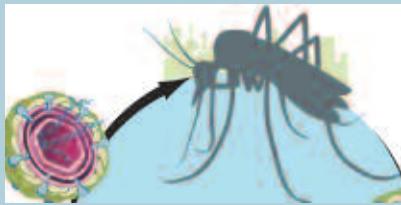


abstract



Since its introduction into North America in 1999, West Nile virus (WNV) has rapidly expanded its range across the continent. There is evidence that it has moved into the Caribbean and South and Central America. The virus has significantly affected public health, causing more than 20,000 cases of associated illness and resulting in the largest WNV epidemic ever recorded.

Although neuroinvasive disease occurs in less than 1% of infections, the risk for encephalitis and other neurological illnesses increases with age. Currently there is no specific therapy for the treatment of WNV-associated disease and a vaccine is not yet available. Decreasing the risk of virus exposure requires seasonal preventative and control measures.

Key Words: West Nile virus, epidemiology, diagnosis, neurological illness, disease prevention

West Nile Virus: A Pathogen of Concern for Older Adults

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Introduction

West Nile virus (WNV) is a mosquito-transmitted virus that belongs to the genus *Flavivirus*, family *Flaviviridae*.¹ The *Flavivirus* genus comprises many important pathogens such as yellow fever and dengue virus as well as viruses more closely related to WNV, including Japanese encephalitis and St. Louis encephalitis viruses. The virus acquired its name after its isolation in 1937 from the blood of a febrile patient in the West Nile province of Uganda.² The structure of the virus takes the form of a spherical, enveloped capsid that is approximately 50 nm in diameter (Figures 1a, b). The genome is comprised of single-stranded RNA that encodes both structural and nonstructural proteins that are involved in virus replication (Figure 1c). The virus is maintained in nature by a cycle involving mosquitoes and birds; mosquitoes may transmit the agent to nonamplifying hosts such as horses and/or humans, neither of which develop significant levels of viremia (Figure 2). Since its incursion into North America in 1999, WNV has spread throughout North America with recent evidence also suggesting its spread into the Caribbean, and Central and South America.³⁻⁵ In this article we review the epidemiology and diagnosis of WNV disease, describe the clinical manifestations associated with infection, and provide an update on the current status of therapeutic approaches and vaccines for treating or preventing viral illness.

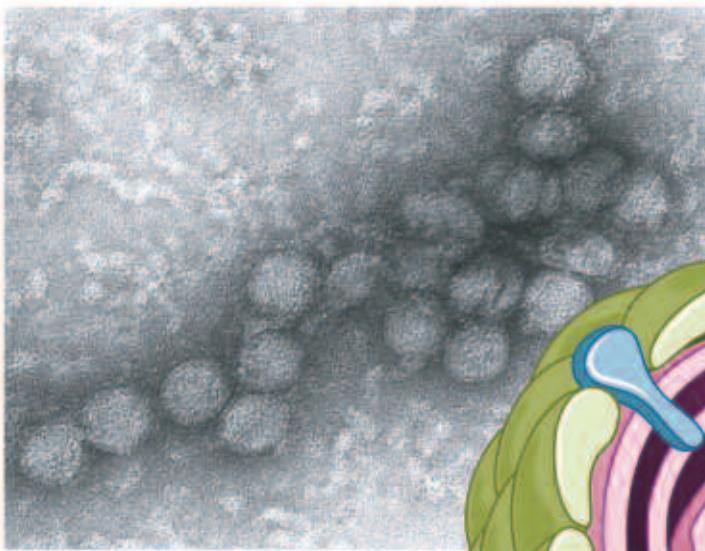
Epidemiology

Although WNV was first detected in New York City during the summer of 1999, the virus probably originated in the Middle East since it was closely related to a 1998 isolate from Israel.⁶ Strains of WNV have been shown to exhibit different phenotypic characteristics including varying degrees of virulence using animal models. As well, the genetic divergence of isolates of this virus can be quite extensive, and strains have been divided by phylogenetic analysis into lineage 1 and 2 genogroups.⁶ Both the North American strain of WNV and related genotypes circulating in Europe and Asia have been associated with outbreaks of severe disease. The North American subtype and genetically related strains may be particularly virulent for both humans and animals.^{1,5}

During its expansion throughout North America WNV has caused over 21,000 symptomatic infections and infected approximately half a million individuals.^{7,8} In 2002 and 2003, WNV was responsible for two of the largest arboviral epidemics ever observed in the Western hemisphere with over 15,000 clinical cases documented in the United States and Canada. Since 1999 over 9,000 cases have been diagnosed as neuroinvasive diseases such as meningitis, encephalitis, or acute flaccid paralysis (AFP). From 2001 to March 12, 2006 a total of 2,179 cases of WNV associated illness and 42 deaths were identified in Canada, and virus activity has been demonstrated in seven provinces.

