

# West Nile Virus Infection in Humans

**Anne Kjemtrup, DVM, MPVM, Ph.D.  
California Department of Health Services  
Vector-Borne Disease Section**

# Introduction

- ▶ WNV responsible for largest encephalitis virus outbreak in U.S. history
  - Large amount of recent research on an organism that was identified in 1947
  - Today you will hear about personal perspectives of the disease
  - My objective is to give the larger public health picture and present some of the recent findings, both from California studies and recent literature

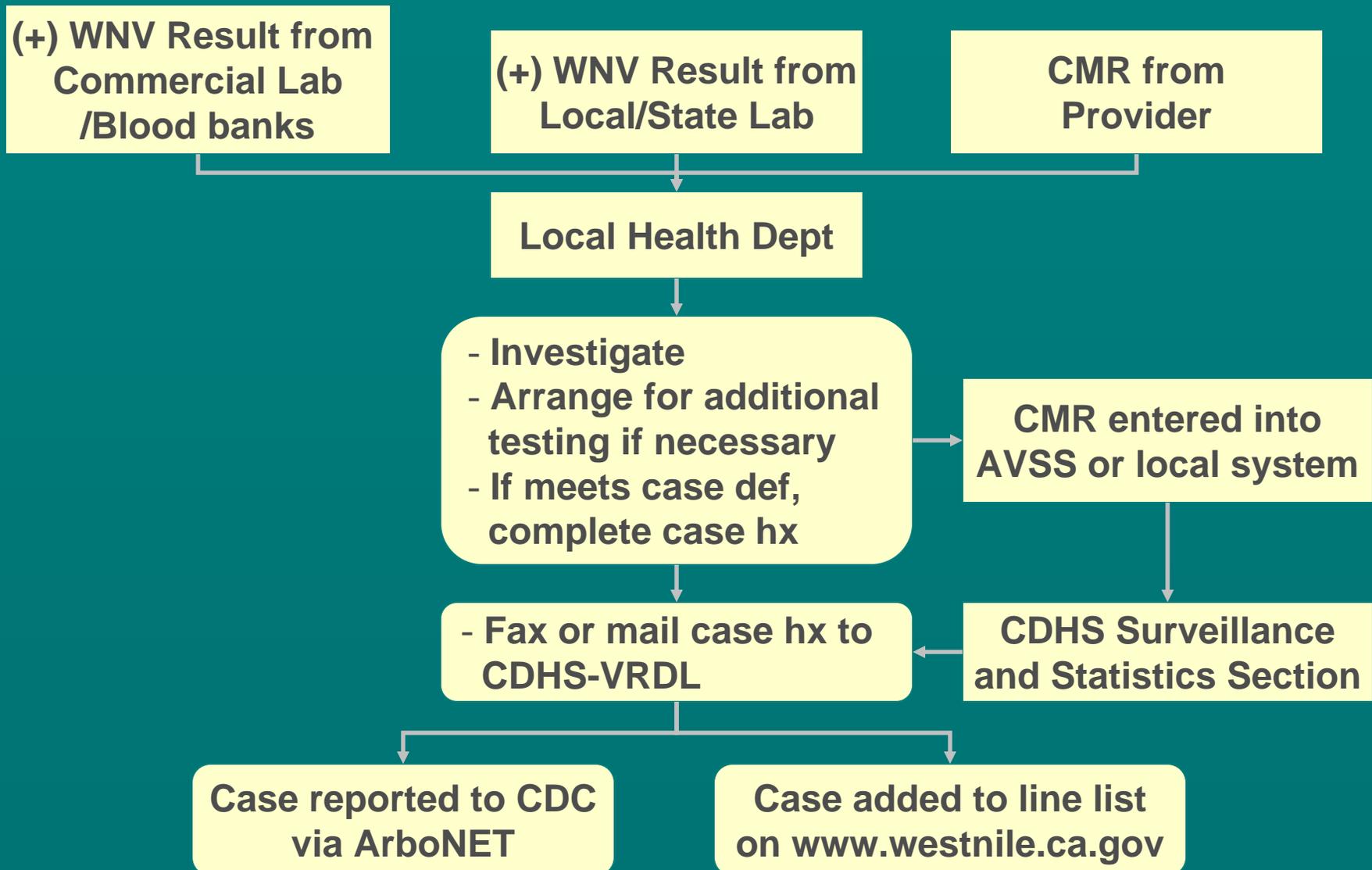
# The Public Health Perspective of WNV

- ▶ Surveillance
- ▶ Clinical Disease and Outcome
- ▶ Treatment
