% CSF+
- WNV activity in birds, mosquito pools, horses, and humans in 48 states

2003 VERIFIED WNV SURVEILLANCE REPORTS

Year	States	Humans/ Fatalities	Birds	Mosquito Pools	Horses
1999	4	62/6	?	16	25
2000	11 + DC	21/2	4305	515	63
2001	27 + DC	66/9	7332	919	731
2002	44 + DC	4156/284	15941	6604	14571* vaccine
2003	46 + DC	9122/223	11613	7856	4533

WEST NILE VIRUS: HUMAN ILLNESS

- Most cases asymptomatic or mild to moderate symptoms
- Fewer than 1% of WNV viral infections result in severe neurological disease
- Median age in 2003 was 47 (0-99 yrs)
  - ✓Fatal cases: median age 77 (0-97 yrs)
- Mortality rate in 2003: 2%
  - ✓7% of WN neuroinvasive disease cases

SUMMARY OF 2003 WNV ACTIVITY

- WNV activity has dramatically increased through out US from 1999 to 2003
- In 2003: human cases in 45 states
  - ✓ No human cases documented in Alaska, Hawaii, Oregon, Washington State, and Maine
- Increased proportion of cases WNV Fever in 2003
  - ✓ More WNV diagnostics available at state, county, private laboratories
- States with greatest WNV activity: Colorado, S. Dakota, N. Dakota

SINGLE HUMAN CASE IN LAC, 2002 (1)

- Individual presented to LA Hospital with aseptic meningitis first week in August 2002
- Denied history of travel outside of LAC, mosquito bites, blood or organ transfusion, IVDU
- Thorough ecological investigation revealed no evidence of WNV in birds, mosquito pools, or sentinel chicken flocks in LAC

SINGLE HUMAN CASE IN LAC, 2002 (2)

- Case remains a mystery
- Laboratory results confirmed at State DHS and CDC
- Individual recovered uneventfully

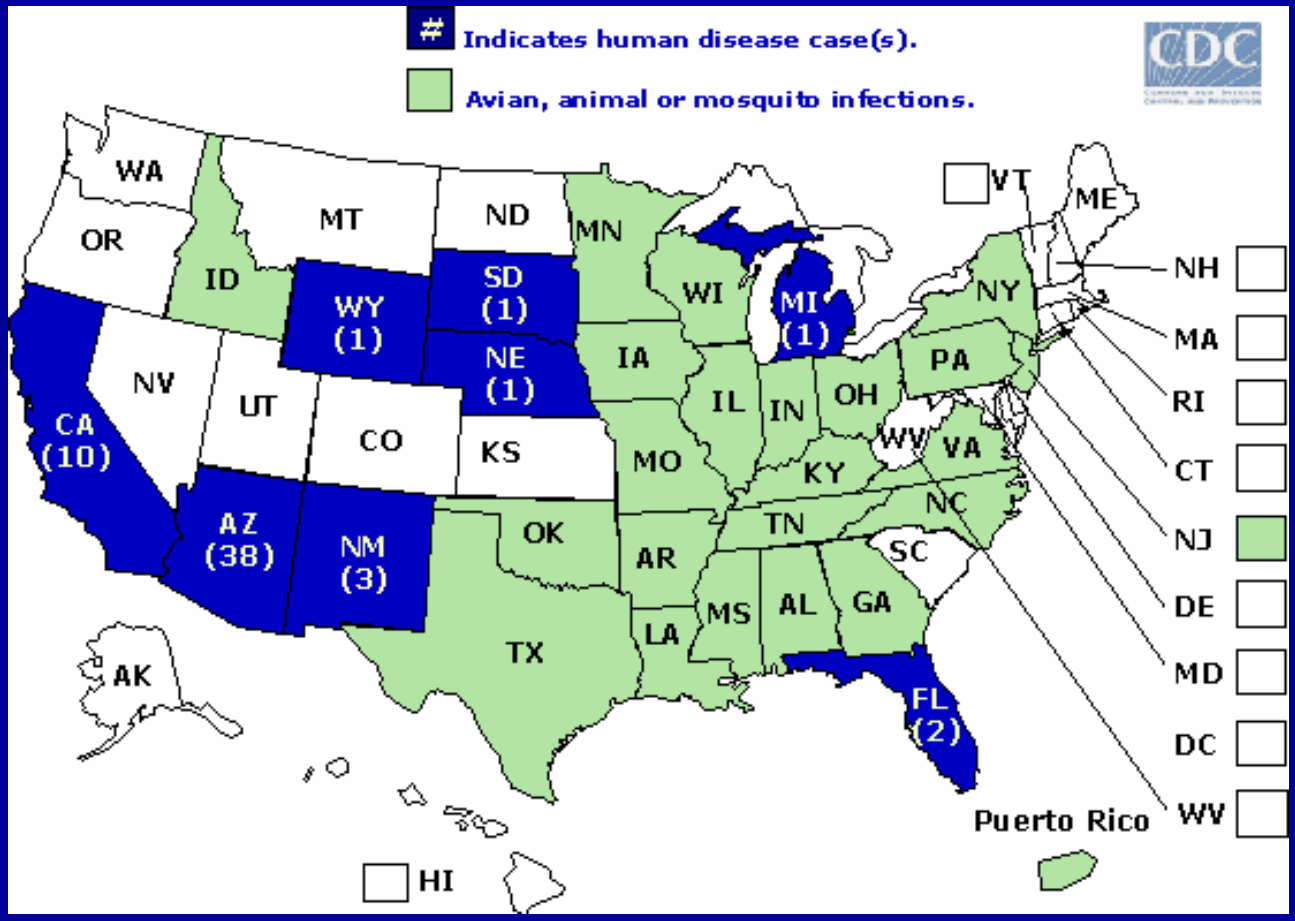
WNV SURVEILLANCE ACTIVITY IN CALIFORNIA 2003

- Sentinel chicken flocks positive from Riverside and Imperial counties July-September 2003
- 32 mosquito pools WNV positive: Imperial, LAC and Riverside
- 96 dead birds positive for WNV throughout So. CA
  - ✓ 64 positive WNV LAC : infected dead birds of 1,615 tested in 2003 (one horse)
  - ✓ The greatest number from the San Gabriel Valley

WEST NILE VIRUS
LOS ANGELES COUNTY 2003

- Only one confirmed case West Nile Fever October 2003
- 61-years-old sx: fever, headache, N&V prior hx Hepatitis B and C, IVDU
- Remembered frequent mosquito bites
- No travel history

SPREAD OF WEST NILE VIRUS IN US AS OF JUNE 29, 2004



www.cdc.gov/ncidod/dvbid/westnile/index.htm

DHS
Acute Communicable Disease Control Unit

WNV: CALIFORNIA 2004 JUNE 30, 2004

- LAC: > 250 infected crows
- California > 593
- Mosquito pools > 21
- Chickens positive > 72
- 11 CA cases: 8 in San Bernadino, 2 in Los Angeles, 1 in Riverside

