

West Nile Virus Disease

1. DISEASE REPORTING

A. Purpose of Reporting and Surveillance

1. To identify areas in which West Nile virus (WNV) is being transmitted.
2. To target public education about reducing mosquito habitats and avoiding mosquito bites.
3. To provide information for mosquito control and environmental health initiatives.
4. To identify periods of time when WNV poses a significant risk to the blood supply.
5. To identify new routes of exposure.

B. Legal Reporting Requirements

1. Health care providers: notifiable to local health jurisdiction within 3 business days.
2. Health care facilities: notifiable to local health jurisdiction within 3 business days.
3. Laboratories: West Nile virus acute infection detected by IgM positivity, PCR positivity, and viral isolation, within 2 business days. Specimen submission is on request only.
4. Veterinarians: Suspected human cases notifiable within 24 hours to the local health jurisdiction; animal cases notifiable to Washington State Department of Agriculture (see: <http://apps.leg.wa.gov/WAC/default.aspx?cite=16-70>).
5. Local health jurisdictions: notifiable to Washington State Department of Health (DOH) Communicable Disease Epidemiology Section (CDES) within 7 days of case investigation completion or summary information required within 21 days.

C. Local Health Jurisdiction Investigation Responsibilities

1. Through investigation, identify unusual exposures and transmission routes other than vector-borne (i.e., donor or recipient of blood products, tissue or organs) within 24 hours of the initial report.
2. Facilitate transport of specimens (e.g., serum or cerebrospinal fluid [CSF]) to the Washington State Public Health Laboratories (PHL) if initial testing or confirmatory testing is needed. Please call CDES prior to submitting specimens (206-418-5500).
3. Report all *confirmed* and *probable* cases and presumptive viremic donors to CDES (see definitions below). Complete the West Nile virus case report form (<http://www.doh.wa.gov/notify/forms/wnv.pdf>) and enter the data into the Public Health Issues Management System (PHIMS) as “West Nile Virus Disease” (*Note:* not “Arboviral Disease”).

2. THE DISEASE AND ITS EPIDEMIOLOGY

Background

West Nile virus (WNV) was first isolated in 1937 from a febrile woman in the West Nile District of Uganda. WNV was first recognized as a cause of severe meningoencephalitis in elderly patients during an outbreak in Israel in 1957. It was first introduced to North

America in 1999 in New York City. Since then, WNV has spread across the United States, and was first known to have reached Washington in 2002.

A. Etiologic Agent

West Nile virus is a single-stranded RNA virus of the family Flaviviridae, genus Flavivirus. It is a member of the Japanese encephalitis virus serocomplex, which contains several medically important viruses that cause encephalitis in humans: Japanese encephalitis, St. Louis encephalitis, Murray Valley encephalitis, and Kunjin (an Australian subtype of West Nile virus). The close antigenic relationship of the flaviviruses, particularly those belonging to the Japanese encephalitis complex, accounts for the serologic cross-reactions observed in the diagnostic laboratory.

B. Description of Illness

Serosurveys have shown that less than 1% of WNV-infected persons develop serious **WNV neuroinvasive disease (WNND)** which includes encephalitis, meningitis, acute flaccid paralysis (“WNV poliomyelitis”), optic neuritis, and cranial nerve abnormalities. Approximately 20% of infected individuals develop **West Nile fever (WNF)** and about 80% remain asymptomatic.

The incidence and case-fatality rate of WNND increase with age, with the greatest risk occurring in persons over 50 years old. Among those with severe illness due to WNV, case-fatality rates range from 3% to 15% and are highest among the elderly. However, this differs by clinical syndrome: WN encephalitis has been associated with 10-15% mortality, and WN “poliomyelitis” may have a case-fatality rate exceeding 50%.

WNF is a febrile illness of sudden onset, often accompanied by headache, myalgias, fatigue, and malaise. Gastrointestinal symptoms, rash, and lymphadenopathy occasionally occur. Symptoms generally last 3 to 6 days but may persist for weeks. WNF rarely results in death.