- ▶ Prevention

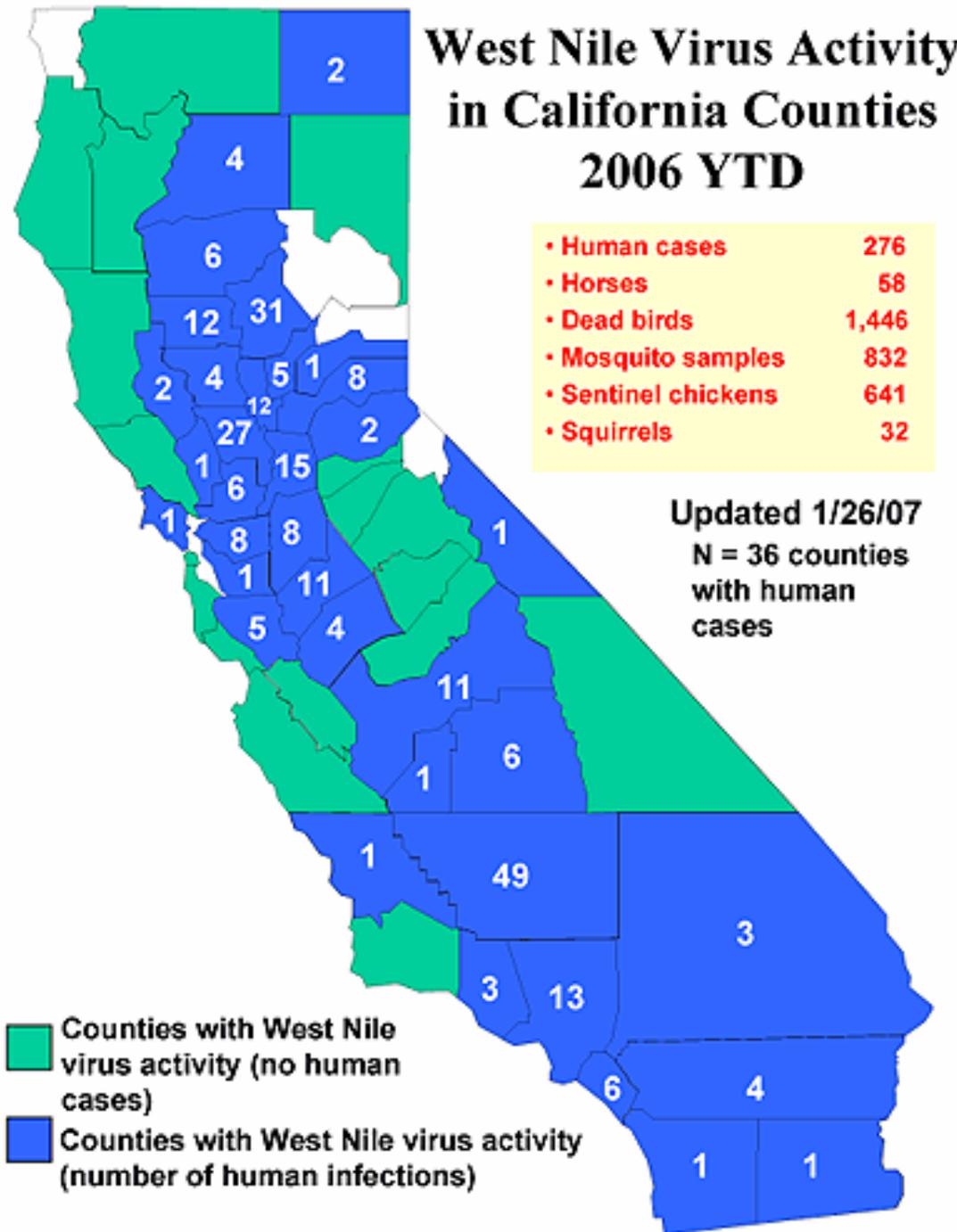


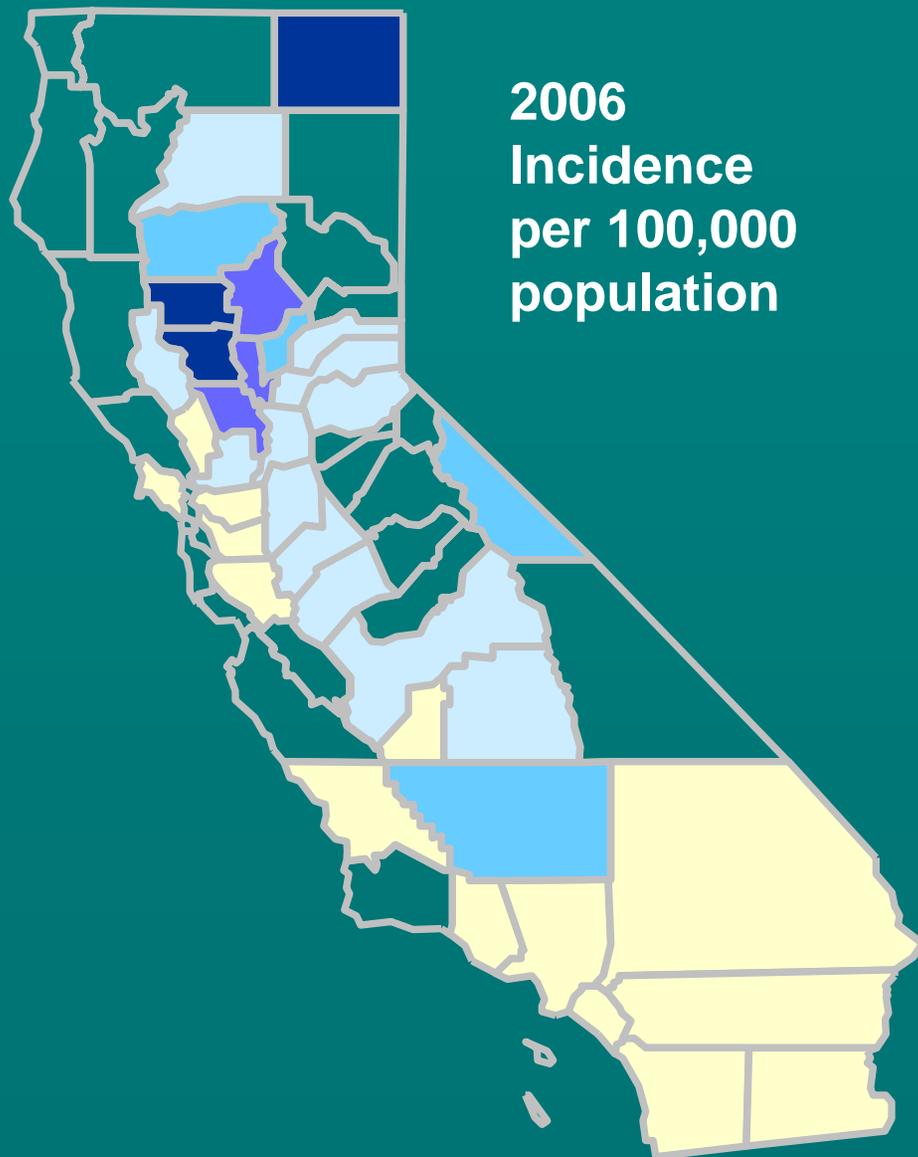
# Surveillance

# Reporting WNV infections



# WNV Infections California 2006



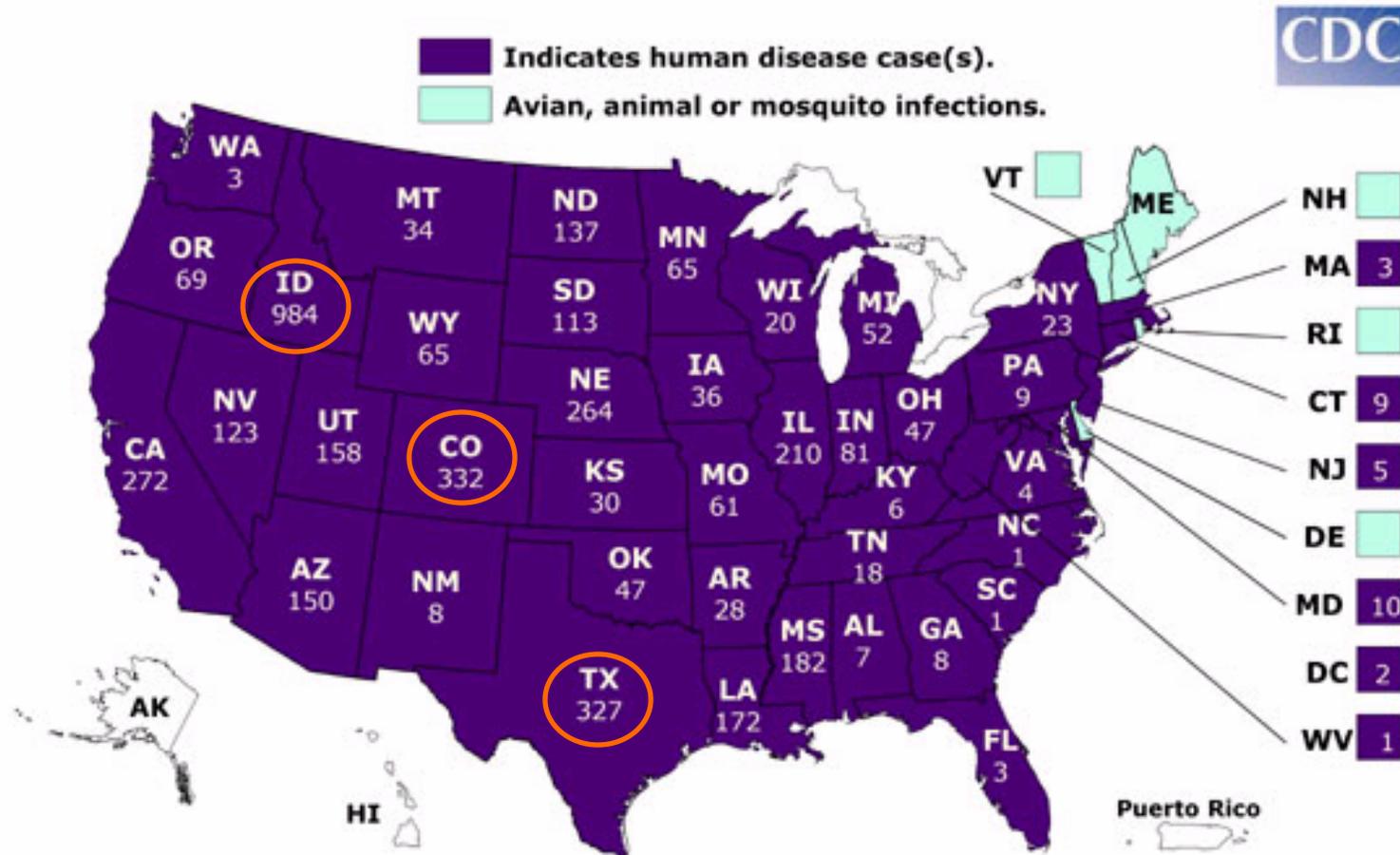


**2006  
Incidence  
per 100,000  
population**

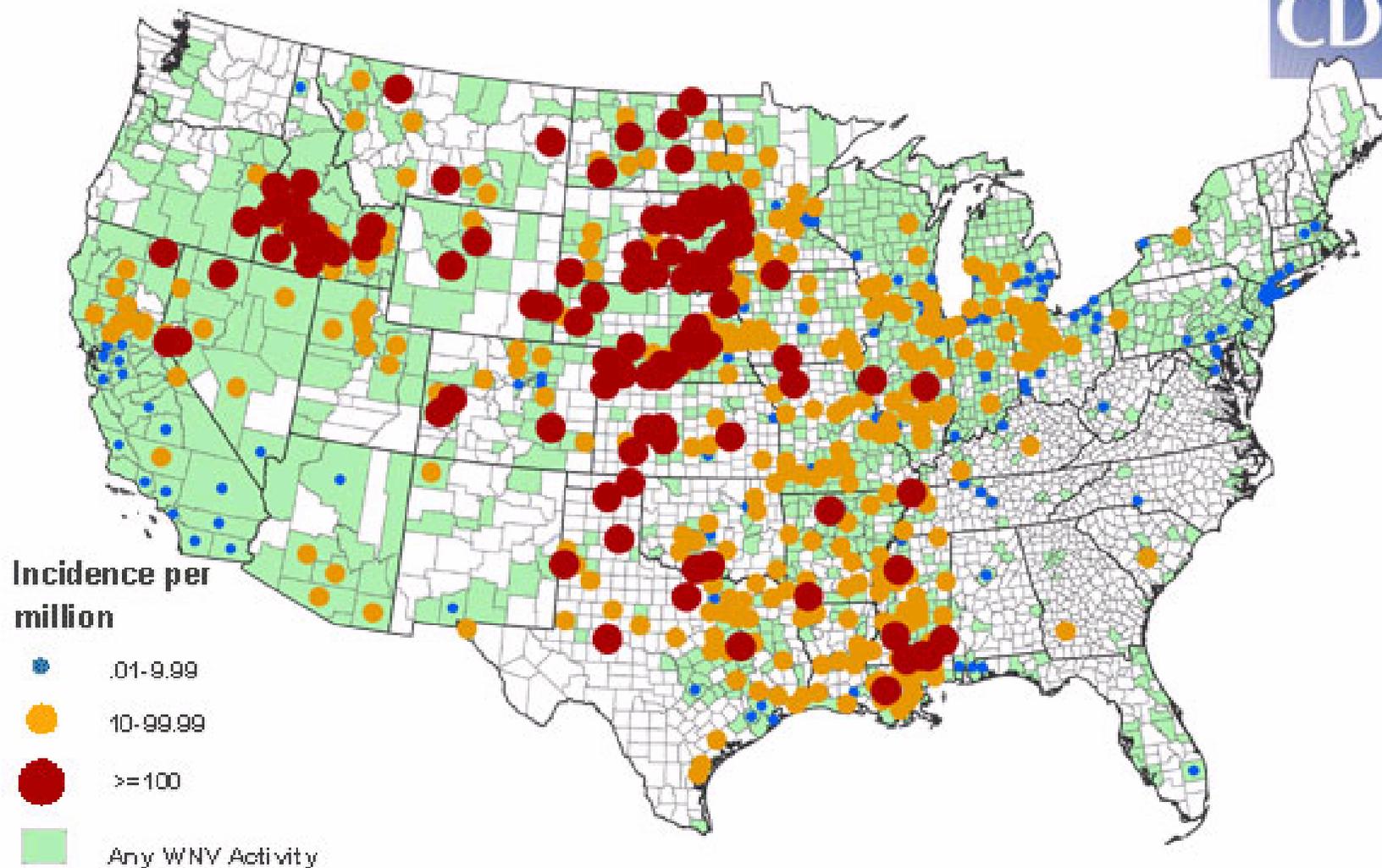
Glenn	45.4		
Colusa	21.3	$\geq 20$	
Modoc	21.2		
<hr/>			
Yolo	16.0		
Butte	15.3	$\geq 15$	
Sutter	15.2		
<hr/>			
Tehama	10.7		
Yuba	8.3	$\geq 5$	
Mono	7.8		
Kern	7.4		
<hr/>			
Lake	3.4		
Placer	3.2		
Stanislaus	2.5		
Shasta	2.5		
Merced	1.9	$\geq 1$	
Tulare	1.6		
Solano	1.5		
San Joaquin	1.4		
Fresno	1.4		
El Dorado	1.3		
Sacramento	1.2		
Nevada	1.1		
<hr/>			
Others		$\geq 0$	

