

# West Nile virus

## *Update for family physicians*

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### ABSTRACT

**OBJECTIVE** To review the epidemiology and disease manifestations of West Nile virus (WNV) in North America and to describe the current status of therapeutic approaches and vaccines for treating or preventing viral illness.

**QUALITY OF EVIDENCE** Since 1999, research initiatives investigating the ecology, epidemiology, and biology of WNV have increased substantially. These studies provide a foundation for understanding current activity and predicting future activity and for describing the effect of WNV on human health.

**MAIN MESSAGE** West Nile virus is transmitted to humans primarily through bites from infected mosquitoes. Most people infected have no symptoms; a few have clinical manifestations ranging from febrile illness to neurologic syndromes and possibly death. Risk of serious disease increases with age, and substantial long-term morbidity has been observed in patients who develop severe neurologic illness. No specific antiviral therapy or vaccine currently exists.

**CONCLUSION** West Nile virus has established itself in North America and has become an important public health concern. Decreasing risk of virus-associated illness requires seasonal preventive and control measures.

### RÉSUMÉ

**OBJECTIF** Faire le point sur l'épidémiologie et les manifestations cliniques du virus du Nil occidental (VNO) en Amérique du Nord et sur les données actuelles concernant les vaccins et traitements utilisés pour prévenir et traiter cette infection virale.

**QUALITÉ DES PREUVES** Depuis 1999, le nombre d'études sur l'écologie, l'épidémiologie et la biologie du VNO a augmenté considérablement. Ces études nous ont permis de mieux comprendre l'activité actuelle de l'infection, de prévoir son activité future et de décrire l'effet du VNO sur la santé humaine.

**PRINCIPAL MESSAGE** Le VNO se transmet à l'homme par les piqûres de moustiques infectés. La plupart des personnes infectées ne présentent pas de symptômes; quelques-unes auront des manifestations variant d'un simple accès fébrile à des syndromes neurologiques parfois létaux. Le risque d'une maladie grave augmente avec l'âge et en cas d'atteintes neurologiques sévères, certains patients ont présenté une morbidité à long terme. Il n'existe présentement aucun vaccin ni traitement antiviral spécifique.

**CONCLUSION** Le VNO est bien installé en Amérique du Nord et il représente maintenant un important problème de santé publique. Des mesures de contrôle et de prévention saisonnières seront nécessaires pour réduire le risque de maladies associées au virus.

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**W**est Nile virus (WNV) is an arthropod-borne virus (arbovirus) belonging to the genus *Flavivirus*, family *Flaviviridae*.<sup>1</sup> The virus is maintained in nature through a bird-mosquito-bird transmission cycle, but mosquitoes can transmit the virus to nonamplifying hosts, such as horses and humans, which do not develop high levels of viremia.<sup>2-4</sup> In temperate climates, risk of human infection with WNV rises during midsummer to late summer when the number of infected mosquitoes that feed on humans increases.

The virus was first isolated in 1937 from the blood of a febrile patient in the West Nile province of Uganda.<sup>5</sup> Since arriving in North America in 1999, WNV has spread throughout the United States and Canada and into Mexico and the Caribbean.<sup>6,7</sup> The virus has emerged as a globally important pathogen with far-reaching implications for public health.

## Quality of evidence

Using PubMED and MEDLINE and the search words "West Nile virus," "arbovirus," and "Flavivirus," we identified more than 900 articles dealing with clinical and basic microbiologic aspects of WNV. Most of these have been published during the last 5 years. We chose articles that provided detailed information on newly documented clinical aspects of viral disease and recent diagnostic developments. Epidemiologic information was obtained from several recent publications, but the most current data were obtained from Centres for Disease Control and Public Health Agency of Canada websites. Currently, there are few treatment options, and their effectiveness requires further study.