C. West Nile Virus Infections in Washington State

Washington State agencies conduct surveillance for WNV infections in humans, birds, mosquitoes, horses and other animals. The first detections of the virus in Washington occurred in 2002; the first locally acquired human infections were reported in 2006. During 2009 there were 38 cases and 2 presumptive viremic blood donors reported, almost all exposed in eastern Washington. For current or historical information about WNV in Washington, visit: <http://www.doh.wa.gov/ehp/ts/Zoo/WNV/WNV.html>

D. Vectors and Reservoirs

WNV is maintained in an enzootic cycle involving vector mosquitoes and many bird reservoir species. Although corvids (crows, ravens, magpies, jays) infected with WNV often become ill and die, many infected birds survive and do not have any symptoms. In the United States more than 300 native and exotic bird species have been found to be infected with WNV. Competent bird reservoirs may have virus circulating in their bloodstream for 1 to 4 days after contracting WNV. Mosquitoes that feed on them during that period can become infected.

WNV is transmitted mainly by mosquitoes in the *Culex* subgenus, which occur in Washington State, though many other mosquito species are also known to become

infected. Humans, horses, and most other mammals do not develop the high-level viremia that infect mosquitoes, and are considered "dead-end" or incidental hosts.

E. Modes of Transmission

The main route of transmission is through the bite of an infected mosquito. In very rare cases, WNV also has been transmitted through blood transfusions, organ transplants, percutaneous injuries in the laboratory, the placenta, and possibly breast milk.

F. Incubation Period

Usually 2 to 14 days.

G. Period of Communicability

Infected people may develop a short lived (2–3 day) low-level viremia that can contaminate donated blood units; blood collection centers screen donated units to prevent this from occurring. Transmission through organ transplantation, transplacentally, and via breast milk are very rare. WNV is not spread through casual contact such as touching or kissing a person with the virus.

H. Treatment

In the absence of an effective antiviral agent, treatment for WNV infection is supportive. Treatment for WNND often involves hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections.

Controlled trials investigating specific antiviral treatments are ongoing.

3. CASE DEFINITION

A. Clinical Description

Most West Nile virus (WNV) infections are asymptomatic. Clinical disease ranges from mild febrile illness to severe encephalitis. For the purposes of surveillance and reporting, based on their clinical presentation, WNV disease cases are categorized into two primary groups: neuroinvasive disease and non-neuroinvasive disease.

Neuroinvasive disease: WNV can 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 stiff neck, altered mental status, seizures, limb weakness, cerebrospinal fluid (CSF) pleocytosis, or abnormal neuroimaging. AFP may result from anterior ("polio") myelitis, peripheral neuritis, or post-infectious peripheral demyelinating neuropathy (i.e., Guillain-Barré syndrome). Less common neurological manifestations, such as cranial nerve palsies, also occur.

Non-neuroinvasive disease: WNV is capable of causing an acute systemic febrile illness that may include headache, myalgias, arthralgias, rash, or gastrointestinal symptoms. Rarely, myocarditis, pancreatitis, hepatitis, or ocular manifestations such as chorioretinitis and iridocyclitis can occur.

B. Clinical Criteria for Diagnosis

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

Neuroinvasive disease

- Fever ($\geq 100.4^{\circ}\text{F}$ or 38°C) as reported by the patient or a health-care provider, **AND**
- 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.

Non-neuroinvasive disease

- Fever ($\geq 100.4^{\circ}\text{F}$ or 38°C) as reported by the patient or a health-care provider, **AND**
- Absence of neuroinvasive disease, **AND**
- Absence of a more likely clinical explanation.