Statewide: 0.8 per 100,000

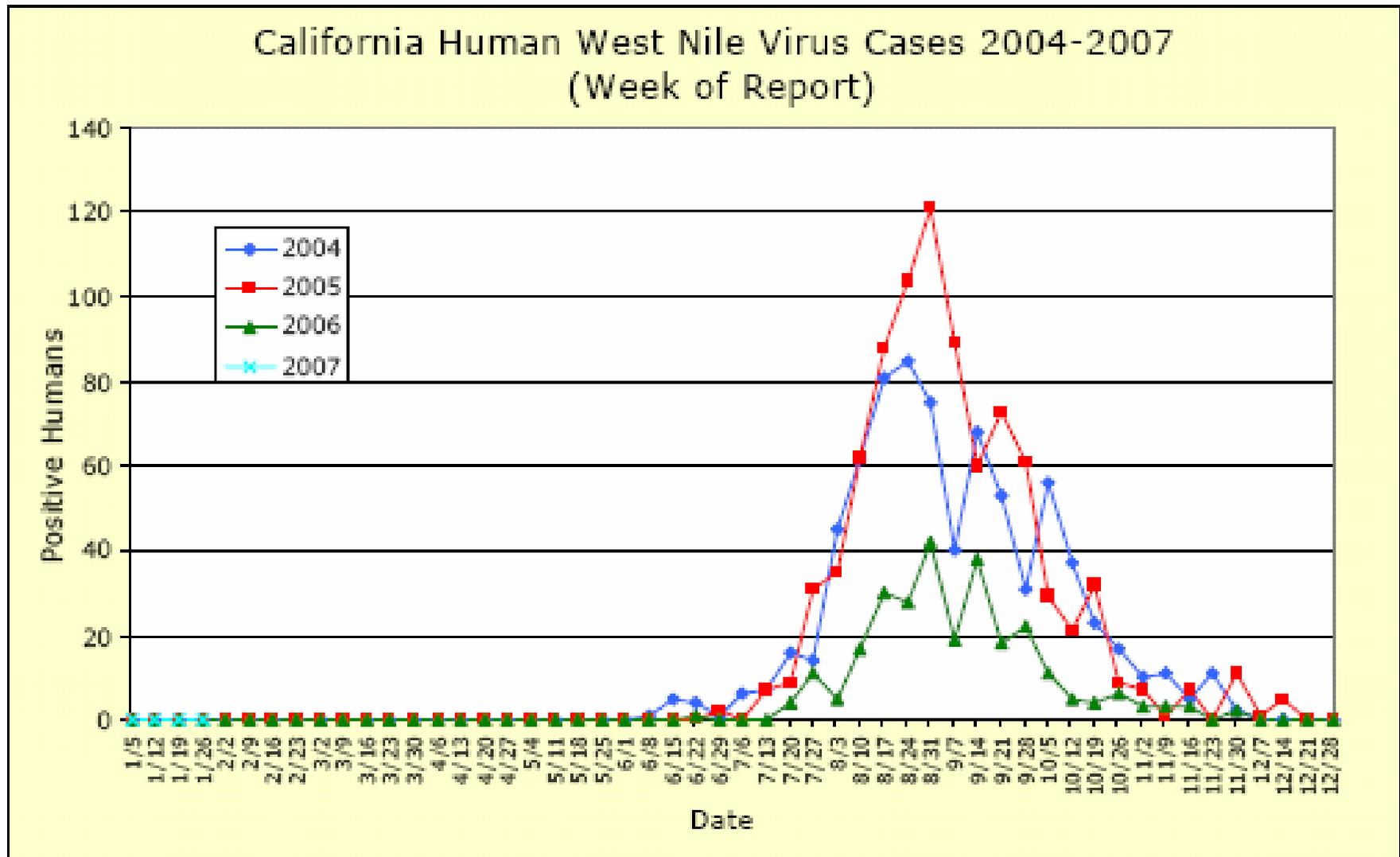
## 2006 West Nile Virus Activity in the United States (Reported to CDC as of January 3, 2007\*)



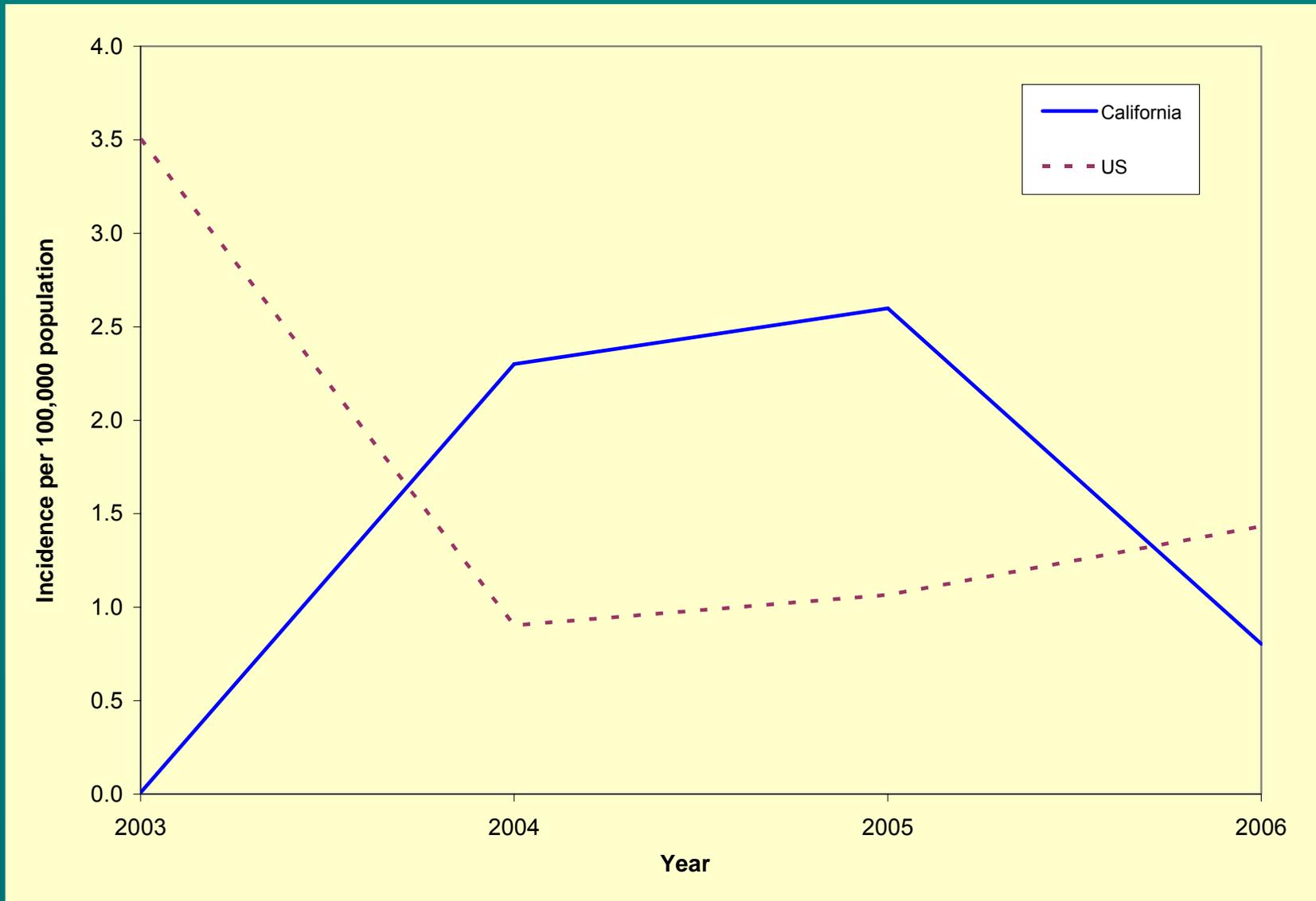
# 2006 West Nile Virus Human Neuroinvasive Disease Incidence in the United States (Reported to CDC as of January 3, 2007)



