WEST NILE VIRUS INFECTIONS

I. DESCRIPTION AND EPIDEMIOLOGY

A. Overview

West Nile virus (WNV) is a mosquito-borne RNA virus from the family Flaviviridae, which includes dengue virus, Zika virus, and yellow fever virus, as well as St. Louis encephalitis virus (SLEV), another endemic virus in California. The primary transmission cycle is between mosquitoes from the genus *Culex* and birds from the order Passeriformes. Humans are infected through the bite of an infected mosquito.

Most WNV infections are asymptomatic. The majority of individuals who become ill present with mild febrile illness. However, some case-patients develop neuroinvasive disease, such as aseptic meningitis, encephalitis, or acute flaccid paralysis, which can lead to death. The risk of severe illness is higher for people over the age of 60 and those with certain medical conditions, including hypertension, diabetes, cancer, and kidney disease, as well as organ transplant recipients.

B. West Nile Virus in California

WNV was introduced to North America via New York City in 1999. The first positive mosquito pools were detected in California in 2003, and the first locally acquired human cases were reported in 2004. From 2004 to 2022, between 112 to 880 symptomatic cases were reported each year, with a median of 382. A total of 372 WNV-related fatalities were reported in that time period. Incidence was highest in Southern California and Central Valley counties. More information can be found in the Vector-Borne Disease Section Annual Reports (https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/VBDSAnnualReports.aspx).

C. Symptoms and Clinical Course

Approximately 80% of individuals infected with WNV do not develop symptoms. Most individuals who develop symptoms present with non-specific febrile illness, which can include headache, body aches, rash, nausea/vomiting, and/or diarrhea. About one percent of infected individuals develop neuroinvasive disease, which typically presents as meningitis, encephalitis, or acute flaccid paralysis. Patients with WNV meningitis present with fever, headache, and neck stiffness, which are clinically indistinguishable from signs of meningitis caused by other viruses or bacteria. WNV encephalitis is a more severe syndrome, with fever, altered mental status, seizures, focal neurological deficits, and/or movement disorders such as tremor. WNV acute flaccid paralysis often presents as isolated limb weakness or paralysis and may progress to respiratory paralysis. Other reported neuroinvasive disease presentations include Guillain-Barré syndrome, optic neuritis, cardiac dysrhythmias, and a variety of other syndromes. Patients with WNV neuroinvasive disease have a 10% fatality rate.

D. Diagnosis

Nucleic acid tests, such as polymerase chain reaction or PCR, are considered the gold standard of diagnostics for WNV, and detection of viral nucleic acid in serum or cerebrospinal fluid (CSF) samples is sufficient to meet the confirmed surveillance case definition. Typically, only blood and organ donors are diagnosed by nucleic acid test, and they frequently remain asymptomatic.

Symptomatic patients are most often diagnosed by serological testing, due to the delay between symptom onset and diagnosis. Detection of WNV IgM antibodies in serum meets the probable surveillance case definition for both neuroinvasive and non-neuroinvasive disease patients. In areas without SLEV co-circulating with WNV, WNV IgM detection in cerebrospinal fluid (CSF) samples from patients with neuroinvasive WNV disease meets the confirmed case definition. However, if both SLEV and WNV have been detected that year in the patient's county of residence, WNV IgM detection in CSF only meets the probable case definition. Please note that CSF is not an appropriate sample for diagnosing non-neuroinvasive cases; if a CSF sample is submitted for testing, neuroinvasive disease should be strongly considered.

Confirmatory testing for all symptomatic patients via plaque-reduction neutralization test (PRNT), available at CDPH Viral and Rickettsial Disease Laboratory, is required for the first case of the year in California or from counties where WNV environmental activity has not been detected. Confirmatory testing is also required for all patients residing in counties with concurrent WNV and SLEV transmission. Serum samples are strongly recommended for PRNTs due to low test sensitivity in CSF samples. Paired sera samples with a four-fold or greater change in WNV IgM titer are also sufficient to meet the confirmed case definition for both neuro- and non-neuroinvasive disease cases.

