“OTHER” MOSQUITO-BORNE FLAVIVIRUSES

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Binational Symposium – Exploration of Environmental and Health Aspects of Zika, Dengue, and Chikungunya

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TOPICS

West Nile Virus
St. Louis Encephalitis
Yellow Fever
Japanese Encephalitis
West Nile virus (WNV) is a single-stranded RNA virus of the family Flaviviridae, genus Flavivirus. First discovered in Uganda in 1937.

WNV belongs to the Japanese encephalitis antigenic complex.

WNV is closely related to:
- Japanese encephalitis
- St. Louis encephalitis
- Yellow fever
- Dengue

Photo credit: CDC
WNV is endemic to 83 countries.

Most often, WNV is spread by bite of an infected mosquito.
  - Mosquitoes become infected when they feed on infected birds \((\text{reservoir for WNV})\).
  - Infected mosquitoes can then spread the virus to humans and other animals when they bite.

WNV has been spread through:
  - Blood transfusions – all blood donations screened in U.S.
  - Organ transplants
  - Breastfeeding
  - During pregnancy from mother to baby
People may develop symptoms 2 to 14 days after they are bitten by infected mosquitoes.

Longer incubation periods have been documented in immunocompromised persons.

WNV is not communicable from person to person, with rare exceptions:

- Blood transfusions
- Organ transplants
- Breastfeeding
- Perinatal transmission
Approximately 80% of those infected with WNV are asymptomatic.

Up to 20% of those infected with virus may develop West Nile fever (WNF).

Clinical features of WNF may include:

- Fever, headache, fatigue
- Skin rash on trunk of the body
- Swollen lymph glands
- Eye pain
Of those infected with WNV, 1 in 150 or <1% may develop severe illness called WN neuroinvasive disease (WNND) because it affects a person's nervous system.

Specific types of WNND may include:

- Encephalitis
- Aseptic meningitis
- Acute flaccid paralysis (AFP)
- Atypical Guillain-Barré Syndrome (GBS)
- Transverse myelitis
Clinical features of WNND may include:

- **Fever, gastrointestinal symptoms, ataxia** *(failure of muscular coordination; irregularity of muscular action)*
- **Extrapyramidal signs** *(e.g., extreme restlessness, involuntary movements, and uncontrollable speech)*
- **Optic neuritis** *(inflammation of the optic nerve)*
- **Seizure, altered mental status**
- **Weakness, flaccid paralysis** *(weakness or loss of muscle tone)*
- **Myelitis** *(inflammation of the spinal cord)*
- **Polyradiculitis** *(inflammation of the nerve roots)*
- **Maculopapular or morbilliform rash involving neck, trunk, arms, or legs**
There is currently no specific treatment for WNV infection.  
More information at:  http://www.cdc.gov/ncidod/dvbid/westnile/clinicians/

Key prevention messages:

• Stay indoors at dawn and dusk
• Avoid mosquito bites; wear long sleeves, long pants, and socks when outdoors
• Use mosquito repellent*
• Keep screens on windows and doors in good repair
• Identify and eliminate standing water sources that can be mosquito-breeding areas around the home

* Information on repellents can be found at:  
http://www.cdc.gov/ncidod/dvbid/westnile/RepellentUpdates.htm
WEST NILE VIRUS- US

WNV Disease Cases† by Year
United States, 2003 – 2016*

† Includes confirmed and probable cases. Does not include asymptomatic blood donors found positive for WNV.
* As of September 22, 2016.

Overall, 2,175 cases of WNV disease in people were reported to CDC. 1,455 (67%) were classified as WNND and 720 (33%) were non-WNND.
Overall, 868 cases of WNV disease in people have been reported to CDC. 448 (52%) were classified as WNND and 420 (48%) were non-WNND.
Dates of symptom onset ranged from February to December, with the majority of cases occurring during July to September.

WNV disease cases reported to ArboNET by week of onset – US, 1999-2015

WNV Disease Cases† by Year
California, 2003 – 2016*

† Includes confirmed and probable cases. Does not include asymptomatic blood donors found positive for WNV.
* As of September 23, 2016.

Data source: CDPH: http://www.westnile.ca.gov
Prepared by: County of San Diego Epidemiology Program, 9/25/16
234 human cases from 27 counties have tested positive for WNV in 2016.