**Comparative Line Graphs of West Nile Virus Activity in 2004, 2005, 2006, and 2007**  
**Updated (1/26/07)**



# Reported Incidence of Human West Nile Virus Illness, California and United States, 2003-2006



# Recent Findings

- ▶ New tests may make detection easier, more rapid, and give a better estimate of true incidence
  - Spectral's Rapid 1 WNV test may make rapid patient identification easier



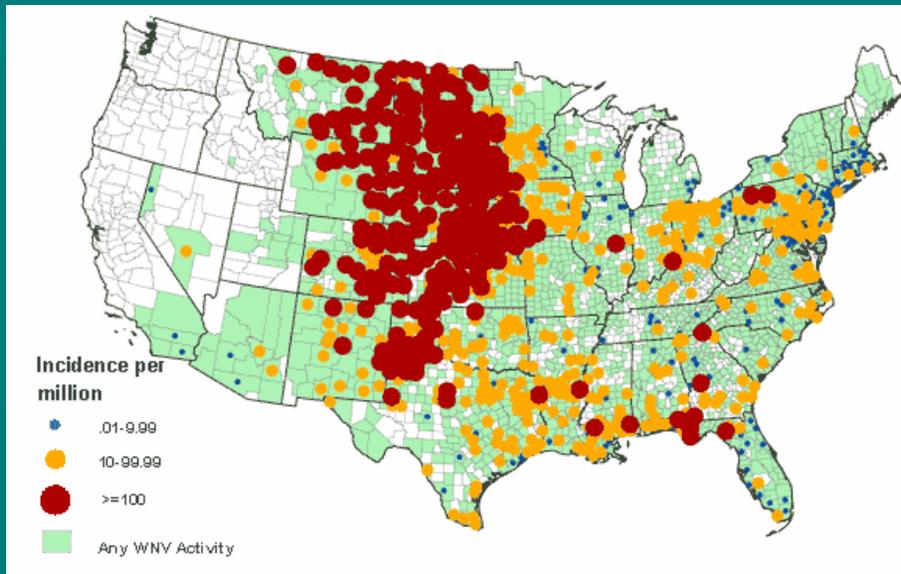
# Recent Findings

- ▶ Blood donor screening data may provide additional estimates of WNV incidence under some circumstances. (Busch et al., EID, March 2006)
  - In 2003, 9,862 WNV cases were reported to ArboNet. If 2003 incidence of blood bank WNV-positive donors extrapolated to population, then an estimated 735,000 (322,000 – 1,147,000) infections may have occurred.



# Recent Findings

► Busch et al., EID, March 2006



Note that geographical impact of WNV remains the same in 2003, regardless of the estimate used (reported cases vs. infection incidence).

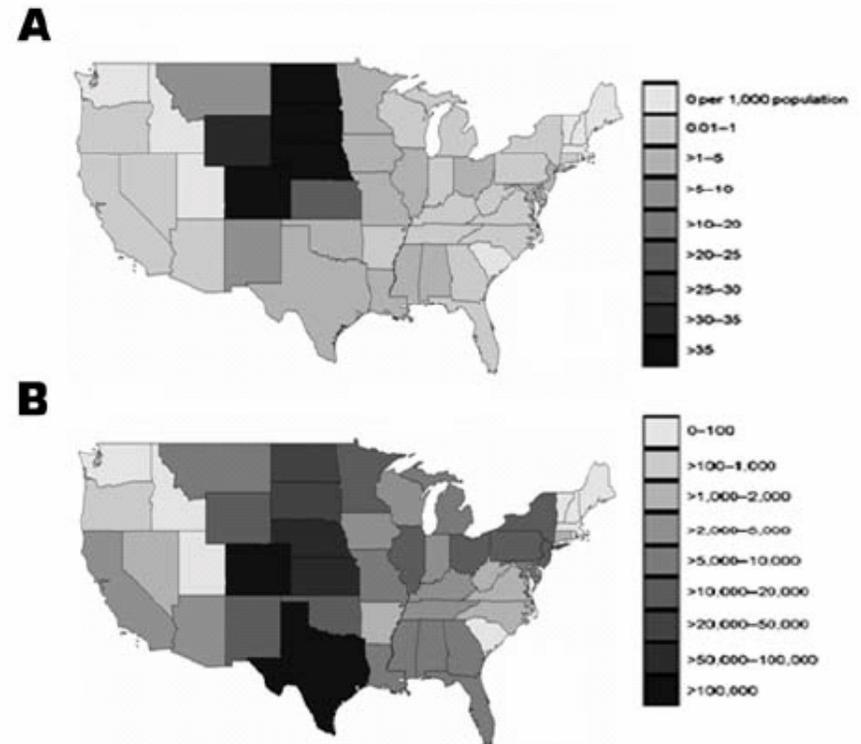


Figure 4. A) Projected number of West Nile virus (WNV) infections per 1,000 persons. B) Estimated total number of WNV infections per state during 2003 epidemic season.

# Recent Findings

- ▶ Seroprevalence studies have demonstrated increased population WNV prevalence following epidemics
  - 2.6% (NYC 1999)- 19.2% (Nebraska 2006 )
    - ▶ Differences attributed to geographical differences such as greater abundance of *C. tarsalis* in NB.
  - In one study,  $\frac{3}{4}$  of the cases identified through active surveillance were homeless individuals
    - ▶ Homeless individuals represent a population at risk for infection

# Implications for Human Case Surveillance

## ▶ Obvious:

### ▪ Direct Prevention and Control Activities

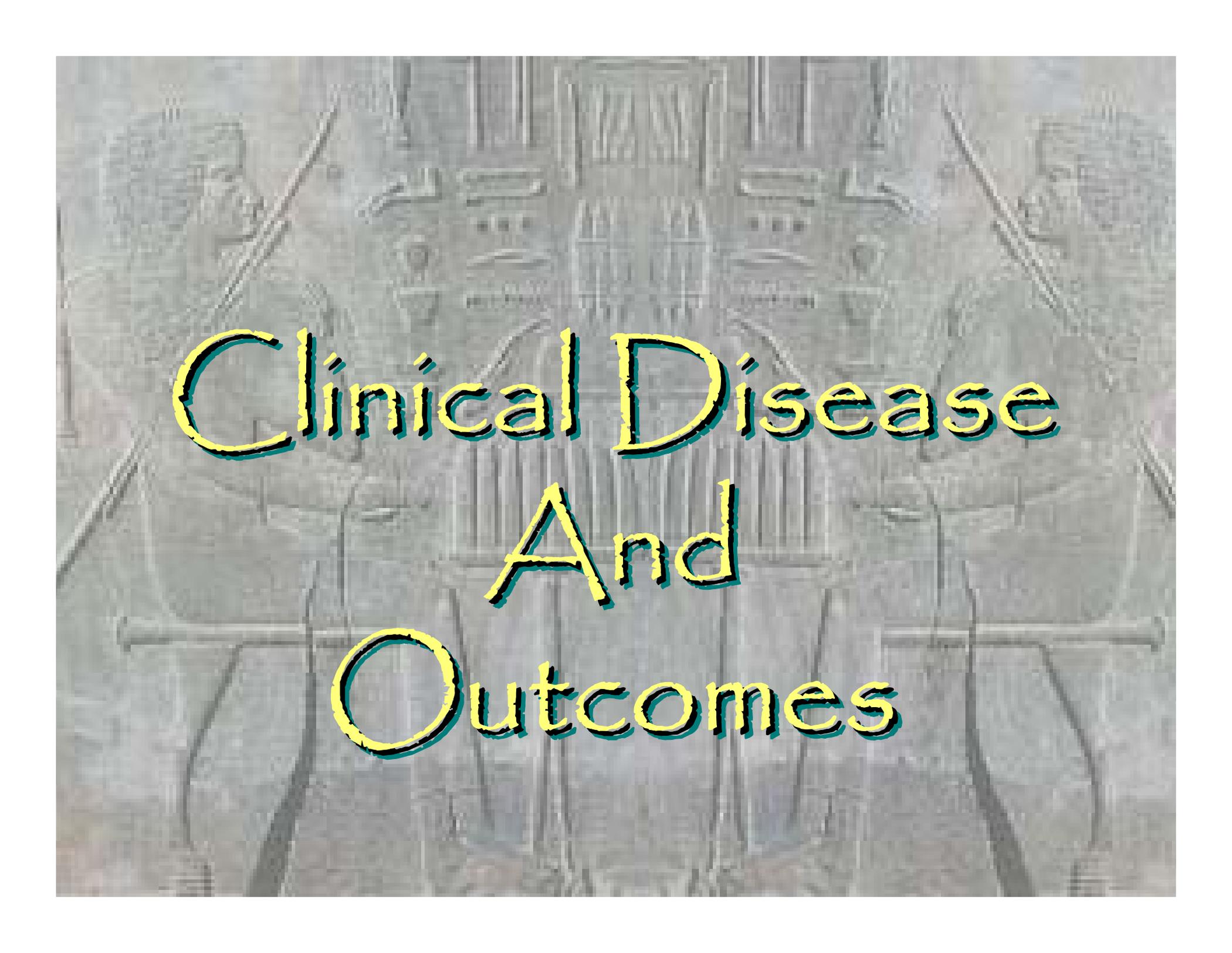
- ▶ Identification of populations at risk to target education intervention
- ▶ Identification of geographic areas for mosquito control