E. Transmission

WNV is transmitted by mosquitoes from the genus *Culex*, which are found in both rural and urban areas of the state. Infections may also be caused by blood transfusion or organ transplant from an infected donor, as well as laboratory exposures. Rare reports of congenital WNV infection exist.

F. Incubation Period

The typical incubation for WNV is 2 to 6 days but can range up to 14 days. Incubation periods of several weeks have been reported in patients who are immunocompromised.

G. Clinical Management

There is no specific treatment for WNV disease; clinical management is mainly supportive. Patients with WNV meningitis typically require pain control for headaches, as well as antiemetics and rehydration for nausea and vomiting. WNV encephalitis patients require monitoring for the potential development of seizures and/or elevated intracranial pressure. Patients with WNV encephalitis and/or acute flaccid paralysis should be monitored for inability to protect their airway, as respiratory failure can develop rapidly, and if necessary, receive ventilatory support. While to date there are no

drugs that have shown specific benefits against WNV disease, the National Institutes of Health maintains a registry of clinical trials conducted in the United States and elsewhere in the world.

II. COUNCIL OF STATE AND TERRITORIAL EPIDEMIOLOGISTS (CSTE) SURVEILLANCE CASE DEFINITIONS

Arboviral Diseases, Neuroinvasive and Non-neuroinvasive 2015

The CSTE surveillance case definitions can be found on the U.S. Centers for Disease Control and Prevention (CDC) Surveillance Case Definitions for Current and Historical Conditions webpage (https://ndc.services.cdc.gov/case-definitions/arboviral-diseases-neuroinvasive-and-non-neuroinvasive-2015/).

CSTE Position Statement

14-ID-04
(https://cdn.ymaws.com/www.cste.org/resource/resmgr/ps1/14_ID_04_clarified_Jan2018.pdf)

Clinical Description

Most arboviral infections are asymptomatic. Clinical disease ranges from mild febrile illness to severe encephalitis. For the purpose of surveillance and reporting, based on their clinical presentation, arboviral disease cases are often categorized into two primary groups: neuroinvasive disease and non-neuroinvasive disease.

Neuroinvasive disease

Many arboviruses cause neuroinvasive disease such as aseptic meningitis, encephalitis, or acute flaccid paralysis (AFP). These illnesses are usually characterized by the acute onset of fever with headache, myalgia, stiff neck, altered mental status, seizures, limb weakness, or cerebrospinal fluid (CSF) pleocytosis. AFP may result from anterior ("polio") myelitis, peripheral neuritis, or post-infectious peripheral demyelinating neuropathy (i.e., Guillain-Barre' syndrome). Less common neurological manifestations, such as cranial nerve palsies, also occur.

Non-neuroinvasive disease

Most arboviruses are capable of causing an acute systemic febrile illness (e.g., West Nile fever) that may include headache, myalgias, arthralgia, rash, or gastrointestinal symptoms. Some viruses also can cause more characteristic clinical manifestations, such as severe polyarthralgia or arthritis due to Chikungunya virus or other alphaviruses (e.g., Mayaro, Ross River, O'nyong-nyong).

Clinical Criteria

A clinically compatible case of arboviral disease is defined as follows:

Neuroinvasive disease

- Meningitis, encephalitis, acute flaccid paralysis, or other acute signs of central or peripheral neurologic dysfunction, as documented by a physician, **AND**
- Absence of a more likely clinical explanation. Other clinically compatible symptoms of arbovirus disease include: headache, myalgia, rash, arthralgia, vertigo, vomiting, weakness and/ or neck stiffness.

Non-neuroinvasive disease

- Fever (chills) as reported by the patient or a health-care provider, **AND**
- Absence of neuroinvasive disease, **AND**
- Absence of a more likely clinical explanation. Other clinically compatible symptoms of arbovirus disease include: headache, myalgia, rash, arthralgia, vertigo, vomiting, weakness and/ or neck stiffness.

Laboratory Criteria for Diagnosis

Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid, **OR**

- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera, **OR**
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen, **OR**
- Virus-specific IgM antibodies in CSF or serum.

Case Classification

Probable

Neuroinvasive disease

A case that meets the above clinical criteria for neuroinvasive disease and the following laboratory criteria:

- Virus-specific IgM antibodies in CSF or serum but with no other testing.

