Ministry of Health

Ontario Public Health Standards:
Requirements for Programs, Services and Accountability

Infectious Disease Protocol

Appendix 1: Case Definitions and Disease-Specific Information

Disease: West Nile Virus Illness

Effective: May 2022

Ontario

West Nile Virus Illness

☐ Communicable

☐ Virulent

Health Protection and Promotion Act (HPPA)

Ontario Regulation (O. Reg.) 135/18 (Designation of Diseases)

Provincial Reporting Requirements

☒ Confirmed case

☒ Probable case

As per Requirement #3 of the "Reporting of Infectious Diseases" section of the *Infectious Diseases Protocol, 2018* (or as current), the minimum data elements to be reported for each case are specified in the following:

- O. Reg. 569 (Reports) under the HPPA;[6]
- The iPHIS User Guides published by Public Health Ontario (PHO); and
- Bulletins and directives issued by PHO.

Type of Surveillance

Case-by-case.

Case Definition

Confirmed West Nile virus Neurological Syndrome (WNNS) Case

Clinical criteria AND AT LEAST ONE of the confirmed case diagnostic test criteria in the Laboratory Confirmation section below.

Probable WNNS Case

Clinical criteria AND AT LEAST ONE of the probable case diagnostic test criteria in the Laboratory Confirmation section below.

Confirmed West Nile Non-Neurological Syndrome (WN Non-NS) Case

Clinical criteria AND AT LEAST ONE of the confirmed case diagnostic test criteria in the Laboratory Confirmation section below.

Probable WN Non-NS Case

Clinical criteria AND AT LEAST ONE of the probable case diagnostic test criteria in the Laboratory Confirmation section below.

Confirmed West Nile virus Asymptomatic Infection (WNAI) Case (See Comments Section #1)

Confirmed case diagnostic test criteria in the Laboratory Confirmation section below, IN THE ABSENCE of clinical criteria.

Probable WNAI Case

Probable case diagnostic test criteria in the Laboratory Confirmation section below, IN THE ABSENCE of clinical criteria.

Outbreak Case Definition

The outbreak case definition varies with the outbreak under investigation. Please refer to the *Infectious Diseases Protocol, 2018* (or as current) for guidance in developing an outbreak case definition as needed.

The outbreak case definitions are established to reflect the disease and circumstances of the outbreak under investigation. The outbreak case definitions should be developed for each individual outbreak based on its characteristics, reviewed during the course of the outbreak, and modified, if necessary, to ensure that the majority of cases are captured by the definition. The case definitions should

be created in consideration of the outbreak definitions.

Outbreak cases may be classified by levels of probability (i.e., confirmed and/or probable).

Clinical Information

Clinical Evidence

West Nile virus Neurological Syndrome (WNNS) Clinical Criteria:

- History of exposure in an area where WNV activity is occurring (See Comments Section#5),

OR

- History of exposure to an alternative mode of transmission (See Comments Section #6);

AND

- Fever;

AND NEW ONSET OF AT LEAST ONE of the following:

- Encephalitis (acute signs of central or peripheral neurologic dysfunction),

OR

- Viral meningitis (pleocytosis and signs of infection e.g., headache, nuchal rigidity),

OR

- Acute flaccid paralysis (e.g., poliomyelitis-like syndrome or Guillain-Barré-like syndrome) (See Comments Section #7).

OR

- Movement disorders (e.g., tremor, myoclonus),

OR

- Parkinsonism or Parkinsonia-like conditions (e.g., cogwheel rigidity,

bradykinesia, postural instability),

OR

- Other neurological syndromes (See Comments Section #8).

West Nile virus Non-Neurological Syndrome (WN Non-NS) Clinical Criteria:

- History of exposure in an area where WNV activity is occurring (See Comments Section #5),

OR

- History of exposure to an alternative mode of transmission;

AND AT LEAST TWO of the following (See Comments Section #8):

- Fever,
- Myalgia (See Comments Section #9),
- Arthralgia,
- Headache,
- Fatigue,
- Lymphadenopathy, and/or,
- Maculopapular rash.