### ▪ Monitor seasonality over time

- ▶ Planning for future years

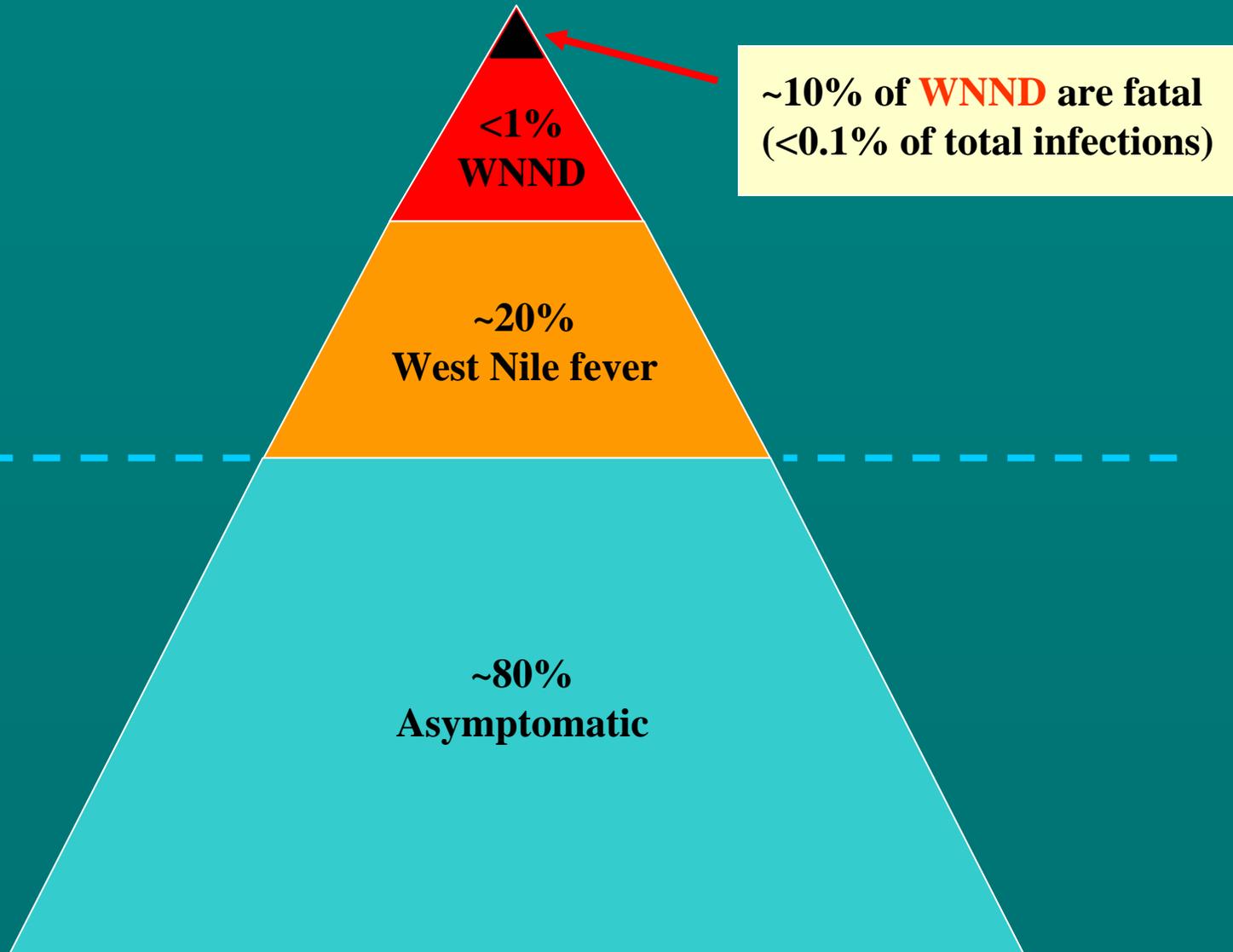
## ▶ Not-so-obvious

- To screen or not to screen blood donor supplies (cost vs. risk)
- Develop future vaccination strategies (benefit vs. risk)



# Clinical Disease And Outcomes

# The "Pyramid Picture" Has Not Changed



# Human WNV Activity, 2006

WNV cases\* reported in California as of February 2, 2007 (n=276)

	Number	(%)
<b>Sex</b>		
Male	177	(64)
<b>Age, in years</b>		
<18	13	(5)
18-44	93	(34)
45-64	114	(42)
65 and older	52	(19)
Median age, all cases	49	(range: 8-86)
Median age, neuroinvasive cases	53	(range: 14-86)

\* Cases of illness in California residents with infection likely acquired in California

# Human WNV Activity, 2006

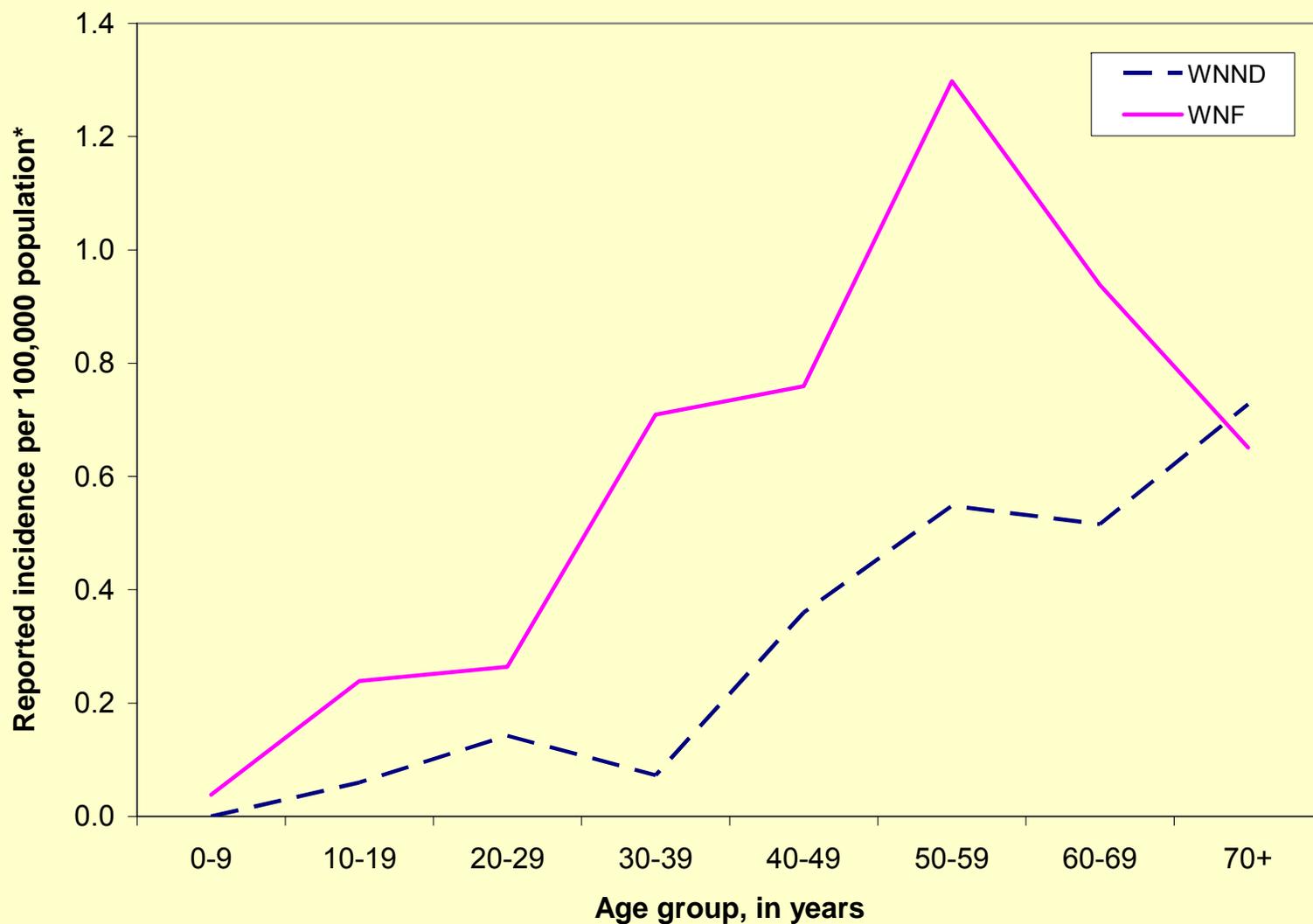
WNV cases\* reported in California as of February 2, 2007 (n=276)

	Number	(%)
<b>Clinical presentation</b>		
Neuroinvasive disease	82	(30)
Encephalitis/meningoencephalitis	37	(45)
Meningitis only	41	(50)
Acute flaccid paralysis <sup>^</sup>	8	(10)
Other/unknown neuroinvasive	3	(4)
West Nile fever	189	(68)
Unknown clinical presentation	5	(2)
<b>WNV-associated fatality</b>	7	(3)

\* Cases of illness in California residents with infection likely acquired in California