5 WNV-related fatalities have been reported

9 confirmed WNV cases in San Diego this year, 1 death, 7 cases pending confirmation by CDPH lab

Source: CDPH. Downloaded 9/25/16 from http://www.westnile.ca.gov/
It is possible that the ongoing drought contributed to increased WNV activity by creating more **limited sources of water** for birds and mosquitoes.

- The lack of water could have caused some sources of **water to stagnate**, making the water sources attractive for mosquitoes to lay eggs.

- As birds and mosquitoes sought water, they came into closer contact and amplified the virus.
WNV Disease Cases† by Year and Outcome
San Diego County, 2003 – 2016*

† Includes confirmed and probable cases. Does not include asymptomatic blood donors found positive for WNV.
* As of September 23, 2016.

Prepared by: County of San Diego Epidemiology Program, 9/25/16
Dead Bird Detections WNV by Month and Year of Report
San Diego County, 2015-2016

Data source: San Diego Vector Control Program
Prepared by: County of San Diego Epidemiology Program, 9/26/16
Human WNV Disease Cases by Month and Year of Report
San Diego County, 2003-2015

Prepared by: County of San Diego Epidemiology Program, 5/16/16
Mosquito Control Spraying Set For Areas of North Torrey Pines, South Del Mar

May 16, 2016 | 3:31pm

The County of San Diego’s Vector Control Program is scheduled to conduct pesticide spraying in several neighborhoods around the Los Peñasquitos Lagoon after finding increasing numbers of adult mosquitoes carrying West Nile virus in the area.
West Nile Virus in San Diego County

Vector Control Program staff monitor WNV by trapping, pooling, and testing mosquitoes and by testing sentinel chickens and dead birds.

Current 2016 WNV activity is given below. Information for prior years is available here, and additional information on WNV can be found here.

**Adult Mosquito Treatment Information**

2016 WNV Activity Map

For more information on a specific source click on the source name (hyperlink) below

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of Positives to Date</th>
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<td>Dead Birds</td>
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<tr>
<td>Sentinel Chickens</td>
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<tr>
<td>Mosquito Pools</td>
<td>99</td>
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<tr>
<td>Horses</td>
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<tr>
<td>Humans</td>
<td>11</td>
</tr>
<tr>
<td>Total Source Positives</td>
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</tbody>
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For More Information On WNV Or Other Vectors Contact:
(858) 594-2888
vector@sdcounty.ca.gov
West Nile Virus - Mexico

Downloaded 9/26/16 from http://wwwnc.cdc.gov/eid/article/9/12/03-0564_article
See also: http://www.ncbi.nlm.nih.gov/pubmed/23141421

Figure 1. Map showing the Mexican states sampled for antibodies to West Nile virus and Venezuelan equine encephalitis virus in equines. Unshaded states were not sampled. The location of the West Nile virus isolation from a dead Common Raven is shown by a star.
Most efficient diagnostic method is detection of antibodies to WNV in serum and/or CSF collected within 7 days of illness onset.

Routine testing for WNV includes tests by enzyme immunoassay (EIA) and/or immunofluorescent assay (IFA).

CDPH Viral and Rickettsial Disease Laboratory (VRDL) continues to accept serum and CSF samples for WNV testing.
WNV Testing capacities at CDPH VRDL include:

- IgM and IgG EIA testing
- IgM and IgG IFA testing
- Plaque Reduction Neutralization Test (PRNT)
- Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR)

* Immunocompromised patients may not mount a demonstrable antibody response in sera. CSF from these patients may be sent to VRDL for virus detection by PCR.

Required specimens are:

- CSF: 1-2 cc (if lumbar puncture was performed)
- Acute Serum: ≥ 2 cc serum collected ≤ 7 days after onset †

† If WNV infection is highly suspected and acute serum is negative or inconclusive, testing of a 2nd or convalescent serum collected 3-5 days after acute serum may be considered.
SAINT LOUIS ENCEPHALITIS

- Discovered in 1933 after outbreak in St. Louis, Missouri.
- 23 strains, with geographic range from Canada to Argentina, but human cases have almost exclusively occurred in U.S.
- SLEV disease cases occur primarily in the late summer/early fall, but can occur year round in southern U.S.
- Majority of cases have occurred in eastern and central U.S., where episodic urban-centered outbreaks have recurred since the 1930’s.
- In western U.S., transmission has followed a more endemic pattern. Found historically in many regions of CA (Central Valley and southern CA), but, since the introduction of WNV into CA in 2003, SLEV detected rarely.
SAINT LOUIS ENCEPHALITIS

• Largest epidemic of SLEV neuroinvasive disease ever recognized occurred in the U.S. in 1975, with nearly 2,000 cases reported, primarily from the central states in the Ohio-Mississippi River Basin.