C. Laboratory Criteria for Diagnosis

Confirmatory:

- Isolation of virus from or demonstration of WNV antigen or nucleic acid in tissue, blood, CSF, or other body fluid, **OR**
- Four-fold or greater change in WNV-specific quantitative antibody titers in paired sera, **OR**
- WNV-specific immunoglobulin M (IgM) antibodies in serum with confirmatory* WNV-specific neutralizing antibodies in the same or a later specimen, **OR**
- WNV-specific IgM antibodies in CSF and a negative result for other arbovirus IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred.

Presumptive:

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

***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).

Note: See “Specimen Collection” section for appropriate timing of specimen collection.
Comments: In some instances, arboviruses from the same genus produce cross-reactive antibodies. In geographic areas where two or more closely related arboviruses occur, it may be epidemiologically important to attempt to pinpoint the infecting virus by conducting cross-neutralization tests using an appropriate battery of closely related viruses. This is essential, for example, in determining that antibodies detected against St. Louis encephalitis virus are not the result of an infection with West Nile virus, or vice versa, in areas where both of these viruses occur (such as eastern Washington State).

West Nile virus IgM antibodies have been documented to persist for up to 500 days in serum. Therefore the presence of IgM antibodies in serum may signify a past infection. Finding WNV IgM antibodies in CSF or a fourfold or greater change in WNV antibody titers between acute- and convalescent-phase serum specimens provides additional laboratory evidence that WNV was the cause of the patient's recent illness. Likewise, 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. Clinical and epidemiologic history also should be carefully considered. See Section 4A for additional details.

D. Case Classification (2011)

Confirmed:

- Neuroinvasive: a case that meets the clinical criteria for neuroinvasive disease and one or more of the confirmatory laboratory criteria.
- Non-neuroinvasive: a case that meets the clinical criteria for non-neuroinvasive disease and one or more of the confirmatory laboratory criteria.

Probable:

- Neuroinvasive: a case that meets the clinical criteria for neuroinvasive disease and the presumptive laboratory criterion.
- Non-neuroinvasive: a case that meets the clinical criteria for non-neuroinvasive disease and the presumptive laboratory criterion.

Comment: Asymptomatic presumptive viremic blood donors (PVDs) should be entered into PHIMS, classified as "Suspect," and manually reported. If WNV illness develops after the PVD is first reported, reclassify the report as a case. See Section 7.

4. DIAGNOSIS AND LABORATORY SERVICES

A. Laboratory Diagnosis

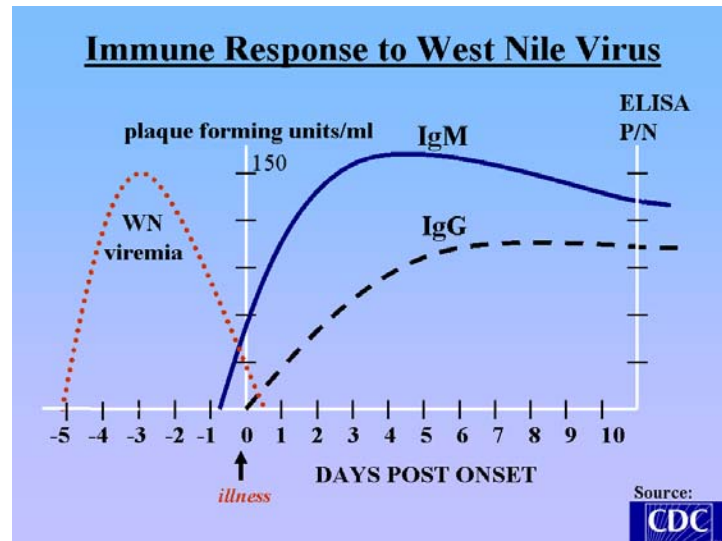
The most efficient diagnostic method for West Nile virus (WNV) infection is detection of virus using the IgM antibody-capture enzyme immunoassay (MAC-EIA) or microsphere immunoassay (MIA) of IgM antibody to WNV in serum collected 8 to 14 days after onset *or* CSF collected within 8 days of illness onset. More than 90% of those infected have detectable serum IgM 8 days after onset. The EIA can exhibit serologic cross-reactivity in patients who have been recently vaccinated against or recently infected with related flaviviruses (e.g., Japanese encephalitis, as well as yellow fever and dengue). In addition, since most WNV infections are asymptomatic and IgM can persist in the serum for up to 500 days, the presence of IgM in residents from an endemic area may indicate a previous rather than current infection.