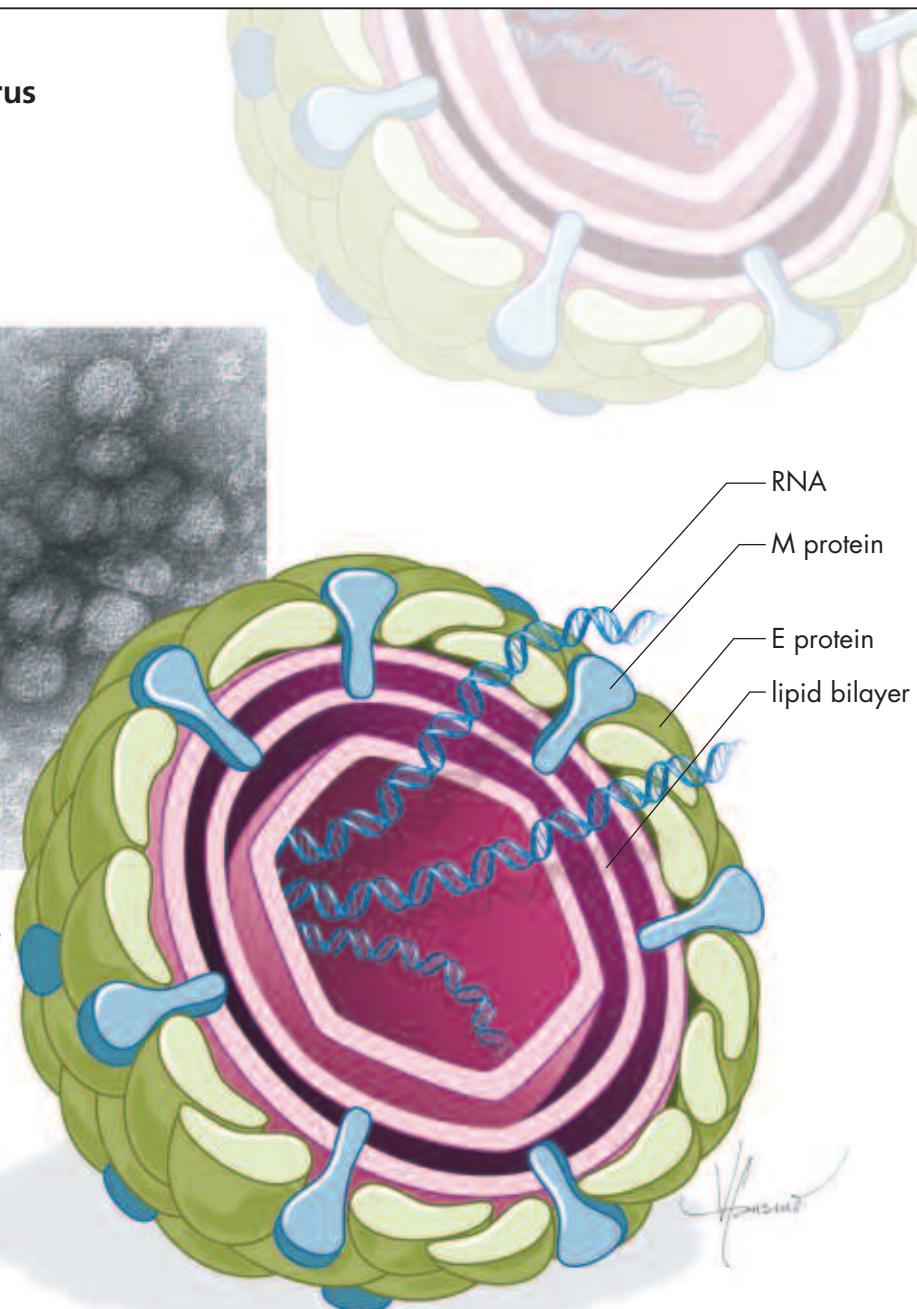
Figure 1:
Structure of the West Nile Virus

(a)



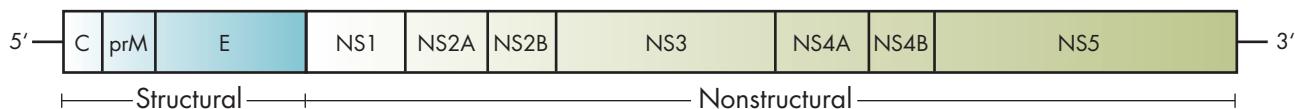
the structure

The structure of the virus takes the form of a spherical, enveloped capsid that is approximately 50 nm in diameter.