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## Epidemiology

In 2002 and 2003, WNV was responsible for two or more of the largest arboviral epidemics ever observed in the western hemisphere; more than 15 000 symptomatic infections were documented in the United States and Canada.<sup>6,8-10</sup> About 6000 of these cases were diagnosed as meningitis or encephalitis, making these outbreaks the largest WNV meningoencephalitis epidemics ever recorded. Between January 2001 and March 14, 2005, 1839 cases of WNV-associated illnesses and 36 deaths were reported in Canada (virus activity was reported in seven provinces).

The 2003 Canadian epidemic of WNV disease was the largest ever documented; most cases occurred in the Prairie Provinces (Manitoba, Saskatchewan, Alberta); 848 cases were in Saskatchewan alone.<sup>10</sup> In 2004, cases were reported in Quebec, Ontario, Manitoba, Saskatchewan, and Alberta, but the number of human cases (26) was substantially lower than the year before, possibly due to a combination of climatic and ecologic factors.<sup>10</sup>

## Transmission and course of infection

Transmission of WNV occurs primarily through bites of infected mosquitoes. Less common modes of transmission include infected blood, tissues, and organs; needle-stick or sharps injuries; and transmission through the placenta or breast milk.<sup>11</sup> A genomic test for detecting WNV in blood donations was introduced in 2003 to screen donors in Canada and the United States; more than 1000 viremic donors were identified.<sup>12-15</sup> Implementation of this program might have saved many lives.

### Levels of evidence

**Level I:** At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

**Level II:** Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

**Level III:** Expert opinion or consensus statements

In humans, incubation ranges from 2 to 15 days before onset of illness<sup>16</sup>; prolonged incubation periods (up to 21 days) have been observed in patients following organ transplantation.<sup>17</sup> Initial replication of WNV probably takes place in dendritic skin cells that migrate to lymph nodes where a second round of viral amplification occurs. The virus then enters the bloodstream. The infectious period can begin up to 6 or 7 days before onset of clinical illness, but ends soon after symptoms start. How the virus travels to organs and tissues has been described.<sup>18</sup> A study involving patients with various types of cancers inoculated with the Egypt isolate of WNV found the virus was most frequently isolated in lungs, spleens, and lymph nodes; less frequently in hearts, small intestines, and spinal cords; and rarely in livers, kidneys, skeletal muscles, large intestines, pancreata, and brains.

## Clinical features of infection and diagnosis

About 80% of WNV infections are asymptomatic, but some patients have symptoms ranging from mild febrile illness (>95% of patients) to meningitis or encephalitis (<1% of patients).<sup>19,20</sup> People infected

with WNV could experience fever, headache, and other nonspecific symptoms that typically last for several days (Table 1, Table 2). Patients can also have a variety of other signs and symptoms including nausea, vomiting, macular-papular rash, chills, abdominal pain, muscle weakness, photophobia, conjunctivitis, movement disorders, parkinsonism, confusion, and slurred speech. For some patients, a febrile prodrome is immediately followed by encephalitis. More severe neurologic manifestations, such as a syndrome resembling poliomyelitis and acute flaccid paralysis, have been seen.<sup>20</sup>

Previous characterizations of West Nile febrile illness have generally described it as a mild, acute syndrome lasting 3 to 6 days, but West Nile fever

**Table 1.** Clinical features of West Nile fever

COMMON SYMPTOMS	
Fever	
Fatigue	
Headache	
Muscle weakness	
Neck pain or stiffness	
Malaise	
Anorexia	
Nausea	
Vomiting	
Eye pain	
Rash	
LESS COMMON SYMPTOMS	
Sore throat	
Cough	
Shortness of breath	
Lymphadenopathy	

**Table 2.** West Nile virus neurologic disease

DISEASE
Encephalitis
Meningitis
Acute flaccid paralysis (can develop without associated encephalopathy or meningeal signs)
ASSOCIATED SYMPTOMS OR SYNDROMES
Fever
Muscle weakness
Gastrointestinal tract symptoms
Headache
Movement disorders (tremor, myoclonus)
Parkinsonism (includes cogwheel rigidity, bradykinesia, postural instability)
LESS COMMON CLINICAL ILLNESSES
Rhabdomyolysis
Optic neuritis
Acute demyelinating encephalomyelitis
Seizure
Facial weakness
Ocular manifestations (including multifocal choroiditis and chorioretinitis)
LONG-TERM PHYSICAL SEQUELAE AND COGNITIVE IMPAIRMENT*
Fatigue
Headache
Muscle pain or weakness
Gait and movement disorders
Lightheadedness
Confusion
Loss of concentration