The diagnosis can also be confirmed by demonstrating a four-fold rise in antibody titer between acute and convalescent (14-21 days after acute) serum specimens. Since serum IgM does not cross the blood-brain barrier, IgM in the CSF strongly suggests central nervous system infection.

The plaque-reduction neutralization test (PRNT) is the most specific test for the arthropod-borne flaviviruses and can be used to help distinguish false-positive results from the MAC-EIA or EIA test.

Reverse transcription polymerase chain reaction (RT-PCR) assay to detect WNV nucleic acid in serum or CSF is useful for evaluation of patients with immune dysfunction, but is not recommended for routine diagnosis of WNV disease.

Other antibody detecting diagnostic assays, such as hemagglutination inhibition and indirect fluorescent antibody tests, may be available at commercial laboratories.



B. Services Available at the Washington State Public Health Laboratories (PHL)

Microsphere immunoassay (MIA) for IgM antibody in serum or CSF is currently the only assay available at PHL. This assay is more rapid and specific than the enzyme immunoassay (EIA) test that is used by most commercial laboratories.

Note that PHL require all clinical specimens have two patient identifiers, a name **and** a second identifier (e.g., date of birth) both on the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

C. Criteria for Testing WNV Specimens at PHL*

All specimens need to be approved by Communicable Disease Epidemiology Section (CDES) prior to submission. In response to increased numbers of human cases in Washington State during 2009, the criteria for testing at PHL were revised as follows:

Initial testing should be performed at a commercial laboratory. PHL will retest positive specimens for each county until 5 positives (i.e., 5 cases) per county have been confirmed.

After the first 5 cases per county have been confirmed, PHL will test under the following circumstances:

1. Persons with commercial laboratory results that indicate only borderline levels of IgM. For instance, PHL would retest if the commercial reference range is >0.9 and

- the test result is 1.5. Note that different tests have different reference values. The exact values should be discussed with CDES on a case-by-case basis in the context of exposure and clinical symptoms.
2. Certain neuroinvasive cases, e.g. those with paralysis or young age.
 3. Fatal cases presumed to be WNV.
 4. Cases with unusual symptoms.
 5. Special cases such as:
 - Pregnant or breastfeeding women symptomatic with suspected WNV infection and their neonates or breastfeeding infants.
 - Recent blood, tissue, or organ donors or recipients suspected to have WNV infection.

Aside from the circumstances above, CDES will shift to accepting commercial results as evidence of WNV infection. (Note: When relying upon commercial results, review the type of laboratory test performed and results to determine if the requirements of the case classification defined in Section 3B are satisfied; consult with CDES as needed).

In cases where the laboratory evidence is inconclusive at PHL, specimens will be forwarded to CDC. Note that the turn-around time for results from CDC is typically 4-6 weeks.

D. Specimen Collection and Shipping

1. Submit ≥ 2 cc of CSF and/or ≥ 1 cc serum (separated serum, not whole blood or plasma).
 - a. Serum should ideally be obtained ≥ 8 days after onset of symptoms. A second serum specimen will be requested if the first is non-reactive or indeterminate and was obtained less than 8 days after onset of symptoms. Convalescent serum should be drawn 14-21 days after the acute specimen.
 - b. CSF should ideally be collected 3-8 days after onset. CSF obtained less than 3 days after onset of symptoms will be accepted, however, if non-reactive, the test does not rule out WNV infection and a serum specimen obtained 8 days after onset will be requested.
2. Specimens should be refrigerated and transported cold (on regular ice packs). Avoid repeated freeze-thaw cycles. If the specimen is already frozen, ship it frozen (on dry ice). Specimens should be submitted with a completed PHL Serology submission form (<http://www.doh.wa.gov/EHSPHL/PHL/Forms/SerVirHIV.pdf>).