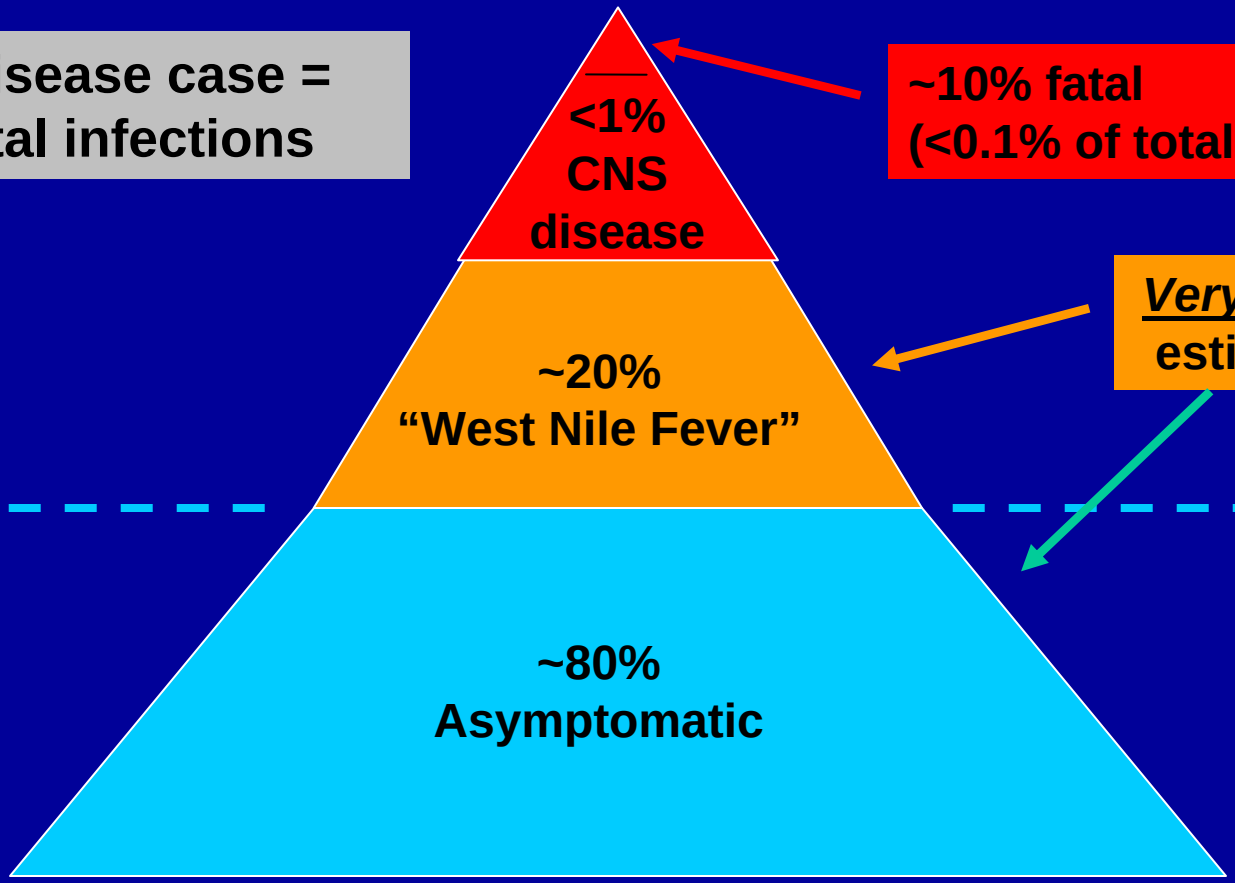
CLINICAL PRESENTATION

WEST NILE DEFINITIONS

- WNND=West Nile neuro-invasive disease:
  - ✓Encephalitis
  - ✓Aseptic meningitis
  - ✓Acute Flaccid paralysis
- West Nile fever – “dengue like”
- Asymptomatic
- 2002: 4,156 cases with 2,946 WNND
- 2003: 9,100 cases with 2,600 WNND

WNV HUMAN INFECTION "ICEBERG"

1 CNS disease case = ~150 total infections



~10% fatal (<0.1% of total infections)

Very **crude estimates**

"BENIGN" WEST NILE FEVER

- 2003 experience suggests it may not be so benign:
  - ✓ Duration of illness=22 days*
- Cohort study Colorado:
  - ✓ Of 40 cases**:
    - Body aches 98%
    - Eye pain 63%
    - Skin rash 63%
    - Swollen lymph nodes 48%
    - Nausea or vomiting 48%
  - ✓ Anecdotal reports: lingering fatigue, weakness, muscle fasiculations for weeks..sometimes months

*International Conference on Emerging Infectious Disease

**Pape J, 5th National Conference on WNV in US

WNV ASEPTIC MENINGITIS (1)

- 722 cases in 2002
  - ✓ 361 (50%) male
  - ✓ Median age:46 years (3 month-91 years)

    Age groups:

    0-39 years: 253 (35%)

    40-69 years: 367 (51%)

    70 and older: 102 (14%)
- Number of deaths: 15 (2%)
  - ✓ Number of males: 11 (73%)
  - ✓ Median age: 74 years (40-91 years)

O'Leary et al. Vector-Borne and Zoonotic Disease 2004

WNV ASEPTIC MENINGITIS (2)

- Fever, HA, nuchal rigidity (100%)
- Nausea, vomiting, neck pain, myalgia (80%)
- Variable frequency:
  - ✓ Low back pain
  - ✓ Tremors
  - ✓ Parkinsonism
  - ✓ Myoclonus
  - ✓ Flaccid paralysis of limb
  - ✓ Cranial Nerve palsies
  - ✓ Cerebellar signs
- Outcome: good

WNV ENCEPHALITIS (1)

- 2,220 encephalitis cases in 2002
  - ✓ 1239 (56%) male
  - ✓ Median age: 64 years (1 month-99 years)

    Age groups

    0-39 years: 359 (16%)

    40-69 years: 974 (44%)

    70 and older: 887 (40%)
- Number of deaths: 261 (12%)
  - ✓ Number of males: 164 (63%)
  - ✓ Median age 78 years (19-99 years)

O'Leary et al. Vector-Borne and Zoonotic Disease 2004

WNV ENCEPHALITIS (2)

- Almost all: fever, headache, altered mental status
- Variable frequency of:
  - ✓ Tremors
  - ✓ Weakness
  - ✓ Cerebellar signs/symptoms (some develop after MS improved)
  - ✓ Brainstem/Cranial nerve >50% (nystagmus, dysphagia, decreased gag)
  - ✓ “locked-in” syndrome
- Outcomes variable : ~70% baseline at 8 months

RISK FACTORS FOR WNV ENCEPHALITIS?

- Older Age -- surveillance data (>50, 10 fold; >80, 43 fold)
- HTN and cerebrovascular disease