• Since 2004, between 1 and 12 cases per year reported.

• Four cases reported so far in 2016, one in Los Angeles County

• Mosquitoes positive for SLEV in Los Angeles, Riverside, Orange and Kern Counties in 2016.
St. Louis encephalitis virus neuroinvasive disease cases reported by state, 2004-2013

Transmission cycle of SLEV

Culex species

Mosquito vector

Dead-end host

Amplifying host

Photo credit: CDC
Less than 1% of St. Louis encephalitis virus (SLEV) infections are clinically apparent and the vast majority of infections remain undiagnosed.

The incubation period for SLEV disease (the time from infected mosquito bite to onset of illness) ranges from 5 to 15 days.

Onset of illness is usually abrupt, with fever, headache, dizziness, nausea, and malaise.

Signs and symptoms intensify over a period of several days to a week.
Some patients spontaneously recover after this period; others develop signs of central nervous system infections, including stiff neck, confusion, disorientation, dizziness, tremors and unsteadiness. Coma can develop in severe cases.

Disease is generally milder in children than in older adults.

About 40% of children and young adults with SLEV disease develop only fever and headache or aseptic meningitis; almost 90% of elderly persons with SLEV disease develop encephalitis.

Overall case-fatality ratio is 5 to 15% - increases with age.
SAINT LOUIS ENCEPHALITIS

No current specific treatment or vaccine for SLEV infection.

Photo: SDCVCP
YELLOW FEVER

- YF has had an important role in the history of Africa, the Americas, Europe, and the Caribbean.
- In the 1600’s, YF was imported into the Western Hemisphere on slave ships from West Africa.
- In 1648, the first definitive evidence of YF in the Americas was in Mayan manuscripts describing an outbreak of the disease in the Yucatan and Guadeloupe.
- Outbreaks were reported in the U.S., including in New York (1668), Boston (1691), and Charleston (1699). Spread to Europe in the 1700’s.
- The Reed Yellow Fever Commission proved that YF infection is transmitted to humans by the *Aedes aegypti*.
- Last U.S. outbreak occurred in New Orleans in 1905.
Following the demonstration that Ae. aegypti mosquitoes are responsible for transmission of the YF virus to humans, intense sanitation programs began in Panama and Havana, Cuba, eradicating the disease in these areas.

In 1930, two YF vaccines were developed, the 17D vaccine and the French neurotropic vaccine. Mass campaigns conducted in the 1940’s.

In 1950’s doctors became concerned with the high rate of postvaccinal encephalitis following administration of the YF vaccine to infants.

The range of YF virus transmission in the Americas expanded, and cases were reported in Panama for the first time in 43 years. Before the end of 1950’s, the disease had spread throughout Central America, finally stopping near the border of Guatemala and Mexico.
Source CDC.
Downloaded 9/25/16 from http://www.cdc.gov/yellowfever/maps/southamerica.html
Distribution of confirmed yellow fever cases in Democratic Republic of The Congo as of 18 September 2016

Outbreak began 1/1/16

2,770 reported cases
116 reported deaths

76 confirmed cases
16 confirmed deaths

Data source WHO.

Downloaded 9/26/16 from: http://apps.who.int/iris/bitstream/10665/250147/1/yellowfeversitrep23Sep16-eng.pdf?ua=1
Geographical distribution of confirmed cases in Angola by district through time, March 2016 to 1 September 2016

Outbreak began 12/5/15 4,065 reported cases 371 reported deaths 884 confirmed cases 121 confirmed deaths

Data source WHO. Downloaded 9/26/16 from http://apps.who.int/iris/bitstream/10665/250077/1/yellowfeversitrep9Sep16-eng.pdf?ua=1
YELLOW FEVER

Africa

Ae. africanus
Monkey

Ae. africanus
Ae. furcifer
Ae. luteocephalus
Ae. taylori
Ae. metallicus
Ae. vittatus
Ae. simpsoni complex

Humans

Ae. aegypti

Humans

Jungle cycle
H. janthinomys
H. leucocelaenus
S. chloropterus

Savannah cycle

Humans

Urban cycle

South America

Humans

• Majority of persons infected with YF have no illness or only mild illness.

