WEST NILE VIRUS

Disease Overview

West Nile virus is caused by a flavivirus and is found worldwide, including Canada. The virus is spread by the bites of infected mosquitoes and can cause illness in people, birds, horses and other animals.

Symptoms

Most infections are asymptomatic. Symptomatic infections include fever and mild flu-like illness including headache, body aches, mild rash or swollen lymph glands. The elderly, the young, and those with weak immune systems, are at greater risk for more serious illness including meningitis, encephalitis, or acute flaccid paralysis.

Reservoir

The reservoir is a cycle between mosquitoes and amplifying vertebrate hosts, particularly bird species.

Mode of Transmission

Spread by the bite of an infected mosquito, usually *Culex* species.

In a very small number of cases, West Nile virus also has been spread through blood transfusions, organ transplants, and during pregnancy.

Incubation Period

Usually 2-6 days; range 2 -14 days.

Period of Communicability

No evidence of person to person transmission.

Risk Factors

Increased risk of acquiring/and or severe illness:

- Travel to endemic areas and exposure to infected vectors.
- Risk of severe illness increases with age, chronic renal disease, immune suppression, alcoholism, diabetes, and hypertension.

Surveillance Case Definition

West Nile virus neuroinvasive disease (West Nile virus neurological syndrome)

Confirmed case

Clinical criteria for West Nile virus neuroinvasive disease (West Nile virus neurological syndrome) **and** at least one of the confirmed case diagnostic test criteria:

- a significant (i.e., fourfold or greater) change in West Nile virus (WNV) neutralizing antibody titres (i.e., plaque reduction neutralization tests (PRNT)) in paired acute and convalescent sera, or cerebrospinal fluid (CSF) sample, **or**
- isolation of WNV from, or demonstration of WNV antigen in tissue or WNV-specific genomic sequences in tissue, blood, CSF or other body fluids, **or**
- demonstration of WNV antibodies in a single serum using a WNV immunoglobulin M (IgM) enzyme-linked immunoassay (ELISA), confirmed by the detection of WNV neutralizing antibodies using a PRNT (acute or convalescent serum), **or**
- demonstration of WNV antibodies in a CSF sample using a WNV IgM ELISA, confirmed by the detection of WNV neutralizing antibodies using a PRNT (CSF or acute or convalescent serum).

See **Clinical Criteria for West Nile virus neuroinvasive disease (West Nile virus neurological syndrome)**

See **Laboratory Comments** for confirmatory PRNT for endemic areas in season and low/non-endemic areas, or out of season; and cross-reactivity among flaviviruses.

Probable case

Clinical criteria for West Nile virus neuroinvasive disease (West Nile virus neurological syndrome) **and** at least one of the probable case diagnostic test criteria:

- detection of flavivirus antibodies in a single serum or CSF sample using a WNV IgM ELISA without confirmatory neutralization serology (i.e., PRNT), **or**
- a significant (i.e., fourfold or greater) change in flavivirus antibodies in paired acute and convalescent sera or demonstration of a seroconversion using a WNV immunoglobulin G (IgG) ELISA without confirmatory neutralization serology (i.e., PRNT).

See **Clinical Criteria for West Nile virus neuroinvasive disease (West Nile virus neurological syndrome)**

See **Laboratory Comments** for confirmatory PRNT for endemic areas in season and low/non-endemic areas, or out of season; and cross-reactivity among flaviviruses.

Suspect case

Clinical criteria for West Nile virus neuroinvasive disease (West Nile virus neurological syndrome) in the absence of diagnostic test criteria or pending diagnostic test criteria **and** in the absence of any other obvious cause.

See **Clinical Criteria for West Nile virus neuroinvasive disease (West Nile virus neurological syndrome)**

See **Laboratory Comments**.

Clinical Criteria for West Nile virus neuroinvasive disease (West Nile virus neurological syndrome)

History of exposure when and where WNV transmission is present historically, or could be present, or history of travel to an area with confirmed WNV activity in birds, horses, other mammals, mosquitoes, or humans

or

History of exposure to an alternate mode of transmission (laboratory-acquired, in utero, receipt of blood components, organ/tissue transplant, and possibly via breast milk)

and

Onset of fever

and

recent onset of **at least one** of the following:

- encephalitis
- viral meningitis
- acute flaccid paralysis
- other neurological syndromes

See **Clinical Comments**

West Nile virus non-neuroinvasive disease (West Nile virus non-neurological syndrome)

Confirmed case

Clinical criteria for West Nile virus non-neuroinvasive disease (West Nile virus non-neurological syndrome) **and** at least one of the confirmed case diagnostic test criteria:

- a significant (i.e., fourfold or greater) change in WNV neutralizing antibody titres (i.e., PRNT) in paired acute and convalescent sera, **or**
- isolation of WNV from, or demonstration of WNV antigen in tissue or WNV-specific genomic sequences in tissue, blood, or other relevant body fluids, **or**
- demonstration of WNV antibodies in a single serum using a WNV IgM ELISA, confirmed by the detection of WNV neutralizing antibodies using a PRNT (acute or convalescent serum).