  Campbell GL, Lancet Infect Dis 2002
- Age>75 years, diabetes risk for death

  Nash D, N Engl J Med 2001
- No association WNE and HTN

  Han LL, J Infect Dis 1999
- Age>51 years, HTN, male

  Lillibridge KM, ICEID conference

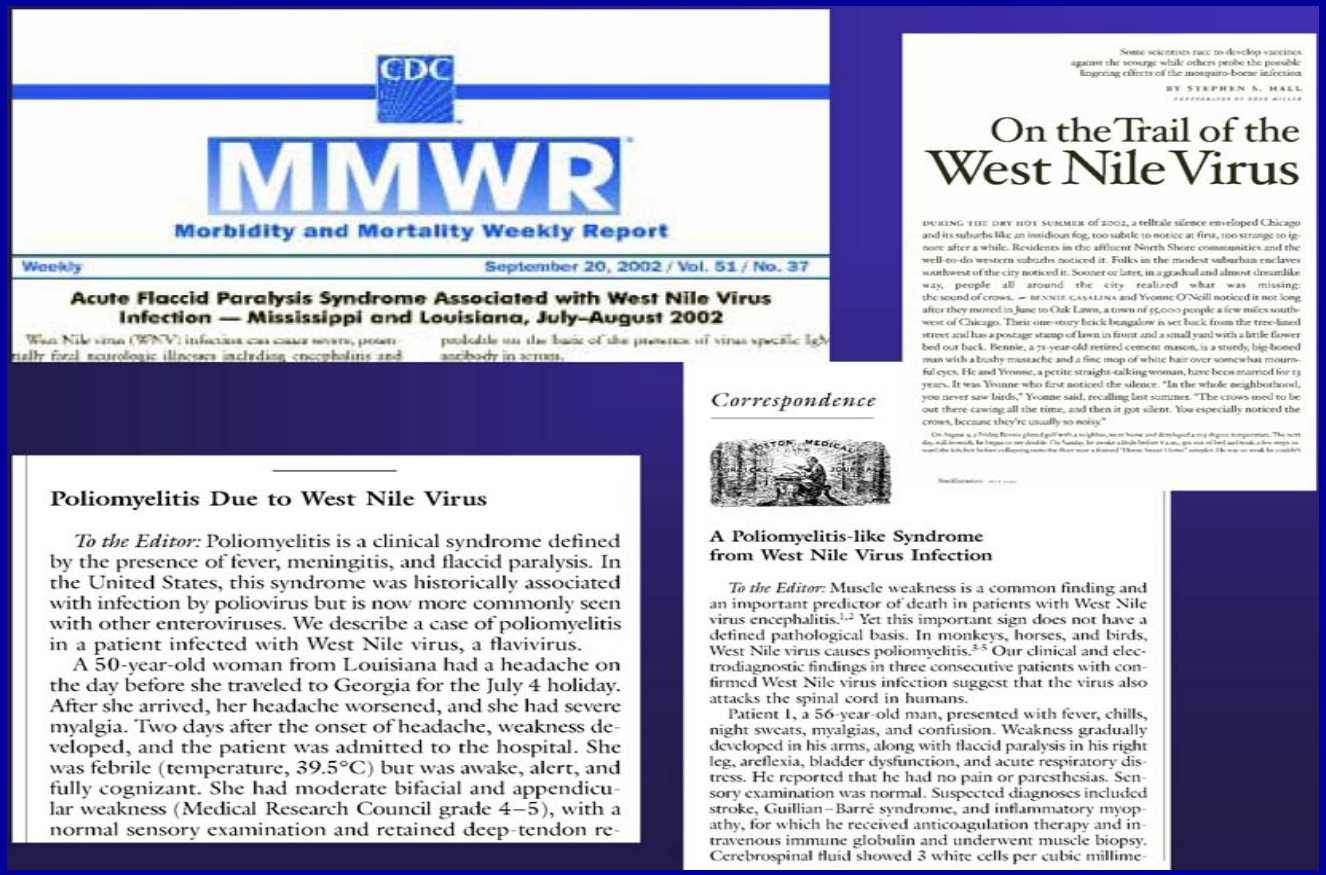
THESE RISKS

- Virus crossing blood brain barrier is enhanced by factors that disrupt above
- Or increased duration of level of viremia due to immune disfunction

INTERESTING FINDINGS FROM COLORADO WNV CASES 2003…

- Average duration of illness: 13.9 days
- Patients still ill at time of interview: 37%
- Known mosquito bite: 67%
- Repellant use: Never=53.7%
  Always =11.2%
- 60% of patients reported a rash
- 45% reported change in mental state
- 31% reported muscle tremors

WNV POLIOMYELITIS - 2002



CDC

MMWR

Morbidity and Mortality Weekly Report

Weekly September 20, 2002 / Vol. 51 / No. 37

Acute Flaccid Paralysis Syndrome Associated with West Nile Virus Infection — Mississippi and Louisiana, July–August 2002

West Nile virus (WNV) infection can cause severe, potentially fatal neurologic illnesses including encephalitis and [illegible] possible on the basis of the presence of virus specific IgM antibody in serum.

Poliomyelitis Due to West Nile Virus

To the Editor: Poliomyelitis is a clinical syndrome defined by the presence of fever, meningitis, and flaccid paralysis. In the United States, this syndrome was historically associated with infection by poliovirus but is now more commonly seen with other enteroviruses. We describe a case of poliomyelitis in a patient infected with West Nile virus, a flavivirus.

A 50-year-old woman from Louisiana had a headache on the day before she traveled to Georgia for the July 4 holiday. After she arrived, her headache worsened, and she had severe myalgia. Two days after the onset of headache, weakness developed, and the patient was admitted to the hospital. She was febrile (temperature, 39.5°C) but was awake, alert, and fully cognizant. She had moderate bifacial and appendicular weakness (Medical Research Council grade 4–5), with a normal sensory examination and retained deep-tendon re-

Correspondence

A Poliomyelitis-like Syndrome from West Nile Virus Infection

To the Editor: Muscle weakness is a common finding and an important predictor of death in patients with West Nile virus encephalitis.[1,2] Yet this important sign does not have a defined pathological basis. In monkeys, horses, and birds, West Nile virus causes poliomyelitis.[3-5] Our clinical and electrodiagnostic findings in three consecutive patients with confirmed West Nile virus infection suggest that the virus also attacks the spinal cord in humans.

Patient 1, a 56-year-old man, presented with fever, chills, night sweats, myalgias, and confusion. Weakness gradually developed in his arms, along with flaccid paralysis in his right leg, areflexia, bladder dysfunction, and acute respiratory distress. He reported that he had no pain or paresthesias. Sensory examination was normal. Suspected diagnoses included stroke, Guillian–Barré syndrome, and inflammatory myopathy, for which he received anticoagulation therapy and intravenous immune globulin and underwent muscle biopsy. Cerebrospinal fluid showed 3 white cells per cubic millime-

Some scientists race to develop vaccines against the scourge while others probe the possible lingering effects of the mosquito-borne infection

BY STEPHEN S. HALL

PHOTOGRAPHS BY DAVE MILLER

On the Trail of the West Nile Virus

DURING THE DRY HOT SUMMER of 2002, a telltale silence enveloped Chicago and its suburbs like an insidious fog, too subtle to notice at first, too strange to ignore after a while. Residents in the affluent North Shore communities and the well-to-do western suburbs noticed it. Folks in the modest suburban enclaves southwest of the city noticed it. Sooner or later, in a gradual and almost dreamlike way, people all around the city realized what was missing: the sound of crows. — BENNIE CASALINA and Yvonne O'Neill noticed it not long after they moved in June to Oak Lawn, a town of 55,000 people a few miles southwest of Chicago. Their one-story brick bungalow is set back from the tree-lined street and has a postage stamp of lawn in front and a small yard with a little flower bed out back. Bennie, a 71-year-old retired cement mason, is a sturdy, big-boned man with a bushy mustache and a fine mop of white hair over somewhat mournful eyes. He and Yvonne, a petite straight-talking woman, have been married for 53 years. It was Yvonne who first noticed the silence. "In the whole neighborhood, you never saw birds," Yvonne said, recalling last summer. "The crows used to be out there cawing all the time, and then it got silent. You especially noticed the crows, because they're usually so noisy."

WNV- ASSOCIATED ACUTE FLACCID PARALYSIS (AFP) (1)

- Acute Flaccid Paralysis (AFP) Syndrome
  - ✓ 6 cases reported in MMWR Sept.20, 2002
  - ✓ Pathologic process: anterior horn cells and motor axons similar to acute poliomyelitis
- Clinical description:
  - ✓ Acute onset of asymmetrical weakness without pain or sensory loss
  - ✓ CSF: pleocytosis, elevated TP
  - ✓ EMG: motor involvement and not demyelinating process

WNV- ASSOCIATED ACUTE FLACCID PARALYSIS (AFP) (2)

- Infrequently reported with WNV infection and other flaviviruses (JEE and SLE)
- Attributed to various etiologies:
  - ✓GBS, Radiculopathy, Transverse myelitis
- Not reported in recent outbreaks outside of US (Romania, Russia, Israel)

WNV- ASSOCIATED ACUTE FLACCID PARALYSIS (AFP) (3)

- Prominent feature in some encephalitis cases in NYC
- 2003: Colorado WNV-AFP cases from 3 counties evaluated to assess clinical outcomes, patterns of weakness, frequency of condition

WNV-AFP CASES FROM 3 CO COUNTIES SUMMER 2003: SUMMARY FINDINGS (1)

- 32 Patients Identified with AFP:
  - ✓ 18 (56%) male
  - ✓ Median age: 56 yrs (range: 15-84)
  - ✓ 26 (81%) with no prior medical conditions
- Attack Rate: 4.4/100,000 comparable to poliovirus epidemics
- Associated neurologic illness:
  - ✓ AFP alone — 3 (16%)
  - ✓ AFP+ meningitis — 11 (34%)
  - ✓ AFP+encephalitis — 16 (50%)