\*Can last 12 to 18 months and might be more severe with increasing age.

can be a serious disease that takes several months to resolve.<sup>21</sup> For patients who develop severe neurologic illness, recovery can take a long time (**Table 2**).<sup>22,23</sup> Some patients experience serious long-term sequelae that include physical symptoms, such as muscle weakness, fatigue, and headache, and effects on cognitive function including confusion, depression, and memory loss. Recovery can take more than a year; in extreme cases, lingering effects might last a lifetime.<sup>22</sup> Sequelae from acute flaccid paralysis are lifelong.

Risk of neurologic disease increases with age and underlying medical conditions; diabetes and heart disease, for example, can increase risk.<sup>7,23</sup> Transplant recipients appear more likely to be severely ill upon exposure to WNV, probably because of immunosuppression.<sup>24</sup>

People of all ages can get WNV-associated illness.<sup>11</sup> Animal studies suggest that genetic factors influence severity of disease.<sup>25</sup> Incidence of viral meningitis in temperate climates is highest in the summer and fall, and outbreaks of enterovirus infection in younger people overlap with increased risk of WNV infection. Although incidence of neurologic disease is low, WNV should be included in the differential diagnosis of children who develop aseptic meningitis or encephalitis during times of mosquito activity.

The front-line laboratory diagnostic assay for WNV infection tests serum (and cerebrospinal fluid if a patient exhibits neurologic disease) for presence of WNV-reactive immunoglobulin-M (IgM) antibody using either in-house or commercial enzyme-linked immunosorbent assays (ELISA).<sup>16,26</sup> If results of IgM ELISA are positive, it might be necessary to evaluate cross-reactivity with other flaviviruses by performing a viral neutralization assay to document cases. A second serum sample obtained 10 to 15 days after the first is helpful in confirming WNV infection by demonstrating a fourfold rise in specific neutralizing antibody titre. The IgM antibody to WNV can persist for more than a year, which might cause confusion when those with compatible illness who reside in places that experienced epidemics the previous year are tested.<sup>27</sup> Demonstration of seroconversion might

be needed to identify patients who test positive, but were exposed during the previous season.

Laboratories can also test cerebrospinal fluid for presence of WNV nucleic acid, and although sensitivity is low (about 50%), positive results confirm WNV infection of the central nervous system.<sup>28</sup> Serum samples taken early during the acute phase of infection (usually less than 1 week after symptom onset) can be negative by serology but positive on a nucleic acid detection test. Combining IgM ELISA and WNV nucleic acid detection tests might be warranted to ensure the most sensitive testing. Sometimes, WNV can be cultured from cerebrospinal fluid and blood, but the sensitivity of viral culture is usually extremely poor, so culturing is not recommended.<sup>29</sup>

## Treatment

To date, the only treatments for WNV infection are supportive. Ribavirin and interferon-alpha-2b inhibit replication of the virus in vitro, but no controlled clinical trials using either agent have taken place.<sup>30</sup> Some human case reports indicate that treatment with intravenous immunoglobulin (IVIG) could help recovery from infection<sup>31</sup> but, because the precise timing of infection is usually unknown and most people do not go to their doctors before severe illness, administering antibodies is unlikely to be useful as a therapy. As a prophylaxis, IVIG could prove useful for those at high risk of infection due to needle-stick exposure. Hamsters who had been given immunoglobulin 24 hours before infection were completely protected from infection.<sup>32</sup> This observation indicates that passive immunization might be effective for short-term, immediate exposures in people at high risk. Before IVIG can be used as therapy, controlled clinical trials should be carried out to better determine the dose, timing, and efficacy of the procedure.