<sup>^</sup> One case presented with acute flaccid paralysis only

## Incidence of WNV Illness, by Age and Clinical Presentation California, 2006 – reported as of December 1, 2006 (n=272)



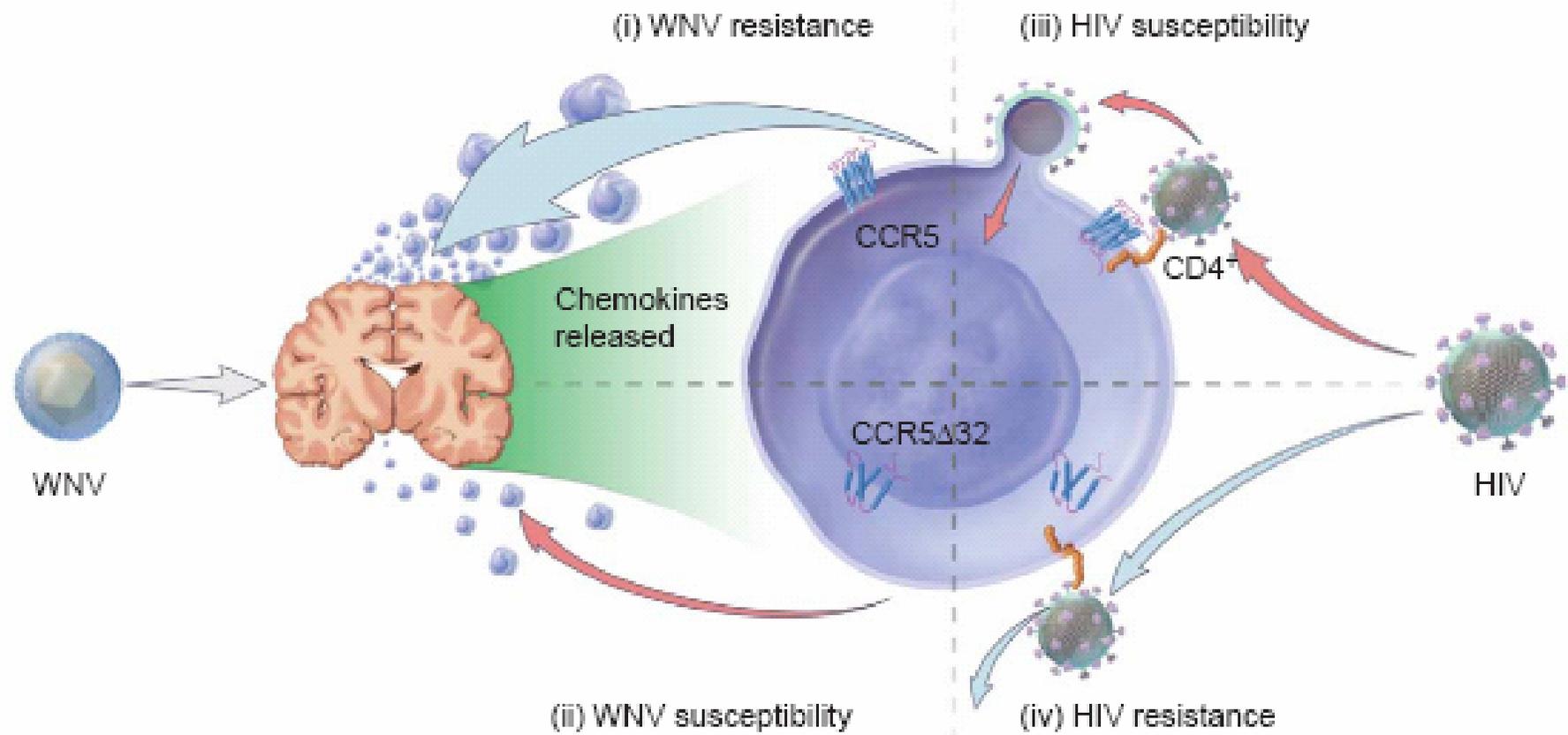
\* 2000 U.S. Census Data

## Preliminary Univariate Analysis (2006): Risk Factors for Developing WNND vs. WN Fever

Characteristic	WNF n (%)	WNND n (%)	OR	95% CI
Diabetes	9 (7)	12 (20)	3.60	1.43 - 9.10
Age (>64 years)	24 (13)	25 (31)	2.96	1.56 - 5.60
Hypertension	36 (26)	26 (44)	2.25	1.19 - 4.27
Gender (male)	114 (62)	56 (69)	1.36	0.78 - 2.37

# Are some people more at risk for disease?

- ▶ A Genetic basis for human susceptibility to WNV (Diamond et al., Trends In Microbiology 2006)
  - Suggests that a genetic mutation normally protective against infection with HIV-1, increases risk of fatal WNV infection.
  - Mutation more common among N. American Caucasians
  - Showed up > 5,000 years ago



# Genetic basis for WNV disease susceptibility

- ▶ Intriguing: an allele that gives almost complete protection against 1 disease but enhances susceptibility for another
- ▶ People with this variant appear more prone to fatal WNV infection than those without. Does not explain age issue and other genetic issues.
- ▶ Although CCR5 may be logical target for new drug development in HIV/AIDS, the benefits of blocking CCR5 could carry cost of increased risk of WNV disease in co-infected patients.

# Children and WNV



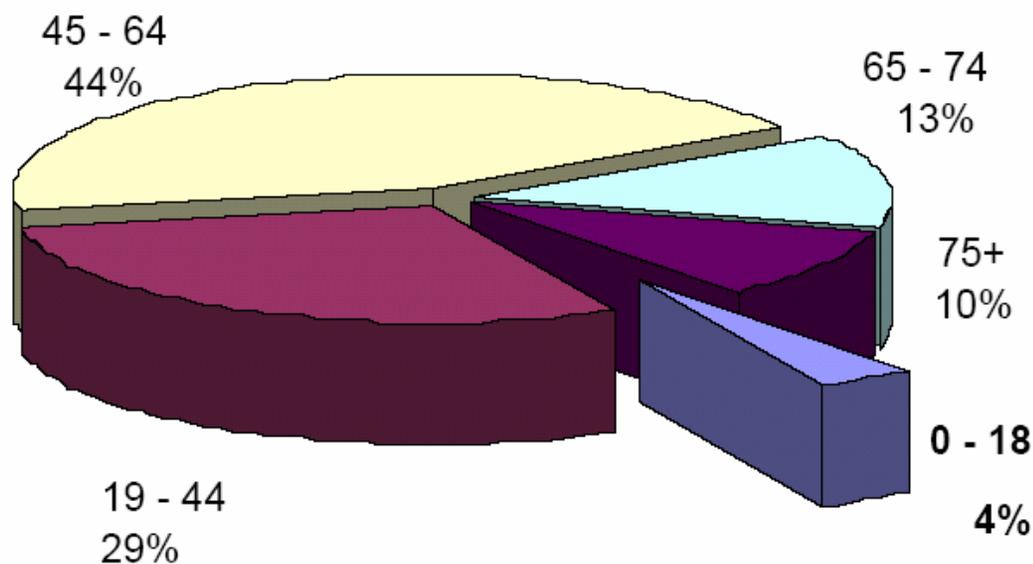
- ▶ Though risk of WNV infection higher in children than adults, risk of WNND in children lower than adults.
- ▶ Most children with uncomplicated WNF recover within several days to weeks. (Hayes NB, PID, 2006)
- ▶ A review of pediatric cases from L.A. County found that pediatric patients reported rash more commonly than in adult patients (Civen R. et al, PID, 2006)

# California Pediatric WNV Cases: 2004-2005

LJ Christie, SS Gavali, C Jean, S Honarmand, CA Glaser

A survey of outcomes was developed and implemented for both WNF and WNND in California pediatric patients from 2004 and 2005.

Figure 1: 2005 West Nile virus cases, by age



# California Pediatric WNV Cases: 2004-2005 Results

**Table 1: Pediatric and Adult West Nile Virus Disease by syndrome (2004-2005):**

Clinical presentation	Pediatric N=72		Adult N=1584	
	n	(%)	n	(%)
West Nile fever	41	(59)	876	(61)
Meningitis	15	(22)	306	(21)
Encephalitis	10	(10)	200	(14)
Acute flaccid paralysis*	6	(9)	59	(4)
Unknown	3	(4)	143	(9)

\* Acute flaccid paralysis may occur with other clinical presentations

# California Pediatric WNV Cases: 2004-2005

## Results (continued)

- ▶ Significant WNV disease does occur in the pediatric population but less frequently than in adults
- ▶ Pediatric patients with WNV presented with significantly more headache ( $p=0.02$ ) and rash ( $p=0.03$ ) than adults.
- ▶ WNF patients in general do well, returning to baseline functioning within a few weeks to months.
  - ▶ Persistent headaches are a concern in WNF pediatric patients.

# California Pediatric WNV Cases: 2004-2005

## Results (continued)

- ▶ WNNND pediatric patients typically returned to baseline within a few months.
  - ▶ Psychosocial impairments lasting months in pediatric WNNND patients are concerns, especially in encephalitis patients.
- ▶ Recall bias and baseline functioning can affect results.
- ▶ Ongoing surveys are being evaluated for pediatric patients from the 2006 WNV season.

# Transplacental/Transmammary Transmission?

- ▶ First possible congenital cases described 2002
- ▶ 2003 – 2004 study reported on 77 women infected with WNV during pregnancy (O'Leary et al., Pediatrics 2006)
  - 71 delivered total of 72 live infants
    - ▶ 7 had major malformations, 3 of whom had defects that could have been caused by maternal WNV infection. No greater incidence of malformations in this group than in general population. No conclusive evidence for WNV infection as cause.
  - 4 miscarriages
  - 2 elective abortions
  - 2/42 breast milk + for WNV RT-PCR. 1 breast-fed infant followed up and remained negative at 7 months.
- ▶ **No conclusive evidence for transplacental/transmammary transmission**

# Encephalitis Outcome Study

Shilpa Gavali-Jani, VRDL

- ▶ 92 WNV 2004 -2005 encephalitis cases requested to complete activities of daily living questionnaire at 3, 6, 12 months after hospital admission for WNV encephalitis.
  - ▶ 62 (67%) individuals completed at least one survey.
  - ▶ Demographics, clinical and laboratory findings, similar between responders and non-responders except that more females than males responded.