WNV-AFP CASES FROM 3 CO COUNTIES SUMMER 2003: SUMMARY FINDINGS (2)

- 3 distinct clinical and pathologic presentations:
  - ✓ "Poliomyelitis": 27 (84%)
  - ✓ GBS: 4 (13%)
  - ✓ Brachial plexus dysfunction/neuritis: 1(3%)
- Clinical features of poliomyelitis
  - ✓ Asymmetric weakness without sensory loss
  - ✓ EMG in 14 c/w anterior horn cell disease
  - ✓ MRI in 3 anterior spinal cord abnormalities
  - ✓ Respiratory paralysis requiring mechanical ventilation in 11/27 cases

WNV-AFP CASES FROM 3 CO COUNTIES SUMMER 2003: SUMMARY FINDINGS (3)

- 3 Month follow-up of 27 cases of AFP
  - ✓ 3 deaths of 27 followed
  - ✓ 2 still on chronic ventilation
  - ✓ 66 days median duration of intubation in 12 persons requiring mechanical ventilation
  - ✓ 15 patients with some improvement in strength with a range of recovery
  - ✓ 7 patients with minimal or no improvement
- Conclusion: Public health burden could be substantial!

WEST NILE VIRUS SPINAL FLUID

CSF:

- 0-1000 cells (85-95% with pleocytosis):
  - PMNs can predominate and persist up to 7 days
  - Often with reactive lymphocytes:
    - Plasma cells, “Mollaret” cells
    - Some cases have been confused with lymphoma
- Most elevated protein (90%)
- Normal glucose

Pepperell, C., JAMC 2003
Lillibridge KM., Emerg Inf Conference, 2003

OTHER DIAGNOSTICS

- MRI: more helpful than CAT SCANS
- Show leptomeningeal or periventricular enhancement

WEST NILE VIRUS LABORATORY AND NON-CNS

- Leukocytosis or leukopenia
- Hyponatremia
- Pancreatitis, lipase elevations
- Hepatitis, abnormal LFTs
- Myocarditis (elevated CPK, troponin, abn EKG)
- Myositis (elevated CPKs)

PEDIATRIC CASES

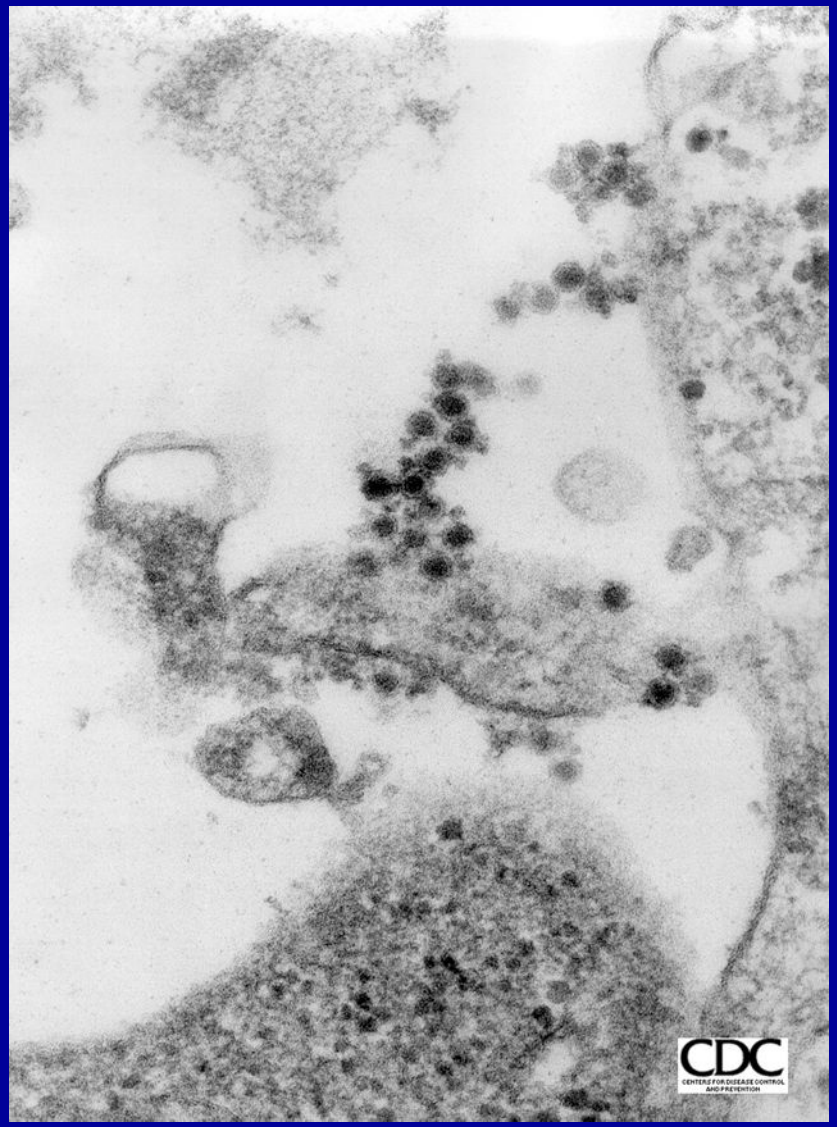
WNV: PEDIATRIC CASES

- 1999: 3% of cases (n=2)
- 2000: 0% of cases (n=0)
- 2001: 0% of cases (n=0)
- 2002: 4% of cases (n=150)
- 2003: 8% of cases (n=763)