• In persons who develop symptoms, the incubation period is typically 3 to 6 days.

• Initial symptoms include sudden onset of fever, chills, severe headache, back pain, general body aches, nausea, and vomiting, fatigue, and weakness. Most persons improve after the initial presentation.

• After a brief remission of hours to a day, 15% of cases progress to develop a more severe form of the disease, characterized by high fever, jaundice, bleeding, and eventually shock and multiple organ failure.
• No specific treatments have been found to benefit patients with YF. Whenever possible, YF patients should be hospitalized for supportive care and close observation.

• Treatment is symptomatic. Rest, fluids, and use of pain relievers and medication to reduce fever may relieve symptoms of aching and fever.

• Avoid certain medications, such as aspirin or other nonsteroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen), which may increase the risk of bleeding.

• YF patients should be protected from further mosquito exposure (staying indoors and/or under a mosquito net) for up to 5 days after fever onset.
• Majority of infected persons will be asymptomatic or have mild disease with complete recovery.

• In persons who become symptomatic but recover, weakness and fatigue may last several months.

• Among those who develop severe disease, 20–50% may die.

• Those who recover from YF generally have lasting immunity against subsequent infection.
There IS a vaccine for yellow fever, but no specific treatment.

Key prevention messages:

• Stay indoors at dawn and dusk
• Avoid mosquito bites; wear long sleeves, long pants, and socks when outdoors
• Use mosquito repellent*
• Keep screens on windows and doors in good repair
• Identify and eliminate standing water sources that can be mosquito-breeding areas around the home

* Information on repellents can be found at: http://www.cdc.gov/ncidod/dvbid/westnile/RepellentUpdates.htm
• YF vaccine is recommended for persons aged ≥9 months who are traveling to or living in areas at risk for YF virus transmission in South America or Africa.

• YF vaccine may be required for entry into certain countries. YF vaccination requirements and recommendations for specific countries are available on the CDC Travelers' Health page.

• Serious adverse events can occur following YF vaccination. Persons should only be vaccinated if they are at risk of exposure to YF virus or require proof of vaccination for country entry.

• To minimize the risk, providers should carefully observe the contraindications and consider the precautions prior to vaccine administration.
• A medical waiver can be given for persons with a precaution about or contraindication to vaccination. More information about medical waivers is available on the CDC Travelers' Health website.

• For more information about the use of YF vaccine in travelers or laboratory workers, see the Advisory Committee on Immunization Practice (ACIP) recommendations.

• This vaccine is administered only at designated vaccination centers. Locations at CDC Travelers' Health Yellow Fever website.
• In February 2015, the CDC Advisory Committee on Immunization Practices (ACIP) approved a new recommendation that a single dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers.

• The updated recommendations also identify specific groups of travelers who should receive additional doses and others for whom additional doses may be considered including:
  • Woman who were pregnant when first vaccinated
  • Persons who received a hematopoietic stem cell transplant following their last dose of YF vaccine
  • Persons who are HIV-infected
  • Travelers who received YF vaccine at least 10 years previously and who will be in a higher-risk setting based on season, location, activities, and duration of their travel
  • Laboratory workers who routinely handle wild-type YF virus
Although ACIP no longer recommends booster doses of YF vaccine for most travelers, clinicians and travelers should review the entry requirements for destination countries because changes to the International Health Regulations (IHR) have not yet been fully implemented.

In 2014, WHO adopted the recommendation to remove the 10-year booster dose requirement from the IHR as of June 2016. Once this change is instituted, a completed International Certificate of Vaccination or Prophylaxis will be valid for the lifetime of the vaccine. Some countries have already adopted this change, however, it is uncertain when and if all countries with YF vaccination requirements will adopt this change.
**Contraindications**

- Allergy to a vaccine component
- Age <6 months
- Thymus disorder associated with abnormal immune function
- Primary immunodeficiencies
- Malignant neoplasms
- Transplantation
- Immunosuppressive and immunomodulatory therapies
- Symptomatic HIV infection or CD4+ T-lymphocytes <200/mm3 (<15% of total in children aged <6 years)

**Precautions**

- Age 6 to 8 months
- Age ≥60 years
- Asymptomatic HIV infection and CD4+ T-lymphocytes 200 to 499/mm3 (15-24% of total in children aged <6 years)
- Pregnancy
- Breastfeeding
Reactions to YF vaccine are generally mild and include headaches, myalgias, and low-grade pyrexia.