Non-neuroinvasive disease

- A case that meets the above clinical criteria for non-neuroinvasive disease and the laboratory criteria for a probable case:
- Virus-specific IgM antibodies in serum but with no other testing.

Confirmed

Neuroinvasive disease

A case that meets the above clinical criteria for neuroinvasive disease and one or more of the following laboratory criteria for a confirmed case:

- Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid, **OR**
- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera, **OR**
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen, **OR**
- Virus-specific IgM antibodies in CSF, with or without a reported pleocytosis, and a negative result for other IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred.

Non-neuroinvasive disease

A case that meets the above clinical criteria for non-neuroinvasive disease and one or more of the following laboratory criteria for a confirmed case:

- Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, or other body fluid, excluding CSF, **OR**
- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera, **OR**
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen.

Comments

Interpreting arboviral laboratory results:

- **Serologic cross-reactivity:** In some instances, arboviruses from the same genus produce cross-reactive antibodies. In geographic areas where two or more closely-related arboviruses occur, serologic testing for more than one virus may be needed and results compared to determine the specific causative virus. For example, such testing might be needed to distinguish antibodies resulting from infections within genera, e.g., flaviviruses such as West Nile, St. Louis encephalitis, Powassan, Dengue, or Japanese encephalitis viruses.
- **Rise and fall of IgM antibodies:** For most arboviral infections, IgM antibodies are generally first detectable at 3 to 8 days after onset of illness and persist for 30 to 90 days, but longer persistence has been documented (e.g., up to 500 days for West Nile virus). Serum collected within 8 days of illness onset may not have detectable IgM and testing should be repeated on a convalescent-phase sample to rule out arboviral infection in those with a compatible clinical syndrome.
- **Persistence of IgM antibodies:** Arboviral IgM antibodies may be detected in some patients months or years after their acute infection. Therefore, the presence of these virus-specific IgM antibodies may signify a past infection and be unrelated to the current acute illness. Finding virus-specific IgM antibodies in CSF or a fourfold or greater change in virus-specific antibody titers between acute- and convalescent-phase serum specimens provides additional laboratory

evidence that the arbovirus was the likely cause of the patient's recent illness. Clinical and epidemiologic history also should be carefully considered.

- **Persistence of IgG and neutralizing antibodies:** Arboviral IgG and neutralizing antibodies can persist for many years following a symptomatic or asymptomatic infection. Therefore, the presence of these antibodies alone is only evidence of previous infection and clinically compatible cases with the presence of IgG, but not IgM, should be evaluated for other etiologic agents.
- **Arboviral serologic assays:** Assays for the detection of IgM and IgG antibodies commonly include enzyme-linked immunosorbent assay (ELISA), microsphere immunoassay (MIA), or immunofluorescence assay (IFA). These assays provide a presumptive diagnosis and should have confirmatory testing performed. Confirmatory testing involves the detection of arboviral-specific neutralizing antibodies utilizing assays such as plaque reduction neutralization test (PRNT).
- **Other information to consider.** Vaccination history, detailed travel history, date of onset of symptoms, and knowledge of potentially cross-reactive arboviruses known to circulate in the geographic area should be considered when interpreting results.

III. CASE SURVEILLANCE, INVESTIGATION, AND REPORTING

A. Purpose of Surveillance, Investigation, and Reporting

WNV is a nationally notifiable disease and is a CDPH reportable condition (Title 17 California Code of Regulations, Section 2500). As there is no vaccine or treatment available for WNV disease, the primary prevention tools are public education and vector control. Prompt identification and reporting of cases to public health allows local and state public health to alert the general public and coordinate with vector control in the areas affected.

B. Local Health Department (LHD) General Case Investigation Guidelines

Local health officials should initiate a follow-up investigation for patients who meet the probable or confirmed surveillance case definitions, including collecting information on recent travel outside of the county and/or state. If a patient with a suspected WNV infection lives in an area serviced by a vector control agency, the LHD should notify the vector control agency of the patient's illness onset date and the nearest cross street to their residence.

If a case-patient reports being a recent blood or organ donor and the LHD was not notified by the donation organization, please contact the organization to stop or limit the distribution of the infected blood products or organs and to identify individuals who may have received a contaminated transfusion or transplant.