See **Clinical Criteria for West Nile virus non-neuroinvasive disease (West Nile virus non-neurological syndrome)**

See Laboratory Comments for confirmatory PRNT for endemic areas in season and low/non-endemic areas, or out of season; and cross-reactivity among flaviviruses.

Probable case

Clinical criteria for West Nile virus non-neuroinvasive disease (West Nile virus non-neurological syndrome) **and** at least one of the probable case diagnostic test criteria:

- detection of flavivirus antibodies in a single serum using a WNV IgM ELISA without confirmatory neutralization serology (i.e., PRNT) **or**
- a significant (i.e., fourfold or greater) change in flavivirus antibodies in paired acute and convalescent sera or demonstration of a seroconversion using a WNV IgG ELISA without confirmatory neutralization serology (i.e., PRNT)

See **Clinical Criteria for West Nile virus non-neuroinvasive disease (West Nile virus non-neurological syndrome)**

See Laboratory Comments for confirmatory PRNT for endemic areas in season and low/non-endemic areas, or out of season; and cross-reactivity among flaviviruses.

Suspect case

Clinical criteria for West Nile virus non-neuroinvasive disease (West Nile virus non-neurological syndrome)) in the absence of or pending diagnostic test criteria **and** in the absence of any other obvious cause

See **Clinical Criteria for West Nile virus neuroinvasive disease (West Nile virus neurological syndrome**)

See **Laboratory Comments**.

Clinical criteria for West Nile virus non-neuroinvasive disease (West Nile virus non-neurological syndrome)

History of exposure when and where WNV transmission is present historically, or could be present, or history of travel to an area with confirmed WNV activity in birds, horses, other mammals, mosquitoes, or humans.

or

History of exposure to an alternate mode of transmission (e.g., laboratory-acquired, in utero, receipt of blood components, organ/tissue transplant, and possibly via breast milk)

and

at least two of the following:

- fever
- myalgia
- anthralgia
- headache
- fatigue
- rash (maculopapular or morbilliform)
- gastrointestinal manifestations (e.g., vomiting, nausea, diarrhea, abdominal pain)
- other (e.g., eye pain, chills, back pain)

See **Clinical Comments**.

West Nile virus asymptomatic infection

Asymptomatic testing should be limited to blood and organ donors as part of blood and organ donor screening programs.

Confirmed case

At least one of the following confirmed case diagnostic test criteria in the absence of clinical criteria:

- a significant (i.e., fourfold or greater) change in WNV neutralizing antibody titres (i.e., PRNT) in paired sera, **or**
- isolation of WNV from, or demonstration of WNV antigen in tissue or WNV-specific genomic sequences in tissue, blood or other relevant body fluids, **or**
- demonstration of WNV antibodies in a single serum using a WNV IgM ELISA, confirmed by the detection of WNV neutralizing antibodies using a PRNT (acute or convalescent serum), **or**
- demonstration of Japanese encephalitis serocomplex-specific genomic sequences in blood by nucleic acid amplification test (NAAT) confirmed by WNV-specific NAAT or sequencing, or demonstration of WNV-specific genomic sequences in blood by NAAT by blood operators (e.g., Canadian Blood Services or Héma-Québec) in Canada.

Probable case

At least one of the following probable case diagnostic criteria in the absence of clinical criteria:

- a significant (i.e., fourfold or greater) change in flavivirus antibodies in paired sera or demonstration of a seroconversion using a WNV IgG ELISA without confirmatory neutralization serology (i.e., PRNT)
- demonstration of Japanese encephalitis serocomplex-specific genomic sequences in blood by NAAT by blood operators in Canada when WNV-specific NAAT was not performed

Suspect case

The following suspect case diagnostic criteria in the absence of clinical criteria:

- detection of flavivirus antibodies in a single serum using a WNV IgM ELISA pending further investigation

See **Laboratory Comments**.

Clinical Comments

The clinical information presented below is not intended to describe the complete range of signs and symptoms that may be used in a clinical diagnosis of WNV disease.

West Nile virus neuroinvasive disease occurs in less than 1% of cases.