# Encephalitis Outcome Study

- ▶ 14/112 (13%) of individuals eligible for follow-up had died.
- ▶ Of the 30 non-responders, at least had 1 died.
- ▶ By 12 months of follow-up, most people were living at home independently.

# Encephalitis Outcome Study

Many patients reported worsened neuropsychological functioning at 6 or 12 months compared with 3 months

<b>New Problem (Example)</b>	<b>3 month (N=36)</b>	<b>6 month (N=44)</b>	<b>12 month (N=51)</b>
<b>depression</b>	<b>28%</b>	<b>20%</b>	<b>37%</b>
<b>problems finding the right word</b>	<b>25 %</b>	<b>39 %</b>	<b>41 %</b>

# Encephalitis Outcome Study

## Conclusions

- ▶ Recovery of neurologic function is maximal during the first 3 months after hospitalization
- ▶ Several psychological/social measures worsened over time and conferred significant morbidity in this population
- ▶ Findings similar to findings from the Tennessee Unexplained Encephalitis Study's unpublished results

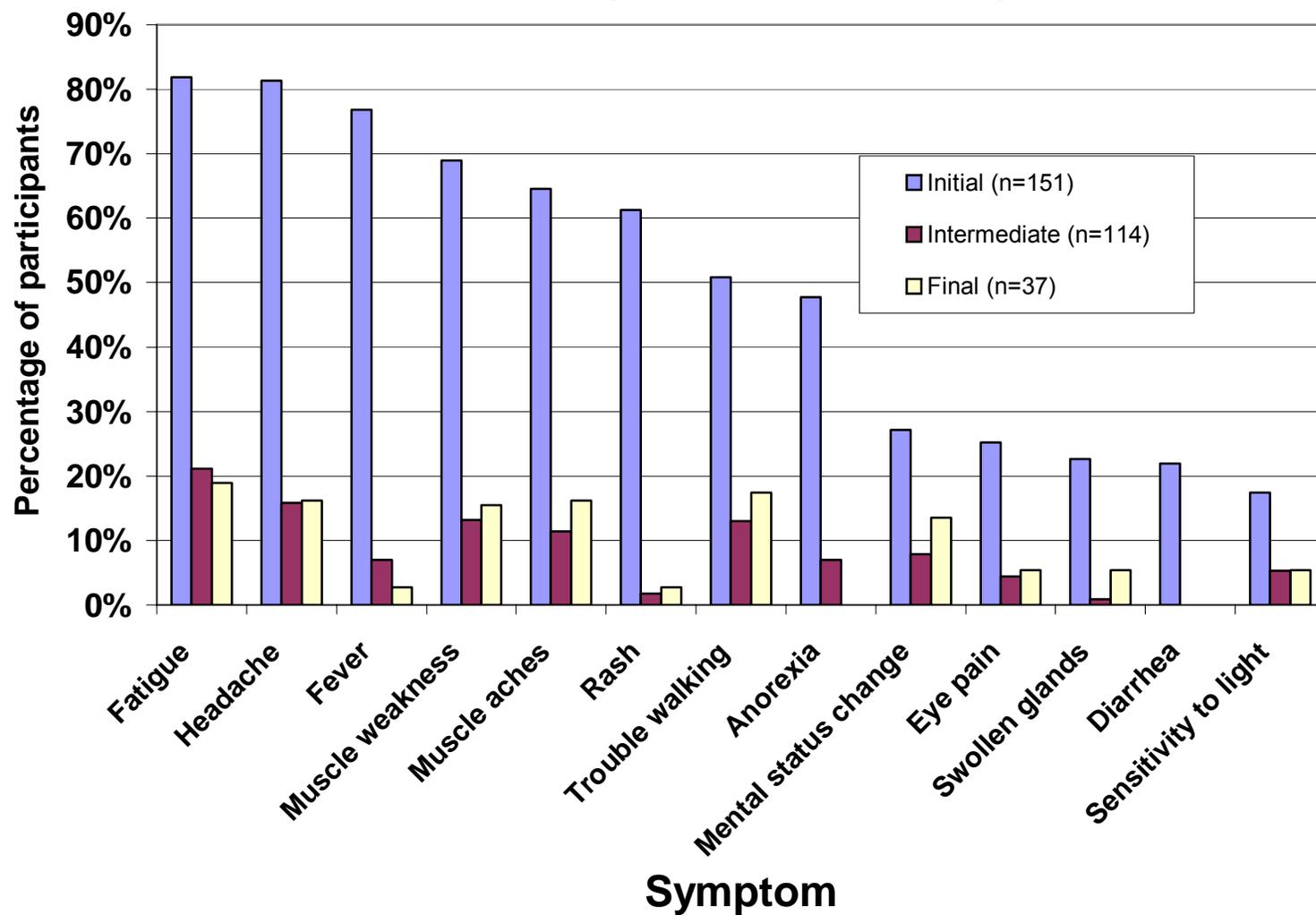
# WNV Fever Follow-up, 2004

A Kjemtrup, J. Riggs-Nagy, C. Jean, C. Glaser, C. Fritz, D. Gillis, D. Vugia

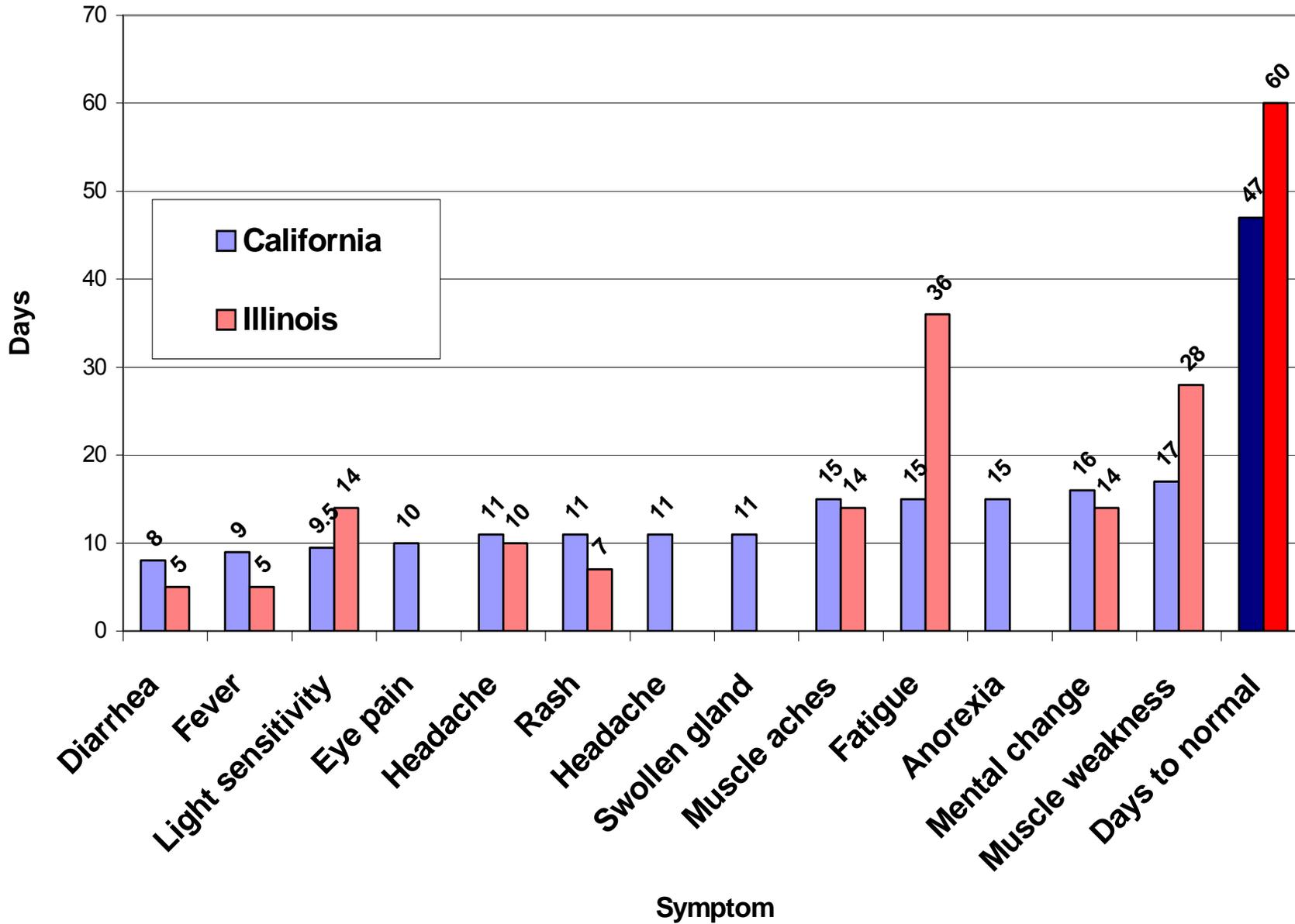
- ▶ WNV fever case participants contacted within 2, 3 and 9 months of onset.
  - ▶ Participants were queried about their acute and persistent symptoms.
  - ▶ Once a participant stated they were “100% back to normal” or reported no continuing or new symptoms, follow-up was discontinued
- ▶ Participating Counties:
  - ▶ Fresno
  - ▶ Kern
  - ▶ Orange
  - ▶ Riverside
  - ▶ San Bernardino

# 2004 Follow-Up

## Frequency of Reported Symptoms



## Medium Duration of Symptoms in WNV Patients, California and Illinois\* Studies Compared



\*Watson JT *et al.* Ann Intern Med 2004; 141:360-5

# WNF Outcome Issues to Address

- ▶ How can quality of life issues be addressed more quantitatively?
- ▶ How does recovery from WNV fever compare with recovery from other illnesses with similar initial presentations?
- ▶ How can potential for recall bias be minimized?