Clinical Presentation

There are three clinical manifestations of WNV; asymptomatic, non-neurological, and neurological. The majority of WNV cases are asymptomatic. About 20% of infected persons develop the usually less severe symptom complex known as WNV fever (non-neurological syndrome). This presents with a mild flu-like illness with fever, headache, and body aches, occasionally with a skin rash and swollen lymph nodes or other non-specific symptoms that last several days. Other symptoms may include nausea, vomiting, diarrhea, eye pain or photophobia.[2,3]

WNV neurological symptoms can present as meningitis, encephalitis as well as conditions similar to acute flaccid paralysis, and Parkinson's disease.[1,4] Less than 1%

of infected people will develop neurological symptoms.[1]

Laboratory Evidence

Laboratory Confirmation

Any of the following will constitute a confirmed case of West Nile virus (WNV):

- Positive WNV culture,
- Positive for WNV antigen in tissue,
- Positive for WNV-specific nucleic acid,
- Positive for WNV-specific antibody, or,
- Diagnostic rise in WNV antibody titre.

Confirmed Case Diagnostic Test Criteria

Confirmed Case Diagnostic Test Criteria (e.g., by Plaque Reduction Neutralization Test [PRNT] on serum or immunoglobulin M [IgM] detection in cerebrospinal fluid [CSF]) should be used to confirm the initial three locally acquired cases within each health region each year. For subsequent cases within that health region, boards of health may use the Probable Case Diagnostic Test Criteria to classify cases in their area as "Confirmed".

AT LEAST ONE of the following:

- A significant (i.e., fourfold or greater) rise in WNV neutralizing antibody titres (using a PRNT or other kind of neutralization assay) in paired acute and convalescent sera, or CSF (See Comments Section #2),

OR

- Isolation of WNV from, or demonstration of WNV antigen or WNV- specific genomic sequences using an assay verified for clinical testing in tissue, blood, CSF or other body fluids,

OR

- Demonstration of flavivirus antibodies in a single serum sample using a WNV

IgM enzyme-linked immuno-sorbent assay (ELISA), confirmed by the detection of WNV specific antibodies using a PRNT (acute or convalescent serum sample) (See Comments Section #3 and #4),

OR

- Demonstration of WNV antibodies in a single CSF sample using a WNV IgM ELISA (See Comments Section #2, #3 and #4),

OR

- A significant (i.e., fourfold or greater) rise in flavivirus hemagglutination inhibition (HI) titres in paired acute and convalescent sera or demonstration of a seroconversion using a WNV Immunoglobulin G (IgG) ELISA (See Comments Section #3 and #4) AND the detection of WN specific antibodies using a PRNT (acute or convalescent serum sample).

Probable Case Diagnostic Test Criteria

AT LEAST ONE of the following:

- Detection of flavivirus antibodies in a single serum sample using a WNV IgM ELISA without confirmatory neutralization serology (e.g., PRNT) (See Comments Section #3),

OR

- A significant (i.e., fourfold or greater) rise in flavivirus HI titres in paired acute and convalescent sera or demonstration of a seroconversion using a WNV IgG ELISA (See Comments Section #3),

OR

- A titre of > 1:320 in a single WNV HI test, or an elevated titre in a WNV IgG ELISA, with a confirmatory PRNT result.

OR

- Demonstration of Japanese encephalitis (JE) serocomplex-specific genomic sequences in blood by nucleic acid amplification test (NAAT) screening on donor blood, by Blood Operators in Canada.

Approved/Validated Tests

- Standard culture for WNV
- NAAT for WNV verified for clinical testing (See Comments Section #1)
- WNV antigen detection in tissue
- WNV IgM antibody detection
- WNV HI, PRNT and/or IgG/IgM immunoassays

Indications and Limitations

- Sensitivity of NAAT testing is approximately 50% when used on plasma/serum samples collected less than 8 days after symptom onset.

For further information about human diagnostic testing, contact the Public Health Ontario Laboratories.

Case Management

In addition to the requirements set out in the Requirement #2 of the "Management of Infectious Diseases – Sporadic Cases" and "Investigation and Management of Infectious Diseases Outbreaks" sections of the *Infectious Diseases Protocol, 2018* (or as current), the board of health shall investigate cases to determine the source of infection. Refer to Provincial Reporting Requirements above for relevant data to be collected during case investigation.

As per the *Infectious Diseases Protocol, 2018* (or as current), notify Trillium Gift-of-Life of any positive human WNV results with organ donation histories.

Contact Management

Not applicable.

Outbreak Management

Please see the *Infectious Diseases Protocol, 2018* (or as current) as well as the ministry's West Nile Virus Preparedness and Prevention Plan (2018,or as current) for the public health management of outbreaks or clusters in order to identify the source of illness, manage the outbreak and limit secondary spread.[7]

Prevention and Control Measures

Personal Prevention Measures

Provide public education regarding:

- The use of insect repellent when outdoors. Consider using federally registered personal insect repellents on exposed skin, such as those containing DEET or other approved repellants. Follow the manufacturer's label for directions on use.
- Wearing long sleeve shirts, long pants, and light coloured clothes.
- Cleaning up mosquito-friendly areas around your home regularly such as standing water.