- **Encephalitis** commonly manifests as extrapyramidal disorders.
    - Common movement disorder manifestations include: coarse tremor (particularly in upper extremities), myoclonus (in upper extremities and facial muscles), features of Parkinsonism and cerebellar ataxia.
- **Meningitis** associated with WNV has clinical manifestations that are similar to other viral meningitides.

    - "Aseptic" meningitis without encephalitis or acute flaccid paralysis occurring in summer and fall when WNV is circulating may be due to non-polio enteroviruses circulating at the same time. This should be considered in the differential diagnosis.
- **Acute flaccid paralysis** typically manifests as rapid-onset, marked muscle weakness that is more frequently asymmetric, usually affecting one or more limbs.
    - The majority of cases of acute flaccid paralysis occur in conjunction with encephalitis or meningitis.
    - The most common form of acute flaccid paralysis is poliomyelitis-like syndrome
    - Other forms of acute flaccid paralysis associated with WNV include radiculopathy and Guillain-Barré syndrome.
    - Electromyography, lumbar puncture and nerve conduction studies should be performed to differentiate between poliomyelitis and other forms of acute flaccid paralysis.
    - WNV should be considered in the differential diagnosis of all suspected cases of acute flaccid paralysis with or without sensory deficit.
    - Respiratory muscle innervation may be involved and lead to respiratory failure.

West Nile virus non-neuroinvasive disease occurs in about 20 to 25% of cases.

- Also commonly referred to as "West Nile fever," although fever is not universally present among those with West Nile non-neuroinvasive disease.
- Younger individuals are more likely to present with WNV non-neuroinvasive disease than WNV neuroinvasive disease.

West Nile virus asymptomatic infection occurs in about 70 to 80% of cases.

Other manifestations described in association with WNV infection include:

- Ocular manifestations:
    - Frequently reported sequelae of WNV infection following neuroinvasive disease
    - Chorioretinitis is the most common manifestation, with lesions that are described as "multifocal" and "target-like," located primarily in the temporal and nasal regions of the periphery of the fundus. The distribution and appearance of these lesions are thought to be distinctive of WNV infection.
    - Other ocular manifestations include: vitritis, choroiditis, retinal haemorrhages, occlusive vasculitis, uveitis.
- Less commonly described clinical manifestations and complications associated with West Nile virus infection include: rhabdomyolysis, hepatitis, pancreatitis, myocarditis, cardiac arrhythmias.

Laboratory Comments

- Confirmatory plaque reduction neutralization test (PRNT) for:

- **Endemic areas in season**: It is currently recommended that health jurisdictions/authorities use the Confirmed Case Diagnostic Test Criteria (i.e., PRNT on serum or immunoglobulin M (IgM) detection in cerebrospinal fluid (CSF)) to confirm the first few index cases (locally acquired) in an endemic area during the WNV transmission season each year; for subsequent cases, health jurisdictions/authorities in endemic areas could use the Probable Case Diagnostic Test Criteria to classify cases in their area as "confirmed", **for the purposes of surveillance**.

  It is recommended that a follow-up serum sample be submitted in addition to the initial CSF sample so a PRNT may be done on the serum.

- **Low or non-endemic areas, or out of season**: For cases where the epidemiology does not support the IgM result in CSF, such as in low endemic areas or results received outside the WNV transmission season, confirmatory antibody testing should be performed on serum, with acute or convalescent PRNT.

  It is recommended that a follow-up **serum sample** be submitted in addition to a CSF sample so a PRNT may be done on the serum.

- Due to high **serological cross reactivity** among flaviviruses, travel and vaccination history should be obtained to determine if other flaviviruses should be tested for (e.g., Dengue virus, St. Louis encephalitis and Japanese encephalitis). False-positive WNV serologic tests may occur because antibodies to other arthropod-borne flaviviruses cross-react with WNV virus. A false-positive result can be due to recent immunization with flavivirus vaccines (namely, yellow fever or Japanese encephalitis) or due to infections with other related flaviviruses (e.g., St. Louis encephalitis, dengue, or Zika). In this situation, a PRNT should only be performed to help confirm the diagnosis if there is concern that the positive serological test results are due to cross-reactivity from a different flavivirus infection (e.g., dengue, yellow fever, St. Louis encephalitis, Zika, Japanese encephalitis viruses) or after recent vaccination for Japanese encephalitis.

