

Why the West in West Nile virus infections?

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West Nile virus (WNV) was initially isolated and identified in 1937 in Uganda (Africa). Over the ensuing decades, outbreaks of WNV were infrequent, usually associated with mild febrile illnesses, and most commonly found in west Asia, Africa and the Middle East (1,2). However, WNV was identified in North America in 1999 following an outbreak of viral encephalitis in New York City (USA) that resulted in 62 confirmed human cases with seven deaths (3). Within the next five years, WNV emerged as an important human, avian and equine disease in the United States (2-7). Following this outbreak in New York City, several Canadian provinces implemented enhanced surveillance for human cases of WNV encephalitis, but none were detected. The first WNV-infected bird was detected in Ontario in 2001, and the first confirmed human cases of WNV infection endemic to Canada occurred in Quebec and Ontario in 2002 (8). During the summer of 2003, WNV became firmly established within the Canadian ecology and a total of 1493 human cases of illness (14 deaths) due to WNV infection were reported, with the majority occurring in western Canada (9). The ensuing three years were relatively quiet with only 26 cases reported in 2004, 225 cases in 2005 and 151 cases in 2006. However, 2007 has seen a record 2035 human cases reported in Canada as of September 15, with more than 99% of the cases occurring in the three Prairie provinces (9).

These observations prompted us to review WNV with respect to its status as an emerging infectious disease within Canada, and to explore why western Canada appears to be the epicentre for its endemicity in Canada.

WNV is a small, single-stranded RNA flavivirus related to the Japanese encephalitis virus complex (10). The complex also includes Alfuy, Cacipacore, Japanese encephalitis, Koutango, Kunjin, Murray Valley encephalitis and St Louis encephalitis virus. WNV is maintained in an enzootic cycle involving several species of mosquitoes and birds before infecting humans. The most common route of WNV transmission to humans is through the bite of an infected mosquito (11,12). Mosquitoes become infected with WNV when they feed on susceptible birds carrying the virus in their blood. Birds in the Corvidae family, including crows, ravens and blue jays, are significant vectors because of their high viremia (13). While it is unclear which mosquito species is primarily responsible for

WNV transmission to humans, *Culex tarsalis*, *Culex pipiens*, *Culex restuans* and *Culex quinquefasciatus* appear to be the virus' most important vectors. Twenty-seven mammalian species have been shown to be susceptible to WNV infection and disease, including horses and humans (11,12). Within 10 to 14 days of becoming infected, a mosquito can transmit the virus in its saliva to another bird or animal. Viral amplification occurs during the bird-mosquito-bird cycle, increasing the likelihood of transmission of WNV infection when an individual is bitten. Certain mosquito species can act as bridge vectors because they bite both birds and humans and, thus, are able to transmit the virus to humans. In Canada, enzootic transmission occurs between May and the first hard frosts, normally in late September to October. Most human cases have been recorded between August and September, although regional variations occur due to climate, daylight hours and vector species.

Although the large majority of human infections have occurred as a result of the bite of infected mosquitoes, transmission of WNV has also been documented through receipt of blood products, organ transplantation, transplacentally and possibly through breast milk (5,14-16). The incubation period for WNV infection ranges from two to 15 days, but more prolonged periods of 21 days or longer have been observed in patients following organ transplantation (13,17). The period of viremia begins several days (up to six to seven days) before the onset of clinical illness, and ends shortly after symptoms start.

A spectrum of illness may occur with WNV infection, ranging from asymptomatic infection to severe meningoencephalitis. New variant syndromes have been identified since WNV infections were first reported in North America. The major syndromes include asymptomatic WNV infection (80% of infected persons), West Nile fever (20% of infected persons) or WNV neurological syndromes (WNNS) (less than 1% of infected persons) (18). Other, more unusual, emerging clinical syndromes identified in recent years have included rhabdomyolysis, peripheral neuropathy, polyradiculoneuropathy, optic neuritis and acute demyelinating encephalomyelitis (19-21). Ophthalmological conditions including chorioretinitis and vitritis have also been reported. The full spectrum of clinical illness associated with WNV infection continues to be defined.

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West Nile fever describes symptomatic infection without neurological disease. Clinical characterization of West Nile fever cases is poor but the typical description is a febrile illness of sudden onset lasting three to six days, often accompanied by malaise, anorexia, nausea, vomiting, eye pain, headache, myalgias and rash. Central nervous system infection can occur when the virus crosses the blood-brain barrier.