5. ROUTINE CASE INVESTIGATIONS

Interview the case or others who may be able to provide pertinent information.

A. Evaluate the Diagnosis

Review the laboratory report, clinical description, and epidemiologic factors such as season and known West Nile virus (WNV) activity in the area. If laboratory testing is positive for immunoglobulin M (IgM) and was done at a laboratory other than Washington State Public Health Laboratories (PHL), Communicable Disease

Epidemiology Section (CDES) may request facilitating transport of that or another specimen to PHL for further testing.

B. Identify Potential Sources of Infection

Obtain a complete travel history and history of mosquito bites during the 15 day period prior to symptom onset. Ascertain whether the case received blood products, tissues or organs within 30 days of their WNV infection, and if so, contact CDES immediately and inform the blood or tissue bank of the potential source.

C. Identify Potentially Exposed Persons

Determine if the patient donated blood, tissues or organs, breastfed, or gave birth during the communicable period. If the patient donated blood, tissues or organs in the 30 days prior to onset, contact CDES immediately and inform the blood or tissue bank of the potential blood contamination. In cases of potential mother-to-infant transmission, notify CDES and monitor the infant for compatible signs and symptoms for 14 days after last possible exposure.

D. Environmental Evaluation

Notify local environmental health program and/or vector control of locally acquired cases. In outbreak settings, an investigation may assist in identifying and controlling factors favoring transmission.

6. CONTROLLING FURTHER SPREAD

A. Infection Control Recommendations / Case Management

1. Hospitalized patients should be treated with standard precautions.
2. Cases do not require isolation.
3. Infected persons should be advised not to donate blood, tissues or organs for at least a month following recovery.
4. Infected lactating women should discuss with their medical care provider the risks and benefits of breast-feeding.

If the patient received blood products, organs, or tissues in the 30 days prior to onset, contact Communicable Disease Epidemiology Section (CDES) immediately and inform the blood or tissue bank of the potential source.

B. Contact Management

No follow up is needed for household and other close contacts since West Nile virus (WNV) is not transmitted by close contact. In cases of potential mother-to-infant transmission, notify CDES and monitor the infant for compatible signs and symptoms for 14 days after last possible exposure. Additional testing may be requested to confirm the WNV transmission. If the patient donated blood products, organs or tissues in the 30 days prior to onset, contact CDES immediately and inform the blood or tissue bank of the potential exposure.

C. Management of Other Exposed Persons

People with recent mosquito bites in areas where WNV is circulating should report

symptoms of fever, headache, loss of appetite, rash, or stiff neck to their health care provider.

D. Environmental Measures

Environmental measures to reduce WNV transmission may include the elimination of mosquito breeding habitats and the use of chemical (i.e., pesticide) and biological controls. Consult with local environmental health or vector/mosquito control programs to determine appropriate intervention measures.

7. MANAGING SPECIAL SITUATIONS

A. Presumptive Viremic Donor (PVD)

1. Blood collection agencies routinely screen blood products for West Nile virus (WNV) using nucleic acid-amplification tests (NAT) during months when there is WNV activity.
2. Blood collection agencies report persons whose blood screens positive to Communicable Disease Epidemiology Section (CDES) which, in turn, reports the person to the local health jurisdiction. Local public health professionals should initiate an investigation using the WNV Case Report Form.
3. Persons whose blood donation screens positive for WNV, with either a) a single reactive NAT with a signal-to-cutoff value ≥ 17 or b) two reactive NATs using two different primers/methods, are considered presumptive viremic donors and no further testing is indicated.
4. If a person's blood donation screens positive for WNV using a less stringent method, the local health jurisdiction should assist in obtaining a serum sample drawn 8-14 days after the date of the donation to test for IgM. If IgM is detected and the person remains asymptomatic, the person is a PVD. If IgM is not detected, the NAT should be considered a false positive and the case should be closed.