Vidwan G, Clin Inf Dis, 2004
Dan O'Leary, CDC, personal communication, 2004

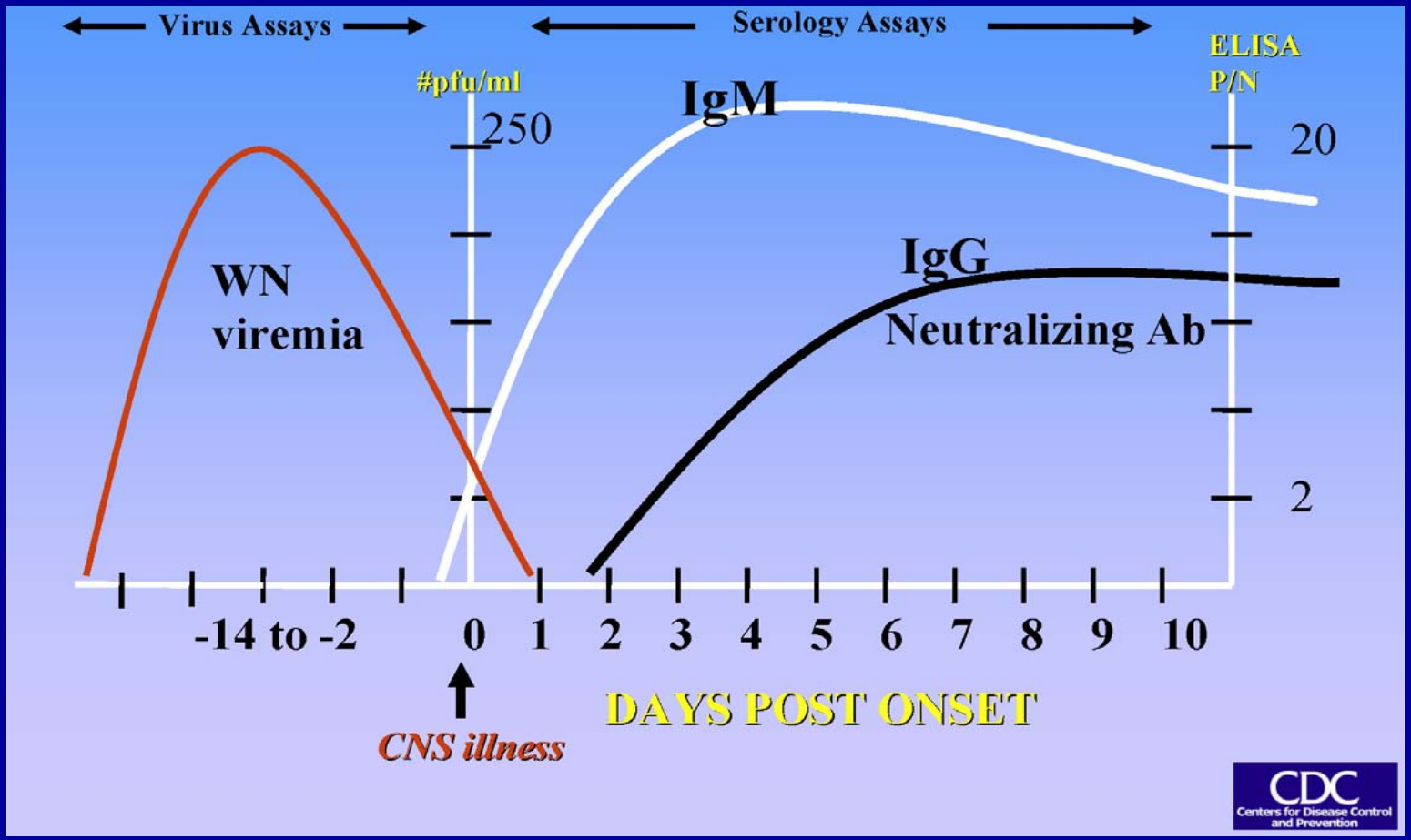
PEDIATRIC DATA 2003

- 763 WNV infections in <18 years:
  - ✓West Nile Fever: 79% (n=604)
  - ✓Meningitis: 11% (n=80)
  - ✓Encephalitis: 4% (n=33)
  - ✓Unspecified neuroinvasive: 5% (n=35)
  - ✓Other/unknown 1% (n=11)



Laboratory Diagnosis of West Nile Virus Infections

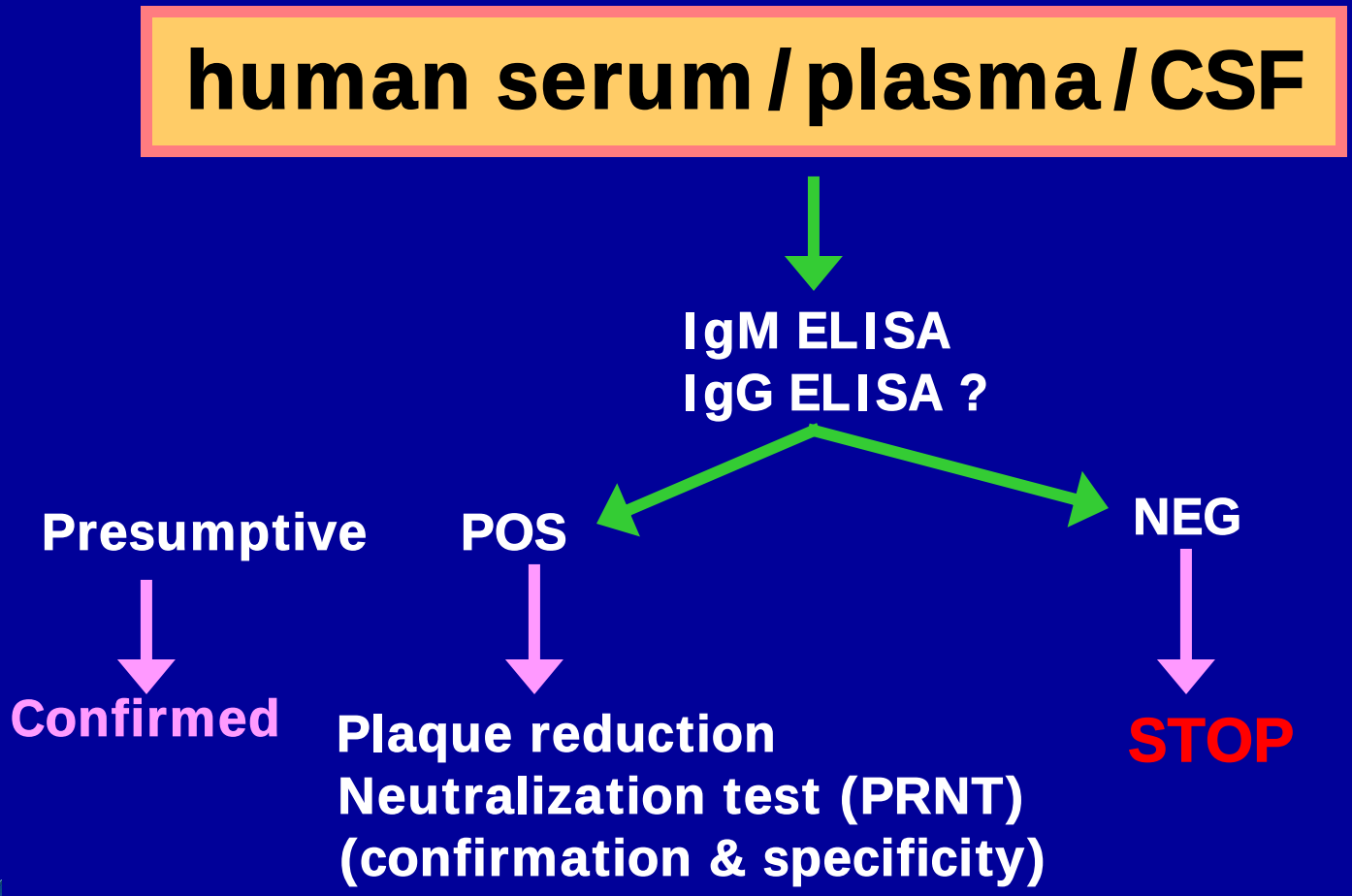
THEORECTICAL DEPICTION OF WNV HUMAN VIREMIA & IMMUNE RESPONSE



TESTING FOR WEST NILE VIRUS

	Bird Surveillance	Mosquito Surveillance	Veterinary Diagnostic	Human Diagnostic
Test Target	Virus	Virus	Antibody	Antibody
Sample Type	Tissues, oral swabs	Mosquito pools	serum	Serum, plasma, CSF tissues
Available Tests	TaqMan RT-PCR NASBA, RT-PCR, Isolation in Vero VecTest	TaqMan RT-PCR NASBA, RT-PCR Isolation in Vero VecTest	IgM ELISA Plaque Reduction Neutralization	IgM ELISA IgG ELISA Plaque Reduction Neutralization IgA ELISA IFA
Comments	Birds have high viremia; 10^6-10^9	Mosquito pool titers vary; VecTest will detect approx. 65%	Tissues from fatal equine cases tested by RT-PCR	Tissues from fatal human cases tested by RT-PCR. Plasma/serum/CSF can be tested by NAT.