# WNF Follow-Up 2005-2006

J. Riggs-Nagy, C. Jean, E. Aquino, A. Kjemtrup

## Case-Control Study

- ▶ Unmatched case-control study
- ▶ **Case**: a person with a fever-like illness who tested positive for West Nile and did not have encephalitis, flaccid paralysis, or aseptic meningitis
- ▶ **Control**: a person with a fever-like illness who tested negative for West Nile and did not have encephalitis, flaccid paralysis, or aseptic meningitis

Study made possible by helpful participation from local health departments.

# WNF Follow-Up 2005-2006

## Methods

- ▶ Initial survey
  - ▶ Contact, consent and establishment of symptoms at onset obtained
- ▶ 3 month and 1 year follow-up surveys
  - ▶ Quality of life assessment (SF-36)
  - ▶ Scores can be compared between cases and controls as well as between cases and the general U.S. population

# WNF Follow-Up 2005-2006

## Methods

- ▶ 36-item Short-Form General Health Survey (SF-36): standardized quality of life assessment tool
  - ▶ Used in the 2 and 9 month surveys
  - ▶ Measures participants' perceived:
    - ▶ Physical functioning
    - ▶ Physical health
    - ▶ Bodily pain
    - ▶ General health
    - ▶ Vitality
    - ▶ Social functioning
    - ▶ Emotional status
    - ▶ Mental health

# WNF Follow-Up 2005-2006

## Initial Results

	Interview 1 (1-2 mo)		Interview 2 (2-3 mo)		Interview 3 (9-12 mo)	
	Case	Control	Case	Control	Case	Control
<b>Number of Participants</b>	204	34	152	22	60	0
<b>Age Range (Mean)</b>	18-88 (51)	20-83 (47)	18-88 (53)	20-83 (49)	28-84 (56)	--
<b>% Female</b>	51%	59%	52%	59%	53%	--

# WNF Follow-Up 2005-2006

## Frequency of Reported Symptoms

Initial symptoms are similar in the case and control populations

Number of participants reporting		
Symptom	cases n=190 (%)	controls n=34 (%)
Fatigue	175 (92)	30 (88)
Headache	159 (84)	29 (85)
Muscle aches	150 (79)	27 (79)
Muscle weakness	146 (77)	25 (74)
Fever	149 (78)	26 (76)
Anorexia	119 (63)	21 (62)
Rash	101(53)	9 (26)
Trouble walking	87 (46)	11 (32)
Eye pain	91 (48)	15 (44)
Swollen glands	47 (25)	12 (35)
Diarrhea	58 (31)	12 (35)
Sensitivity to light	83 (44)	13 (38)
Loss of balance	82 (43)	12 (36)

# WNV Follow-Up 2005-2006

## Initial Results

- ▶ Certain measures such as mental health and vitality appear to be decreased in WNV fever patients at 2-3 months post onset when compared to the general population.
- ▶ Early data indicates that WNV fever patients show no difference in these scores at the 9 month post infection point when compared to the general population
- ▶ Too early in study to discuss comparison with control population

# Other Recent Outcome Studies

- ▶ Patients with WNV infection (both WNF and WNND) experience long-term morbidity (1 year follow up). Patients with more severe illness did not report more chronic symptoms than patients with milder illness. WNF may not be a self-limited benign illness and may be a subclinical encephalitis.  
(Carson et al., CID 2006)

# Other Recent Outcome Studies

- ▶ Mental status comparison between WNND and WNF patients 9 months after illness showed greater confusion and difficulty in concentrating in WNND than WNF patients. (Haaland et al EID 2006).

# WNV Outcome Picture

- ▶ Risk factors for severe disease include increasing age, immunosuppression, diabetes, and possible genetic predisposition.
- ▶ Most WNF patients recover in first few months. For some, problems may linger (subclinical encephalitis? Other risk factors?).

The background is a grayscale image of a stone relief. It features a central figure with a prominent, ornate headdress and a serene expression. This central figure is flanked by two other figures, each also wearing a headdress and holding a long staff or scepter. The entire scene is set within a rectangular frame, with decorative elements at the top and bottom. The overall style is reminiscent of ancient Egyptian or Mesopotamian art.

# Treatment

# Treatment

## Experimental:

- ▶ Clinical trial of interferon for meningoencephalitis patients underway based on decreased mortality seen in mice given interferon before WNV infection.
  - ▶ Ribavarin to inhibit WNV replication.
  - ▶ I.V. high WNV titered immunoglobulin has reported benefit for WNV encephalitis patients in Israel.
  - ▶ Role of steroid treatment unknown
  - ▶ Antisense oligimers that bind to WNV RNA to inhibit translation: phase II (efficacy) trials underway
- 
- ▶ Supportive Care



# Prevention

# Prevention

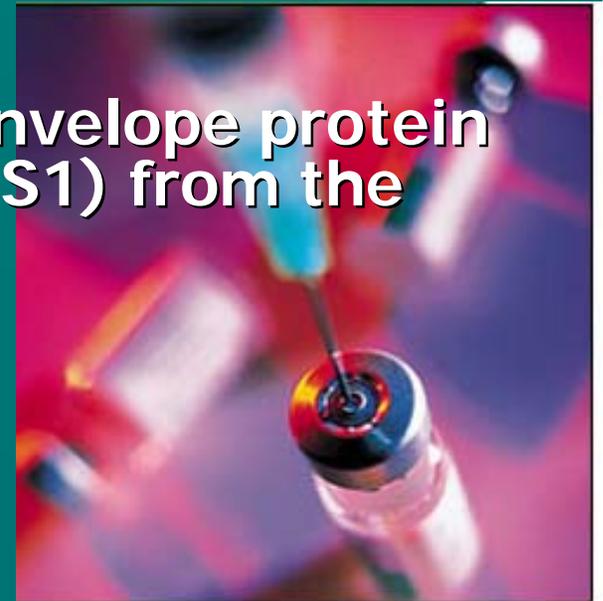
- ▶ Personal Protection
  - Vaccination

- ▶ Mosquito Control



## WNV Vaccines

- ▶ A live, attenuated WNV (veterinary) vaccine
- ▶ A formalin-inactivated WNV (veterinary) vaccine
- ▶ A “naked” DNA vaccine encoding the prM and E genes
- ▶ A live, attenuated dengue serotype 4-WNV chimera
- ▶ A live attenuated Yellow Fever-WNV chimera
- ▶ A recombinant envelope protein vaccine expressed in *E. coli* or *Drosophila* cells
- ▶ A canarypox virus vectored vaccine
- ▶ A recombinant vaccine (truncated envelope protein 80E and a non-structural protein –NS1) from the WNV New York Flamingo strain.



## ...But will people want to be vaccinated?

“Universal vaccination would unlikely result in societal savings unless the incidence of disease increases substantially over what has been seen in the past six years, or the cost of vaccination were <\$12.00 per person vaccinated” (Zohrabian et al., EID 2006)



**Aerial Pesticide Spraying for WNV  
Mosquito Control and the Incidence of  
Respiratory Complaints in Sacramento  
County, August 2005**

**Este Geraghty, MD, MS, MPH  
University of California Davis**

# Geraghty Study

- ▶ Research Question
  - ▶ Does aerial spraying with a pyrethrin pesticide for West Nile virus mosquito control increase an individual's risk for a respiratory problem?
- ▶ Hypothesis
  - ▶ Aerial spraying does not increase the incidence of respiratory complaints as measured by hospital discharge and emergency room data.

# Geraghty Study : Emergency Room Visits



- ▶ Medical Information Reporting for California (MIRCaI), 01/01/05
  - ▶ ED Data
    - ▶ Data elements: DOB, service date, principle diagnosis, zip code, disposition, gender, ethnicity, among others
    - ▶ Hospital Inpatient Discharges
- ▶ Case-crossover design and GIS will be used to evaluate timing of ED-room visits with spray time and location
- ▶ Study underway 2006 -2007

# Prevention

Rests with mosquito control and personal protection.



# Conclusion

- ▶ Public health efforts to understand the dynamics of human disease help focus our prevention efforts

# Acknowledgements

- ▶ Jamie Riggs-Nagy (VBDS)
- ▶ Cynthia Jean (VRDL)
- ▶ Ervic Aquino (VBDS)
- ▶ Shilpa Gavali (VRDL)
- ▶ Many local agencies who have helped out on our follow-up work



**Murchison Falls**

Where it all began...  
West Nile Region of  
Uganda

**Mt. Luku Islandmountain**



• [www.game-reserve.com/uganda\\_murchison\\_falls.html](http://www.game-reserve.com/uganda_murchison_falls.html)

• [www.min.uni-kiel.de/.../ugandaweb/wnile.html](http://www.min.uni-kiel.de/.../ugandaweb/wnile.html)