C. LHD Reporting to CDPH

WNV case-patients who meet the confirmed or probable CSTE case definition should be reported to CDPH by electronic transmission, telephone, or mail within one working day of identification of the case. The CDPH WNV Infection case report form (CRF; CDPH 8687) should be used to interview all case patients, both symptomatic and asymptomatic, and is available as a download in the CalREDIE document repository. This form includes demographic characteristics, as well as information required to meet the CSTE case definitions, including clinical, laboratory, and epidemiological data.

All cases are reviewed by the CDPH IDB WNV Subject Matter Expert (SME). For SMEs to adequately review a case, data for the following fields are required to be entered into the case record: presence of clinically compatible symptoms and laboratory results. All probable and confirmed cases reviewed by the state SME are included in CDPH's year-end state case counts and CDC's national counts.

Instructions for CalREDIE-participating Jurisdictions:

- Enter the patient information into CalREDIE upon notification of the case by the clinical laboratory or healthcare provider. For "Disease Being Reported", please select the appropriate clinical syndrome: "West Nile Virus – Asymptomatic", "West Nile Virus – Neuroinvasive", or "West Nile Virus – Non-neuroinvasive (West Nile fever)".

Instructions for Extended Data Exchange Jurisdictions:

- For jurisdictions not currently participating in CalREDIE, a WNV Infection CRF (CDPH 8687) or other form including the same information, must still be submitted. Jurisdictions may contact IDB for the WNV CRF (8687) if needed.

D. Laboratory Resources

If SLEV is also circulating within a county and/or the individual has traveled out of the country to an area with dengue or Zika virus transmission, samples should be submitted to VRDL for confirmatory testing.

IV. CASE MANAGEMENT AND PUBLIC HEALTH CONTROL MEASURES

A. Management of Cases

There are no specific applicable sections within the CCR Title 17 guiding the management of cases of WNV.

B. Management of Contacts

There are no specific applicable sections within the CCR Title 17 guiding the management of contacts of patients because WNV is not transmitted from person to person.

C. Infection Control Measures

Stress appropriate biosafety and personal protect equipment use in laboratory settings.

V. APPLICABLE STATE STATUTES AND REGULATIONS

- Title 17, California Code of Regulations (CCR) Section 2500. Reportable Diseases and Conditions: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ReportableDiseases.pdf
- Title 17, California Code of Regulations (CCR), Section 2505. Reportable Conditions: Notification by Laboratories to Public Health: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/LabReportableDiseases.pdf

VI. ADDITIONAL RESOURCES

General information and educational materials on West Nile virus include:

- CDPH WNV website: https://westnile.ca.gov/
- CDC WNV website: https://www.cdc.gov/westnile/index.html
- CDPH VBDS Annual Reports: https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/VBDSAnnualReports.aspx
- CDPH VRDL West Nile and St. Louis Encephalitis Viruses in California: Guidelines for Human Testing, Surveillance and Reporting: https://www.westnile.ca.gov/pdfs/WNV_SLEV_Guidelines.pdf
- California Mosquito-Borne Virus Surveillance & Response Plan: https://westnile.ca.gov/pdfs/CAMosquitoSurveillanceResponsePlan.pdf
- Mosquito and Vector Control Association of California: https://www.mvcac.org/
- California VectorSurv Maps: https://maps.vectorsurv.org/arbo

VII. UPDATES

Original version finalized and completed in May 2023.

VIII. SUMMARY OF ACTIONS STEPS: WEST NILE VIRUS

Action	Specific Steps
☐ Begin case investigation as soon as WNV is reported from clinical laboratory or healthcare provider	• Obtain and review clinical documentation, medical reports, and lab reports as applicable. • Contact patient for interview. • Contact local vector control agency, if applicable, with illness onset date and nearest cross street to suspect case's residence.
☐ Classify case per CSTE surveillance case definitions	• To count as a probable or confirmed case of WNV, both clinical and laboratory criteria must be fulfilled.
☐ Report to CDPH; both confirmed and probable WNV cases must be reported	• Create CalREDIE incident for WNV. OR • Extended data exchange jurisdictions must complete corresponding forms.