For more information on prevention measures refer to the West Nile Virus Preparedness and Prevention Plan (2018, or as current) from the Ministry of Health (ministry).[7]

Infection Prevention and Control Strategies

The board of health shall develop and utilize a local vector-borne management strategy in order to mitigate risk. This strategy shall include measures such as:

- Local risk assessments;
- Public education; and
- Source reduction when and where applicable.

For healthcare settings, implementing routine practices is sufficient.

For more information on vector-borne management strategies refer to O. Reg. 199 *(Control of West Nile Virus)* under the HPPA and the West Nile Virus Preparedness and Prevention Plan (2018, or as current).[7,8]

Refer to PHO's website to search for the most up-to-date information on Infection Prevention and Control (IPAC).

Disease Characteristics

Aetiologic Agent - West Nile Virus (WNV) is a ribonucleic acid (RNA) virus of the genus Flavivirus.[1]

Modes of Transmission - WNV is transmitted to humans primarily through bites of infected *Culex* mosquitoes.[1] In Ontario, the main vectors of concern are *Culex pipiens* and *Culex restuans*.[5]

Person-to-person WNV transmission can occur through blood transfusion and solid organ transplantation. Intrauterine transmission and probable transmission via human milk also have been described but appear to be uncommon.[1,2]

Incubation Period – Usually 2-6 days but ranges from 2-14 days and can be as long as 21 in immunocompromised people.[1,2]

Period of Communicability - Viraemia in humans usually last fewer than 7 days in immunocompetent persons.[2]

Reservoir - Birds are the main reservoir of WNV in North America. WNV is transmitted in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily birds. Birds infect feeding vector mosquitoes that then transmit the virus to humans and other mammals during subsequent feedings. The concentrations of the virus in human blood is generally too low to infect mosquitoes, making humans incidental or "dead-end" hosts.[2]

Host Susceptibility and Resistance - Risk of WNV infection is generally determined by exposure to infected vectors and is dependent on many factors including environmental conditions, season and human activities. Once infected, older age, chronic renal disease, immune suppression, history of alcohol abuse, diabetes and hypertension have been associated with higher risk of severe disease.[2]

Please refer to PHO's Reportable Disease Trends in Ontario reporting tool for the most up-to-date information on infectious disease trends in Ontario.

For additional national and international epidemiological information, please refer to the Public Health Agency of Canada and the World Health Organization.

Comments

#1

This category includes asymptomatic blood donors whose blood is screened using a NAAT, by Blood Operators (i.e., Canadian Blood Services or Hema-Quebec) and is subsequently brought to the attention of public health officials. The NAAT that is currently used by Blood Operators in Canada is designed to detect all viruses in the Japanese encephalitis (JE) serocomplex. The JE serocomplex includes WN virus and nine other viruses, although from this group only WNV and St. Louis encephalitis virus are currently endemic to parts of North America. The NAAT test used by Blood Operators is not approved for clinical diagnostic testing but can be used for surveillance case classifications and would result in a classification of a probable case.

#2

Whenever submitting a CSF for testing, a serum sample should be submitted for parallel testing. Although PRNT can be performed on CSF, this testing is usually not required, as the presence of IgM in CSF, which has excellent specificity in the acute setting, is sufficient for case confirmation.

#3

Both CDC and commercial IgM/IgG ELISAs are now available for front line serological testing. Refer to appropriate assay procedures and kit inserts for the interpretation of test results. Due to high serological cross reactivity among flaviviruses, travel history should be obtained to determine if other flaviviruses should be tested for (e.g., Dengue virus, St. Louis encephalitis and Japanese encephalitis).

#4

Early in infection, the immune system generates antibodies that bind relatively weakly to viral antigen (low avidity). As the infection proceeds, an increasing percentage of newly generated IgG antibody displays higher binding affinity to virus antigen and thus avidity also rises (Note: avidity is usually measured based upon the ability of IgG to dissociate from antigen preparations after incubation with a solution of urea). As long as high avidity IgG is not yet detected in the serum it can be assumed that the individual was exposed to the viral agent during a recent exposure. With respect to WNV infection it has not been precisely determined when (i.e., post-exposure) high avidity antibodies reach levels in serum that can be accurately detected by serological assays (there may be significant variation depending on the individual). However, it has been shown that > 95% of sera collected from individuals exposed to WNV 6-8 months previously will have IgG antibodies that bind strongly to viral antigen and will give high avidity scores using both indirect fluorescent antibody (IFA) and ELISA testing formats. **Note:** Avidity testing will not replace confirmatory neutralization testing, non-WNV flavivirus IgG antibody (e.g., Dengue, St. Louis encephalitis) may bind to the antigen preparations used in avidity assays.