Among the less than 1% of infected persons with the more severe neurological form of the illness (WNNS), meningitis, encephalitis, meningoencephalitis and flaccid paralysis are the most commonly encountered clinical syndromes. West Nile meningitis is characterized by fever, headache, stiff neck and pleocytosis. West Nile encephalitis is characterized by fever, headache and altered mental status ranging from confusion to coma with or without additional signs of brain dysfunction, such as paresis or paralysis, cranial nerve palsies, sensory deficits, abnormal reflexes, generalized convulsions or abnormal movements. More than 90% of patients with neurological disease will have fever accompanied by gastrointestinal symptoms and headache (22).

Elderly and immunocompromised individuals, as well as those with disruption of the blood-brain barrier from conditions such as hypertension, appear to be at greater risk of WNNS (23). Risk of illness in those older than 50 years of age is 10 times higher than in those younger than 20 years of age (24). The case fatality rate of severe neurological WNV infection is approximately 10% overall, but is higher in older age groups (24). Symptoms of persistent fatigue, headache and myalgia are common and can persist for months after illness. Patients with signs of acute flaccid paralysis can have poor long-term outcomes with limited recovery (25).

Laboratory tests for WNV are available through provincial public health laboratories, and supplementary testing is available at the National Microbiology Laboratory in Winnipeg, Manitoba. The most efficient diagnostic method for WNV infections uses an immunoglobulin (Ig) M antibody-capture ELISA, which is confirmatory when IgM is present in the cerebrospinal fluid. Given that IgM does not cross the blood-brain barrier, IgM antibody to WNV detected in the cerebrospinal fluid strongly suggests central nervous system involvement (26). False-positive results may occur with serum specimens collected from individuals exposed to related viruses, such as St Louis encephalitis and dengue virus, due to serological cross-reactivity. In addition, IgM ELISA false-positive results may occur in individuals vaccinated against Yellow fever or Japanese encephalitis but are relatively uncommon. Some patients with WNV may have false-negative results early in the course of their illness and, therefore, a follow-up serum sample is necessary to document a WNV seroconversion. Because WNV IgM may persist in the serum for longer than 500 days, the presence of IgM antibodies in individuals from endemic areas may not necessarily be diagnostic of an acute WNV infection, and alternate methods may be required for diagnosis. Seroconversion of IgG ELISA between acute and convalescent sera demonstrates a current WNV infection. In addition, the use of IgG avidity testing may be used to aid in distinguishing between current and past infection. The presence of both IgM antibody and low-avidity IgG in a convalescent serum sample is consistent with recent illness, whereas results that demonstrate the presence of IgM and high-avidity IgG are suggestive of exposures that have occurred in the more distant past. Confirmatory testing to

detect an increase in specific neutralizing antibody titres between serum specimens obtained in the acute and convalescent stages of disease is also available.

There is no established treatment for WNV infection. Overall management is supportive and focuses mainly on respiratory support, intravenous fluids, management of cerebral edema and prevention of secondary bacterial infection. High-dose ribavirin and interferon alpha-2a and alpha-2b have shown efficacy in vitro (27). However, high-dose ribavirin did not show any benefit during WNV outbreak in Israel in 2000, and evidence from case reports and case series has been conflicting regarding the use of interferon therapy (28-30). The use of corticosteroids, antiseizure medications and osmotic agents has been suggested but not yet studied using controlled trials. An intravenous Ig preparation containing high titers of anti-WNV antibodies has been successfully used in an immunosuppressed patient (31).

Fortunately, most persons infected with WNV infection make a full recovery. However, even among those who make a full recovery, many experience severe long-term sequelae with physical, cognitive and functional deficits including fatigue, difficulty walking, muscle weakness, memory loss and depression (25). Long-term follow-up is recommended for patients with WNNS.

Prevention can be divided into three general categories – preventing exposure to mosquitoes infected with WNV, reducing the number of mosquitoes and public education on WNV. Of these, mosquito control is the most effective means to prevent WNV transmission. Prevention of exposure to mosquitoes is considered the mainstay of prevention of WNV infection. Insect repellents containing DEET (N,N-diethyl-m-toluamide, also known as N,N-diethyl-3-methylbenzamide) are the most effective mosquito repellents available. Concentration determines length of effectiveness, and the minimum concentration necessary to decrease exposure should be used.