- Throughout the remainder of the transmission season, health jurisdictions/authorities may wish to document PRNT antibody titres to WNV a proportion of cases, to be determined by that health jurisdiction/authority, in order to rule out the possibility of **concurrent activity by other flaviviruses**.
- If a CSF sample appears to contain blood, non-specific reactivity may be observed; therefore, it is recommended that the IgM result be interpreted with caution.
- Demonstration of WNV IgM antibodies in a single serum sample with no clinical history should not be used as a diagnostic approach. **WNV IgM antibodies may persist for more than a year**, and the demonstration of IgM antibodies in a patient's serum, particularly in residents of areas with a history of exposure may not be diagnostic of an acute WNV infection. IgM antibodies usually remain detectable in serum for at least one to two months following clinical resolution, but may persist for 12 months or more. Thus, patients from endemic areas may have detectable IgM antibody from a previous WNV infection that is unrelated to their current clinical illness.

- **Seroconversion** demonstrates a current WNV infection. IgM seroconversion usually develops between 4 and 10 days after infection. Therefore, the collection of acute and convalescent sera for serologic analysis is particularly important to rule out diagnostic misinterpretation and to identify initial cases in a specific jurisdiction. However, it should be noted that seroconversions may not always be documented because of the timing of acute sample collection (i.e., titres in acute sera may have already peaked). If static titres are observed in acute and convalescent paired sera, it is still possible the case may represent a recent infection.
- **Immunocompromised individuals** may not be able to mount an immune response necessary for a serologic diagnosis. For immunocompromised patients, viremia may be prolonged and antibody development may be delayed or absent. Viral detection methods may be helpful for confirming diagnosis. West Nile virus diagnostic test criteria for these individuals should be discussed with a medical microbiologist.
- For asymptomatic blood donors, blood is screened using a nucleic acid amplification test (NAAT) by blood operators and is subsequently brought to the attention of public health officials. Blood operators may use a WNV-specific NAAT or a NAAT designed to detect viruses in the Japanese encephalitis serocomplex, including West Nile virus. Supplementary tests (WNV-specific NAAT) following a positive screening from blood donor screening may be performed by provincial/territorial lab or National Microbiology Laboratory.

Diagnosis and Laboratory Guidelines

Antibodies directed towards members of the flavivirus genus (dengue, West Nile virus, yellow fever) can cross react significantly in some serological assays.

Serological detection of IgG and/or IgM antibodies by ELISA testing is available at regional laboratories.

Due to the cross-reactive nature of flavivirus antibody, the detection of flavivirus IgG in a single sera indicates a past or present exposure to this agent or a related agent from the same virus genus. The presence of flavivirus specific IgM in a single serum sample is consistent with an acute infection to this agent or a related flavivirus. A 4 fold rise or greater in neutralizing antibody titre, or an IgG or IgM seroconversion in paired sera, is required to document a "confirmed case" of infection with associated illness. There is increasing evidence for IgM persistence in blood/serum for up to a year or more after arbovirus exposure. Thus, detection of IgM by itself may not always be a confirmation of acute infection.

The National Microbiology Laboratory does ELISA and hemagllutination inhibition tests (HAI) (turnaround time is 14 days). Confirmatory testing is done at the National Microbiology Laboratory. Samples that are reactive (HAI or ELISA) are then tested for the presence of neutralizing antibodies by the Plaque Reduction Neutralization Test (PRNT). The PRNT is a more specific assay and can be used to document the presence of serum antibodies specific for a particular flavivirus. Note: if the patient has experienced more than one flavivirus infection, cross-reactive results could in fact yield uninterpretable results with this assay despite increased specificity. PRNT is not a routine test and turnaround time is 14 calendar days after the completion screening testing (IFA or ELISA).

Reporting

Per Policy 2.2 Disease and Event Notification to OCMOH and Disease and Event Reporting section.

- Enhanced surveillance. For all confirmed and probable cases an enhanced surveillance form should be completed and information sent to OCMOH within 5 days of completing interview.
- Routine Surveillance (RDSS) for all confirmed cases.

For laboratory confirmed cases who have a history of donation or transfusion (blood/blood products), a *Disclosure of Information to Canadian Blood Services Transfusion Transmissible Infections (TTI)* form must be completed and sent to the CD Specialist at Canadian Blood Services at Confidential Fax: 1-844-836-6843 upon receipt of information.

Case Management

Education

Case or relevant caregiver should be informed about:

- Nature of infection, length of communicable period, mode of transmission and disease ecology
- Mosquito Bite Prevention

Investigation

Obtain symptom history and onset, travel and immigration history and mosquito exposure. Determine patient's history for donation or receiving blood (or plasma or blood component) in the 8 weeks prior to test date.

Exclusion/Social Distancing

Not applicable

Treatment

Not applicable

Immunization

Not applicable

Contact Management

Per case management

Outbreak Management

Activate local outbreak management plan.