RECOMMENDED SEROLOGICAL TESTING ALGORITHM FOR ARBOVIRUSES



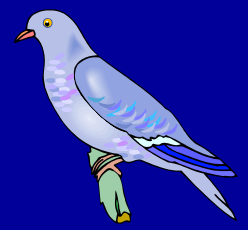
LABORATORY DIAGNOSIS WEST NILE VIRUS (1)

- Serological Diagnosis primary method of diagnosis
- IgM and IgG Capture ELISA preferred diagnositic test: simple, sensitive and can be used for serum and CSF (MAC Elisa)
  - ✓ 80% IgM positive at clinical presentation(WNV fever)
  - ✓ 95% IgM positive within 8th Day of symptom onset
  - ✓ 500 days after infection IgM can still be positive
  - ✓ This is a troubling problem for blood bankers
- People immunized against yellow fever, JE or dengue Hx can be false positive

LABORATORY DIAGNOSIS WEST NILE VIRUS (2)

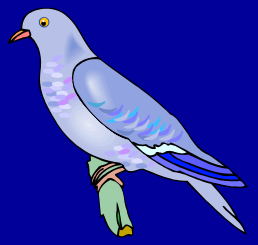
- PCR poor sensitivity 14%-57%
- Nearly impossible to culture the virus
- Plaque reduction neutralization test (PRNT):
  - ✓ Most specific test for arthropod-borne flaviviruses
  - ✓ Can help distinguish false-positive IgM, IFA
  - ✓ Distinguish between SLE and WNV
  - ✓ Used for confirmatory testing of WNV vs. SLE
- Need 4 fold Ab titers increase

TREATMENT (1)



- Supportive treatment
  - ✓About 25% require ICU care; 10% mechanical ventilation
- Interferon trials ongoing
- Ribavirin and interferon-alph-2b
  - ✓In-vitro activity in high doses
  - ✓One reported comatose patient did not improve
  - ✓Worse outcome with ribavirin in open-label trial in Israel—unclear patient selection

TREATMENT (2)



- Case reports stimulated interested in use passive immunization for treatment of WNV disease
- IVIG might help or abort established WNV infection*
- Need to treat early-all mice treated during viremic phase, before virus entered brain
- Need earlier diagnostics

*Agrawal, Peterson JID2003:188;1-14

WEST NILE TREATMENT TRIAL: INTRAVENOUS IMMUNOGLOBULINS

- Omrix=Israeli IVIG product
- "dramatic response" to Omr-IgG-am; 70-yrs-old, immunocompromised patient,
- "rapid improvement;" 42-yrs-old lung transplant**
- ~6 other cases: 2 improved, 2 no change, 2 death[§]

*Emerg Inf Dis 2001, **Transplant ID 2002
[§]Journal Infect Dis 2003

WEST NILE TREATMENT TRIAL: COLLABORATIVE ANTIVIRAL STUDY GROUP (CASG) OMRIX TRIAL

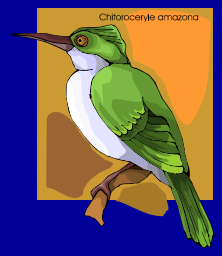
- Clinical trial in US:
  - ✓ Omrix (Israeli company) partnering with NIAID;
    - Immunoglobulin that contains antibodies to WNV
    - Developed from plasma of Israeli donors with high level of antibodies to WNV
    - Goal to enroll 100 hospitalized patients >18 years with WNV-related encephalitis
    - 3 groups:
      - standard IVIG (from U.S.)
      - WNV-IVIG (Omr-Ig-am)
      - Placebo

CONTACTS FOR COLLABORATIVE ANTIVIRAL STUDY GROUP (CASG) OMRIX TRIAL

- Laura Riser, CASG Clinical Administrator, University of Alabama (205) 934-2424
- Penny Jester, CASG Project Manager, University of Alabama (205) 996-7800
- Will need Human Subjects approval in place ahead of time

VACCINE DEVELOPMENT

- Media reports in 2002, 2003 suggested vaccine available by “next season”
- A number of human vaccine development efforts underway but probably at least a few years away
  - ✓ChimeriVzx-WNV (Acambis)/Phase I trial



WEIGHTED MODES OF TRANSMISSION

- Blood transfusion
  - Soft tissue transplantation
- Intrauterine infection
  - Breast feeding
  - Percutaneous exposure-occupation
- **Mosquito bite**

SCREENING OF THE US BLOOD SUPPLY FOR WNV IN 2003 (1)

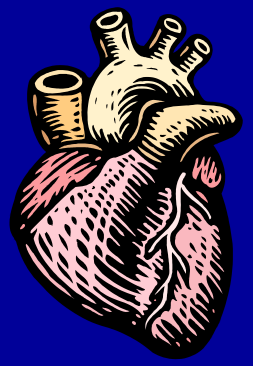
- All blood donors are being screened for WNV infection beginning June 2003
  - ✓ All donors screened for history of headache and fever one week prior to donation
  - ✓ Screen blood donations for WNV RNA using investigational nucleic acid amplifications tests (NAT)
  - ✓ All positive specimens confirmed by ELISA method and PRNT
  - ✓ WNV Positive units removed from donor pool

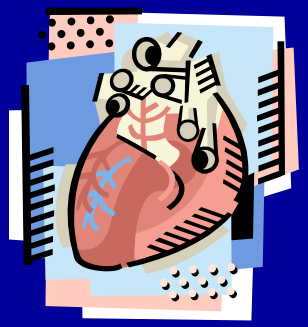
SCREENING OF THE US BLOOD SUPPLY FOR WNV IN 2003 (2)

- Blood donation poses no risk to the donor for acquiring WNV
- Screening of the national blood supply will decrease the risk of WNV associated with blood transfusions
- Screened over 8 million units in 2003, removed 1,000 viremic donors

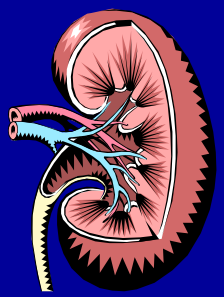
SCREENING OF THE US BLOOD SUPPLY FOR WNV IN 2003 (3)

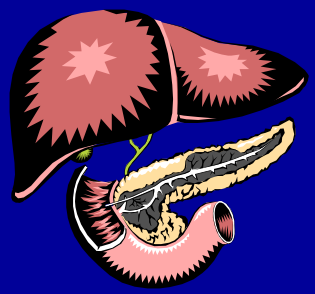
- 806 new WNV infections diagnosed by blood donor screening
- 23 cases possible transmission associated; 6 confirmed
- Viral loads in infected donations (.06-.5 pfu/mL) were lower in 2003 than 2002