Note: Clinical Syndrome and Case Classification: All PVDs should be entered into PHIMS, classified as "Suspect," and manually reported to CDES unless WNV illness is documented. If WNV illness develops after the PVD is first reported, please revisit PHIMS to reclassify the patient as a case (see Section 3D).

8. ROUTINE PREVENTION

A. Immunization Recommendations

Currently there is no human West Nile virus vaccine available.

B. Prevention Recommendations

1. Reduce exposure to mosquitoes.
 - Make sure windows and doors are "bug tight." Repair or replace screens.
 - Stay indoors at dawn and dusk, if possible, when mosquitoes are most active.
 - Wear a long sleeve shirt, long pants, and a hat when going into mosquito-infested areas, such as wetlands or woods.

- Use mosquito repellent when necessary. The most effective mosquito repellents contain the EPA approved active ingredients DEET (N, N-diethyl-m-toluamide), Picaridin, oil of lemon eucalyptus, or IR3535. Read and follow label instructions. Permethrin is another long-lasting repellent that is intended for application to clothing and gear, but not directly to skin. In general, the more active ingredient (higher concentration) a repellent contains, the longer time it protects against mosquito bites. Do not over use repellents. Take special care when using repellents on children.
 - Additional information regarding the use of mosquito repellents can be found on the CDC website at: <http://www.cdc.gov/ncidod/dvbid/westnile/RepellentUpdates.htm> and http://www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm
2. Reduce the number of mosquitoes in breeding sites outdoors by draining sources of standing water.
- Empty anything that holds standing water—old tires, buckets, plastic covers, and toys.
 - Change water in your birdbaths, fountains, wading pools, pet bowls, and animal troughs at least twice week.
 - Recycle unused containers that may collect water—bottles, cans, and buckets.
 - Make sure roof gutters drain properly and clean clogged gutters in the spring and fall.
 - Fix leaky outdoor faucets and sprinklers.

C. Prevention of Laboratory-Associated Infections

Laboratory-associated infections have been reported, attributed to both aerosol and parenteral inoculations. Biosafety Level 2 practices are recommended for testing human diagnostic specimens. Biosafety Level 3 practices are recommended for WNV cultures and PRNT.

ACKNOWLEDGEMENTS

This document is a revision of the Washington State Guidelines for Notifiable Condition Reporting and Surveillance published in 2002 which were originally based on the Control of Communicable Diseases Manual (CCDM), 17th Edition; James Chin, Ed. APHA 2000. We would like to acknowledge the Oregon Department of Human Services for developing the format and select content of this document.

UPDATES

March 2008: In Section 1C, the guideline for timeliness of initiating an investigation was removed.

July 2008: In Section 1C, the CDC WNV Enhanced surveillance form was added. In Section 4A, additional information was added regarding laboratory tests. In Section 8B, IR3535 was added as an EPA approved effective mosquito repellent.

June 2009: In Section 2B, case-fatality rates and new terminology for clinical syndromes were updated. In Section 3C, case classification for presumptive viremic donors was updated. In Section 4B, the change in laboratory tests available at PHL were noted. In section 4D, information about the timing of specimen collection was clarified. In Section 8C, prevention of lab-associated infections was moved from Section 4.

August 2009: In section 1C, request to complete a separate CDC enhanced surveillance form was removed.

May 2010: Case definitions (Section 3) and criteria for testing at PHL (Section 4C) were updated.

January 2011: The Legal Reporting Requirements section has been revised to reflect the 2011 Notifiable Conditions Rule revision. Section 3 was nearly completely replaced to reflect the 2011 CSTE case definition and required laboratory evidence changes. Changes to the type of testing available at WA PHL were made in Section 4B.