Note: WNV IgM antibody may persist for more than a year and the demonstration of IgM antibodies in a patient's serum, particularly in residents of endemic areas, may not be diagnostic of an acute WN viral infection. Seroconversion (by hemagglutination inhibition [HI], IgG ELISA or PRNT assays) demonstrates a current WNV infection. Therefore, the collection of acute and convalescent sera for serologic analysis is particularly important to rule out diagnostic misinterpretation early in the WNV season (e.g., May, June) and to identify initial cases in a specific jurisdiction. However, it should be noted that seroconversions may not always be documented due to 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. To help resolve this, the use of IgG avidity testing may be considered to distinguish between current and past infection. The presence of both IgM antibody and low avidity IgG in a patient's convalescent serum sample are consistent with current cases of viral

associated illness. However, test results that show the presence of IgM and high avidity IgG are indicative of exposures that have occurred in a previous season. Immunocompromised individuals may not be able to mount an immune response necessary for a serological diagnosis. WNV diagnostic test criteria for these individuals should be discussed with a medical microbiologist.

#5

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

#6

Alternative modes of transmission, identified to date, include: laboratory-acquired; in utero; receipt of blood components; organ/tissue transplant; and, possibly via breast milk.

#7

A person with WNV-associated acute flaccid paralysis may present with or without fever or mental status changes. Altered mental status could range from confusion to coma with or without additional signs of brain dysfunction (e.g., paralysis, cranial nerve palsies, sensory deficits, abnormal reflexes, generalized convulsions and abnormal movements). Acute flaccid paralysis with respiratory failure is also a problem.

Note: A significant feature of WNV neurological illness may be marked muscle weakness that is more frequently unilateral but could be bilateral. WNV should be considered in the differential diagnosis of all suspected cases of acute flaccid paralysis with or without sensory deficit. WNV- associated weakness typically affects one or more limbs (sometimes affecting one limb only). Muscle weakness may be the sole presenting feature of WNV illness (in the absence of other neurologic features) or may develop in the setting of fever, altered reflexes, meningitis or encephalitis. Weakness typically develops early in the course of clinical infection. Patients should be carefully monitored for evolving weakness and in particular for acute neuromuscular respiratory failure, which is a severe

manifestation associated with high morbidity and mortality. For the purpose of WNV Neurological Syndrome Classification, muscle weakness is characterized by severe (polio-like), non-transient and prolonged symptoms. Electromyography (EMG) and lumbar puncture should be performed to differentiate WNV paralysis from the acute demyelinating polyneuropathy (Guillain-Barré syndrome). Lymphocytic pleocytosis (an increase in WBC with a predominance of lymphocytes in the CSF) is commonly seen in acute flaccid paralysis due to WNV.

Other emerging clinical syndromes, identified in 2002 included, but were not limited to the following: myelopathy, rhabdomyolysis (acute destruction of skeletal muscle cells), peripheral neuropathy; polyradiculoneuropathy; optic neuritis; and acute demyelinating encephalomyelitis. Ophthalmologic conditions including chorioretinitis and vitritis were also reported. Facial weakness was also reported. Myocarditis, pancreatitis and fulminant hepatitis have not been identified in North America but were reported in outbreaks of WNV in South Africa. "Aseptic" meningitis without encephalitis or flaccid paralysis occurring in August and September when WNV is circulating may be due to non-polio enteroviruses circulating at the same time. This should be considered in the differential diagnosis.

#8

It is possible that other clinical signs and symptoms could be identified that have not been listed and may accompany probable case or confirmed case diagnostic test criteria. For example, gastrointestinal (GI) symptoms were seen in many WNV patients in Canada and the USA in 2003 and 2004.

#9

Muscle weakness may be a presenting feature of WNV illness. For the purpose of WNV Non-Neurological Syndrome classification, muscle weakness or myalgia (muscle aches and pains) is characterized by mild, transient, unlikely prolonged symptoms that are not caused by motor neuropathy.

References

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Case Definition Sources

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Document History

Revision Date	Document Section	Description of Revisions
April 2022	Entire Document	New template. Appendix A and B merged. No material content changes.
April 2022	Epidemiology: Occurrence section	Removed.
April 2022	ICD Codes	Removed.