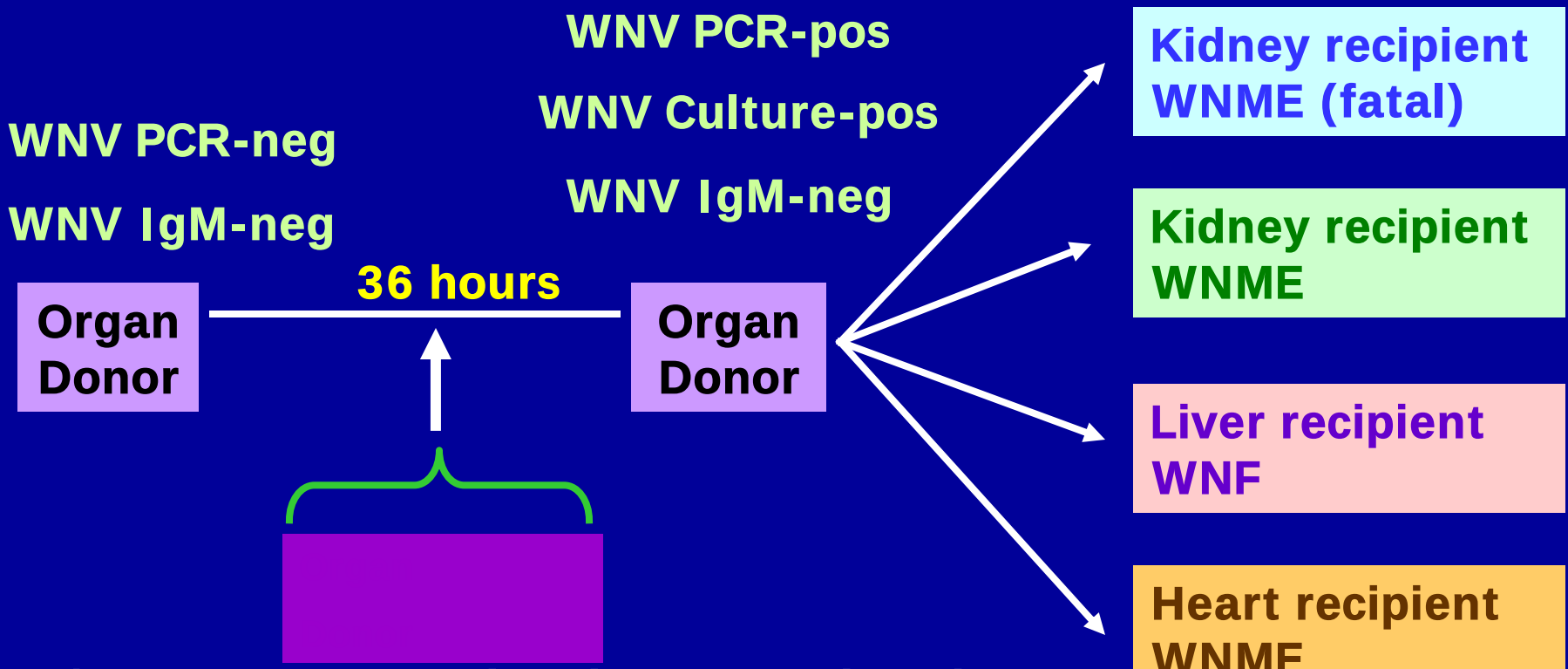


TRANSPLANT-ASSOCIATED WEST NILE INFECTION





WNV INFECTION IN ORGAN DONOR AND FOUR ORGAN RECIPIENTS, AUGUST 2002



F/U: 1 seroconverting donor; Retrieved, stored plasma – WNV PCR-positive

NEJM, May 2003

TRANSPLACENTAL WNV TRANSMISSION

TRANSPLACENTAL FLAVIVIRUS TRANSMISSION

- 2002: 1ST Documented WNV– late 2nd trimester infection (27 week gestation)
- Full term infant
  - ✓Chorioretnitis
  - ✓Cystic destruction cerebral tissue
  - ✓Laboratory evidence congenital WNV
- Other flavivirus associated with abortion/neonatal illness, no birth defects

MMWR: December 2002

TRANSPLACENTAL FLAVIVIRUS TRANSMISSION (1)

- 53+ live births evaluated to date:
  - ✓4 with WNV infections:
    - 1 documented intrauterine infection;
      - Infant normal
    - 3 possible intrauterine transmissions
      - Transient neonatal rash → normal
      - Neuroinvasive disease (9 d)
      - Lissenecephy/fatality (WNV causative vs. coincidental?)

Personal communication, Ned Hayes/Dan O'Leary, Fort Collins

TRANSPLACENTAL FLAVIVIRUS TRANSMISSION (2)

- 2003: Pregnancy registry for WNV/pregnancies
- Relatively reassuring
- More data needed

Personal communication, Ned Hayes/Dan O'Leary, Fort Collins

CDC INTERIM GUIDELINES FOR PREGNANT WOMEN

- Screening for WNV NOT recommended in asymptomatic
- Test individuals with (endemic area):
  - ✓Encephalitis
  - ✓Meningitis
  - ✓AFP or
  - ✓Unexplained fever

MMWR Feb 2004: 53(7): 154-157

CDC INTERIM GUIDELINES FOR PREGNANT WOMEN

- If WNV positive/evaluation of fetus:
  - ✓Detailed ultrasound exam fetus at least 2 weeks after onset of illness
  - ✓Amniotic fluid, chorionic villi or fetal serum can be tested
  - ✓Sensitivity? Specificity?

MMWR Feb 2004:53(7):154-157

CDC INTERIM GUIDELINES (1)

- If WNV positive/evaluation of newborn:
  - ✓Clinical evaluation:
    - Physical exam: neurologic,
    - WNV testing, IgG and IgM;
      - Umbilical cord or from infant w/in 2 days
      - If negative and maternal illness late (≤8 days before delivery)
        - Repeat testing ≥2 weeks after 1st sample
      - Hearing exam
      - Placental exam by pathologist

MMWR Feb 2004:53(7):154-157

CDC INTERIM GUIDELINES (2)

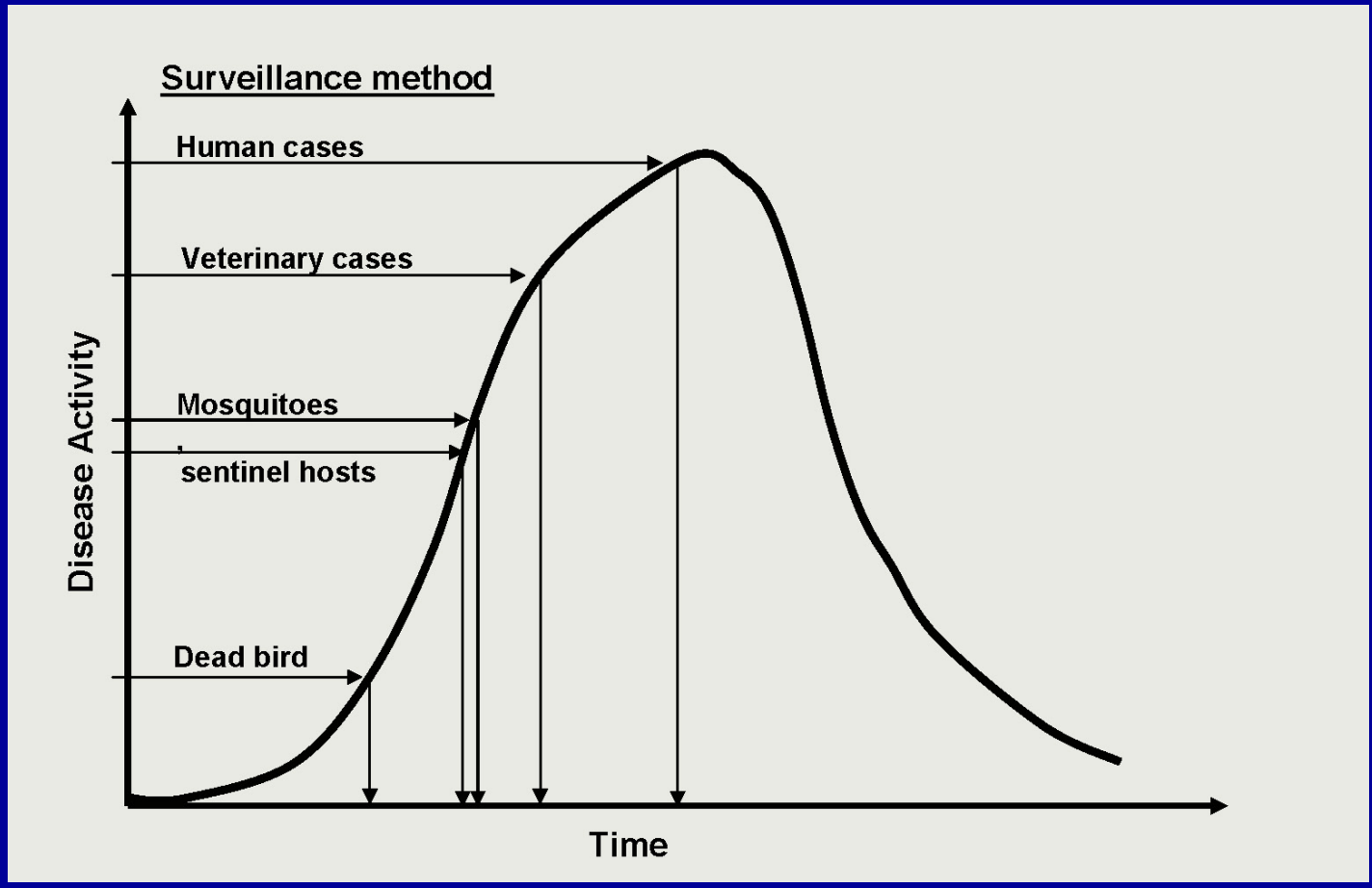
- If Infant positive for WNV:
  - ✓CT head—if abnormal, ped neurologist
  - ✓Ophthalmologic exam
  - ✓CBC, LFTs, consider LP
  - ✓Evaluation by geneticist
  - ✓Repeat hearing at 6 months
  - ✓Follow growth/development closely