The question remains as to why there has been so much WNV activity in western Canada during the summer of 2007. The answer is undoubtedly complex, but it may be worthwhile to examine the evidence related to the mosquitoes that carry the virus and the ecosystem in which they exist. There are 74 known species of mosquitoes in Canada, but not all of the 74 different species are found in all parts of the country. In addition, WNV infection has been found in only 10 mosquito species in Canada, but in at least 49 species that may be found throughout North America (32). The actual numbers of mosquitoes in different areas of the country will also vary according to the time of year, temperature and rainfall.

WNV is most common in mosquito species that feed on birds and include *C pipiens*, *C restuans* and *C tarsalis*. Of the various species of mosquitoes that may carry WNV, *C tarsalis* is one of the most efficient laboratory vectors of WNV tested from North America (33,34). This species is abundant throughout much of western North America, where it is also involved in the maintenance and amplification of Western equine encephalitis and St Louis encephalitis virus (34). Considering its central role in the transmission of arboviruses in avian hosts, and its susceptibility to WNV infection in the laboratory, *C tarsalis* has the greatest potential of any of the mosquito species studied to date to amplify and maintain WNV (34). *C tarsalis* is believed to be the principal transmitter of WNV to humans in the Canadian prairies due to its multivoltine production (multiple generations per season),

regular habit of taking more than one blood meal and willingness to feed on both birds and mammals, making this an important 'bridge' vector moving WNV outside its normal bird-to-bird cycle of infection to one including humans (32). *C. tarsalis* is most active at dusk, and makes persistent efforts to enter houses in search of blood meals. In addition, vertical transmission of WNV from parent mosquitoes to offspring may also aid in propagating viral transmission. Of the other *Culex* species, *C. restuans* seems to prefer bird hosts and may have only limited capacity to spread WNV. *C. pipiens*, also known as the northern house mosquito, is the most common mosquito in urban and suburban areas of eastern Canada and British Columbia and is thought to be the most likely vector of WNV in eastern Canada. This latter species is not found on the Canadian prairies.

Climatic conditions may play a major role in the propagation of *C. tarsalis*, with a wet spring and warmer than usual summer providing the most favourable conditions (32). In 2003, which saw the second highest number of WNV cases in the West, it was warmer than usual on the Canadian prairies and there had been a longer frost-free period, which resulted in four generations of *C. tarsalis* in southern prairie areas, and three in the parkland and boreal transition areas of Saskatchewan, much higher than normal (32). Areas in the southern halves of the three Prairie provinces, which have higher heat units for development, higher levels of precipitation and greater wetland densities would favour higher proportions of *C. tarsalis*. In Saskatchewan in 2003, the proportion of *C. tarsalis* in two major urban centres was 500-fold greater than at any point in the previous 10 years (32). There

were specific weeks in August 2007 when *C. tarsalis* numbers reached as high as 67% of the total mosquito population at some sites in Saskatchewan. With these types of proportions, the risk of being bitten by a WNV-infected *C. tarsalis*, when this species is abundant and the virus has been amplified within the local bird population, would be considered relatively high. The summer of 2007 in the West has many similarities to 2003 with a relatively higher amount of precipitation and a much warmer July than normal. The numbers of positive *C. tarsalis* mosquito pools in Alberta has exceeded the numbers recorded in 2003, with a cumulative total of 223 WNV-positive *C. tarsalis* mosquito pools having been found in Alberta since July 15, 2007 (35), reaching a peak of almost 40% of all mosquito pools tested in the third week of August. In Saskatchewan, 460 mosquito pools have been found to be positive to date in 2007 (36).

Since its initial appearance just over five years ago, WNV has likely become endemic in Canada and it is possible that western Canada, particularly the Prairie provinces, may have the appropriate ecological and climatic niche to be cyclically affected in a significant manner by WNV. With the impacts of global climate changes – with warmer winters, warmer minimum daily temperatures, greater accumulations of heat units required for development and longer frost-free periods – the conditions for greater proportions of *C. tarsalis*, the most efficient vector for WNV, may be expected to increase over the coming years. Although the majority of WNV infections are asymptomatic or mild, severe disease can occur and, thus, prevention of mosquito bites is paramount to the prevention of West Nile viral illness.

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