Rare reports of serious events following YF vaccination, including:

- Anaphylaxis
- YF vaccine-associated viscerotrophic disease (YEL-AVD)
- YF vaccine-associated neurologic disease (YEL-AND)

CDC can provide lab testing support for suspected YEL-AVD and YEL-AND.

Healthcare providers are encouraged to report all adverse events that might be caused by vaccination to the CDC/FDA Vaccine Adverse Events Reporting System (VAERS)
Approximately 67,900 JE cases typically occur annually (overall incidence: 1.8 per 100,000), of which only about 10% are reported to WHO. (Campbell, et al. 2011)

Approximately 33,900 (50%) of cases occur in China (excluding Taiwan) and approximately 51,000 (75%) occur in children aged 0-14 years (incidence: 5.4 per 100,000).

Approximately 55,000 (81%) cases occur in areas with well established or developing JE vaccination programs, while approximately 12,900 (19%) occur in areas with minimal or no JE vaccination programs.
JAPANESE ENCEPHALITIS

Endemic / natural cycle

Culex tritaeniorhynchus (other Culex spp.)

„rice fields“

dead-end hosts

rural infections

Amplification cycle

Culex tritaeniorhynchus (other Culex & Aedes spp.)

„farms“

rural & peri-urban infections

Less than 1% of people infected with Japanese encephalitis (JE) virus develop clinical illness.

In persons who develop symptoms, the incubation period (time from infection until illness) is typically 5 to 15 days.

Initial symptoms often include fever, headache, and vomiting.

Mental status changes, neurologic symptoms, weakness, and movement disorders might develop over the next few days.

Seizures are common, especially among children.
No specific treatments have been found to benefit patients with JE, but hospitalization for supportive care and close observation is generally required.

Treatment is symptomatic. Rest, fluids, and use of pain relievers and medication to reduce fever may relieve some symptoms.

Among patients who develop encephalitis, 20% - 30% die.

Although some symptoms improve after the acute illness, 30%-50% of survivors continue to have neurologic, cognitive, or psychiatric symptoms
There IS a vaccine for JE, but no specific treatment.

Key prevention messages:

- Stay indoors at dawn and dusk
- Avoid mosquito bites; wear long sleeves, long pants, and socks when outdoors
- Use mosquito repellent*
- Keep screens on windows and doors in good repair
- Identify and eliminate standing water sources that can be mosquito-breeding areas around the home

* Information on repellents can be found at:
  [http://www.cdc.gov/ncidod/dvbid/westnile/RepellentUpdates.htm](http://www.cdc.gov/ncidod/dvbid/westnile/RepellentUpdates.htm)
JE VACCINE RECOMMENDATIONS

• JE vaccine is **recommended** for travelers who plan to spend 1 month or more in endemic areas during the JE virus transmission season. This includes long-term travelers, recurrent travelers, or expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high-risk period of JE virus transmission.

• JE vaccine is **not recommended** for short-term travelers whose visits will be restricted to urban areas or times outside a well-defined JE virus transmission season.
JE VACCINE RECOMMENDATIONS

• Vaccine should also be considered for the following:

• Short-term (<1 month) travelers to endemic areas during the transmission season, if they plan to travel outside an urban area and their activities will increase the risk of JE virus exposure. Examples of higher-risk activities or itineraries include:
  
  • spending substantial time outdoors in rural or agricultural areas, especially during the evening or night;
  
  • participating in extensive outdoor activities (such as camping, hiking, trekking, biking, fishing, hunting, or farming); and
  
  • staying in accommodations without air conditioning, screens, or bed nets.

• Travelers to an area with an ongoing JE outbreak.

• Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel.
Inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine is the only JE vaccine licensed and available in the U.S.

Vaccine was approved in March 2009 for use in people aged 17 years and older and in May 2013 for use in children 2 months through 16 years of age. Other JE vaccines are manufactured and used in other countries but are not licensed for use in the U.S.

IXIARO is given as a two-dose series, with the doses spaced 28 days apart. The last dose should be given at least 1 week before travel.

For persons aged 17 years and older, a booster dose may be given if a person has received the two-dose primary vaccination series one year or more previously and there is a continued risk for JE virus infection or potential for re-exposure.

Although studies are being conducted on the need for a booster dose for children, data are not yet available.
QUESTIONS?
For more information contact:

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