BREASTFEEDING-ASSOCIATED WNV INFECTION

WNV TRANSMISSION IN MILK

- WN viral illnesses in children aged <1 year infrequently reported
- 1999-2001, no reports
- 2002, **SIX** persons <1 year old with WN virus infection reported (excluded one transplacental infection)
- Ages: 0, 1, 3, 6, 9 & 11 mos.
  - ✓ 1 asymptomatic
  - ✓ 5 WNME cases
    - 1 breastfed but mother without infection
    - 4 not breast fed in month prior to illness

ESTIMATED SENSITIVITY OF WEST NILE VIRUS SURVEILLANCE METHODS



BIRDS AND WEST NILE VIRUS

- WNV replicates well in bird – competent bird reservoirs sustain an infectious viremia for 1-4 days after exposure, subsequent life-long immunity
- Birds: house sparrow, crows, herons, pigeons, doves, chickens, and many other bird
- Drought periods and amplification of WNV spread
- Dead bird surveillance as a predictor of local WNV activity

CX QUINQUEFASCIATUS MOSQUITO ON A HUMAN FINGER

Photograph Courtesy of the CDC

MOSQUITO HABITAT ELIMINATION

Mosquito Control

Habitat Elimination

Adulticiding

Larviciding

DHS
Acute Communicable Disease Control Unit

MOSQUITOES AND WNV: VECTOR COMPETENCE OF CA

- 10 CA common mosquito vectors that are known vectors for other arboviral species were able to be infected and transmit WNV at some level
- Cx. P. quinquefasciatus from So. CA were the least efficient vectors
- Cx. tarsalis, CX. stigmatosoma, Cx. Erythrothorax, Cx. pipiens complex were more efficient lab vectors

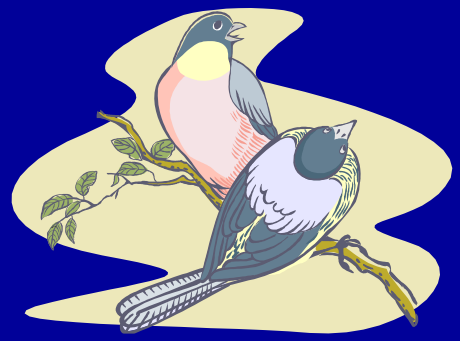
EID December 2002

MOSQUITO SURVEILLANCE AND CONTROL CARRIED OUT BY 5 VECTOR CONTROL DISTRICTS WITHIN LAC

- Chicken sero: surveillance done by Vector Control flocks throughout LAC and CA; blood collected every two weeks for serological testing for local arboviral diseases spring through November
- Mosquito pools: Vector Control place mosquito traps
- Lab testing of mosquito pools: CA DHS
- Testing results reported every 2 weeks

PUBLIC INFORMATION GOALS

- Residential Habitat Elimination
- Personal Protection
  - ✓Avoidance
  - ✓Clothing
  - ✓Repellant



PERSONAL PROTECTION: MOSQUITO REPELLANTS (1)

- DEET: based products provide long-lasting mosquito protection
- Non-DEET: based repellents cannot be relied on to provide prolonged mosquito-protection
- Fewer than 50 cases of serious toxic effects reported in the literature since 1960

N Engl J Med 2002;347:13-7

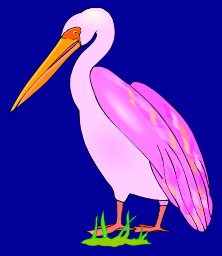
PERSONAL PROTECTION: MOSQUITO REPELLANTS (2)

- DEET Safety Profile
  - ✓1998 EPA review: "normal use of DEET does not present a health concern to the general U.S. population"
- 40 years history of use and over 8 billion human applications
- Can use in children>2mo,don't put repellant on hands

N Engl J Med 2002;347:13-7

REPORT CASES

- If child has meningitis, encephalitis, 7 days of fever with history of mosquito bite, living in endemic area (San Gabriel Valley!!)—CALL for testing
- 213-240-7941 (24/7)
- Need CSF (1-2cc.) Blood 5-10 ml. red top



CONCLUSIONS (1)

- The US WNV outbreak of 2002-03 was the Largest arboviral epidemic ever documented in North America.
- It will be here for the foreseeable future!
- WNV has a huge impact on the medical system!
  - ✓ CO 2003
    - 861 hospitalized cases= $22.4 million
    - Not calculated: missed work, outpatient costs, rehab, long term disability
  - ✓ One Medical Center
    - 10-12 admissions daily at peak season
    - 10% of all admissions July-August 2003

CONCLUSIONS (2)

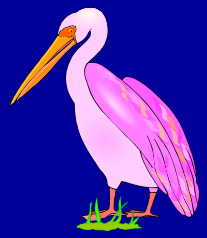
- WNV infection will be a greater problem than SLE because of the large number of bird and mosquito species which can be infected and transmit WNV:
  - ✓162 native American bird species in 2002 producing high levels of viremia
  - ✓Thirty-seven species of mosquitoes are competent vectors in US

CONCLUSIONS (3)

- Factors contributing to huge WNV outbreak in CO 2003:
  - ✓ Second Year Phenomenon
    - Whole season to amplify in a naïve local bird populations
  - ✓ Ideal weather for mosquito production:
    - Wet spring and hot weather!
  - ✓ Abundance of various *Culex sp.* especially *Culex tarsalis* (highly competent vector for WNV transmission)

CONCLUSIONS (4) WNV IN CALIFORNIA 2004

- Will WNV be a problem in CA? **YES**
- Will WNV over-winter in CA? **YES**
- Will the WNV epidemic expand to other areas of CA? **YES**
- Will you be surprised by the “speed” and intensity of the outbreak? **YES**
- Will there be lot of WNV testing in 2004? **YES**



CONCLUSIONS (5)

- WNV Control will require collaboration between mosquito control, public health professionals, clinicians, and the community as a whole.
- WNV will be public health challenge for years to come-especially in Southern California!

RESOURCES

WEBSITES:

- Los Angeles County Acute Communicable Disease Control
  http://lapublichealth.org/acd/VectorWestNile.htm
- **Los Angeles County Public Health Nursing**
  www.lapublichealth.org/phn/healthed.htm
- **Centers for Disease Control and Prevention (CDC)**
  http://www.cdc.gov/ncidod/dvbid/westnile/index.htm
- **California Department of Health Services**
  www.westnile.ca.gov

RESOURCES

HOTLINES:

- **Los Angeles County:**

  (800) 975-4448 or (213) 240-7786 24 hours

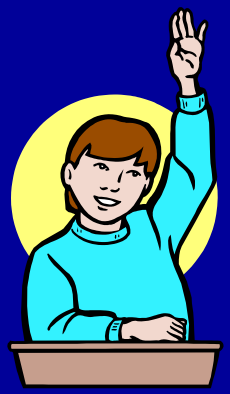
  Report dead birds to (877) 747-2243

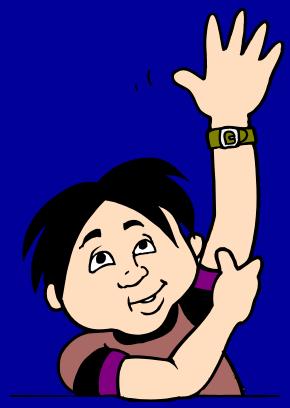
- **Centers for Disease Control and Prevention:**

  English (888) 246-2675
  Spanish (888) 246-2875
  TTY (888) 874-2646

  Monday – Friday 5 a.m. to 8 p.m. PT
  Saturday – Sunday 7 a.m. to 5 p.m. PT

QUESTIONS AND ANSWERS






OOPS! I finished.


THANK
YOU!