## Vaccines

Vaccines for WNV vaccine are in various stages of development and testing.<sup>33</sup> An experimental recombinant WNV vaccine was constructed by inserting

the premembrane (prM) and envelope (E) genes from the New York 1999 virus into an infectious clone of the yellow fever 17D vaccine virus. This hybrid elicits a strong and potentially long-lasting humoral immune response in hamsters, and additional trials involving non-human primates have promising results.<sup>34</sup> Other vaccine candidates include recombinant DNA vaccines expressing the prM and E or capsid proteins and a recombinant E protein subunit preparation.<sup>33</sup> Several of these vaccines might be effective, but the benefits and risks of vaccination remain to be determined. Due to the low incidence of disease in humans and the sporadic nature of most outbreaks, it could be difficult to select human populations for vaccination and to assess the practical aspects of a human vaccine. The most appropriate initial use for vaccines might be for immunizing elderly people in high-risk areas.

## Prevention

Although various modes of transmission have been identified, the major risk factor for exposure is being bitten by an infected mosquito. In many areas, coordinated mosquito-control programs have been put in place as part of preventive measures against WNV.<sup>35</sup> Personal protective measures should still be emphasized as a strategy for reducing risk. People should apply insect repellent to their skin, wear protective clothing when exposed to mosquitoes, and minimize outdoor activities during peak mosquito-feeding times.

The most effective repellent for use on the skin against mosquitoes is N,N-diethyl-m-toluamide (DEET)<sup>36</sup>; DEET or permethrin also can be applied directly to clothing to repel mosquitoes. The Canadian Paediatric Society recommends use of formulations no greater than 10% DEET on children older than 2 years and advises against using DEET on infants younger than 6 months. Although DEET is absorbed into the system through the skin and has been shown to cross the placenta, studies of both animals and humans indicate that DEET can be used during pregnancy without adversely affecting fetuses.<sup>37</sup>

### EDITOR'S KEY POINTS

- Since 1999, West Nile virus has established itself firmly in North America; 15 000 cases were documented in the United States and Canada in 2002 and 2003. In Canada, 1839 cases were identified between January 2001 and March 2005; 36 deaths were attributed to West Nile virus.
- About 80% of people infected are asymptomatic; 95% of the rest have symptoms of only mild viremia. Very few (<1%) go on to develop symptoms of encephalitis or flaccid paralysis. Risk of serious disease increases with age and in immunocompromised people.
- Vaccines are currently under development, but targeting the vulnerable population is challenging. Personal protection against mosquitoes and reducing mosquito populations remain the main protection strategies.

### POINTS DE REPÈRE DU RÉDACTEUR

- Apparu en 1999, le virus du Nil occidental est maintenant solidement établi en Amérique du Nord; en 2002 et 2003, 15 000 cas ont été diagnostiqués aux États-Unis et au Canada. Au Canada, 1839 cas ont été identifiés entre janvier 2001 et mars 2005 et 36 décès ont été attribués à ce virus.
- Environ 80% des personnes infectées demeurent asymptomatiques; parmi les autres, 95% présenteront les symptômes d'une viremie bénigne. Très peu (<1%) développeront des symptômes d'encéphalite ou de paralysie flasque. Le risque de présenter une forme grave augmente avec l'âge et chez les immunodéprimés.
- Des vaccins sont en préparation, mais il sera difficile de cibler la population vulnérable. Les principales mesures préventives demeurent la protection contre les piqûres et la réduction de la population de moustiques.

## Conclusion

In Canada and the United States, WNV has been responsible for large outbreaks of febrile and neurologic disease. Although people of all ages can be affected, elderly and immunocompromised people are most at risk of serious illness. No specific treatments currently exist for WNV disease, so continued monitoring and surveillance of the virus is warranted since measures to prevent and control it are critical for decreasing risk of infection. The long-term effect of this virus on public health in North America is unknown; future epidemics and spread of the virus remain distinct possibilities.



### Competing interests

*None declared*

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