(b) West Nile virus cross-section

(c)



the genome

The genome is comprised of single-stranded RNA that encodes both structural and nonstructural proteins that are involved in virus replication.

Almost all provinces have had imported cases due to exposures in endemic areas of North America.⁸

The first human cases of WNV contracted in Canada were recognized in 2002, with 426 diagnosed cases primarily in Ontario but also in Quebec.³ The 2003 Canadian epidemic of WNV disease was the largest ever documented in this country (1,494 confirmed infections); the majority of cases occurred in the prairie provinces (Manitoba, Saskatchewan, Alberta) with 848 cases in Saskatchewan alone.⁸ In 2004 there was repeat activity in those provinces; however, the total number of human cases recorded decreased to 25. During 2005, the case numbers increased almost 10-fold with 229 infections documented. The year-to-year fluctuation of WNV activity may be due to a combination of climatic and ecological factors. However, continued WNV activity has been demonstrated in states such as New Jersey and New York since 1999 in Ontario since 2001 indicating that the virus has established itself in North America and has the potential to affect (albeit with variable intensity) public health for years to come.

Transmission and Clinical Features of Disease

Transmission of WNV is primarily by the bite of an infected mosquito. Less common modes of transmission include infected blood, tissues, and organs, needle stick or sharps injuries, transplacental transmission, and breast milk.⁹ Since the screening of blood donors was initiated in 2003 over eight million donations are tested per year, and over 1,400 viremic individuals have been identified, indicating that the blood testing program has prevented transmission in a significant number of cases.^{8,10} At least two cases of transmission by organ donation have been identified in the United States, and guidelines for organ and tissue screening have been established in Canada.¹¹⁻¹³

In humans the incubation period ranges from 3–15 days prior to onset of illness; prolonged periods of up to 21 days have been observed in patients following organ transplantation.¹⁴ The initial repli-

cation 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 blood stream. The detection of virus in the blood may begin several days (up to 6–7 days) prior to onset of clinical illness, but ends soon after symptoms start. Dissemination of the virus to various organs and tissues has been described in a number of studies. A recent report showing that WNV persisted in the organs of an immunocompromised individual months after infection indicates that the virus can maintain itself in tissues over a significant periods of time.¹⁵

Approximately 80% of WNV infections are asymptomatic; however, when it occurs WNV disease can range from mild febrile illness (>95% of symptomatic infections) to neurological manifestations including meningitis and/or encephalitis.^{14,16} Fever, headache, and other non-specific symptoms typically last for several days. Symptomatic individuals can also display a wide variety of other symptoms including nausea, vomiting, macular papular rash, chills, abdominal pain, muscle weakness, photophobia, conjunctivitis, movement disorders, parkinsonism, confusion, and slurred speech. For certain patients a febrile prodrome is immediately followed by encephalitis. The occurrence of more severe neurological manifestations such as poliomyelitis-like syndrome and AFP have been documented.¹⁷

Previous characterizations of West Nile febrile illness have generally described it as a mild, acute syndrome lasting three to six days; however, West

Nile fever can be a serious disease, and patients may require several months before full recovery.¹⁸ For patients who develop severe neurological illness, recovery periods may be prolonged. Certain individuals may experience significant long-term sequelae that include physical symptoms such as muscle weakness, fatigue, headache, and effects on cognitive function including confusion, depression and memory loss.^{19,20} Recovery may take more than a year; in extreme cases, lingering effects of infection may be life-long.

The risk for both febrile and neurological disease increases with age, and underlying medical conditions such as diabetes and heart disease may also heighten the risk for serious illness (Figure 3).²⁰ Individuals age 50 and older are more prone to neuroinvasive disease such as encephalitis and AFP.^{5,20} Transplant recipients also appear to be more likely to acquire severe illness upon exposure to WNV, possibly due to immunosuppression.²¹ It should be noted that all age groups manifest WNV-associated illness, and recent studies suggest that genetic factors may influence severity of disease.²² In temperate climes where WNV is active, the risk for human infection rises during mid-to-late summer when the number of infected mosquitoes that feed on humans increases.³

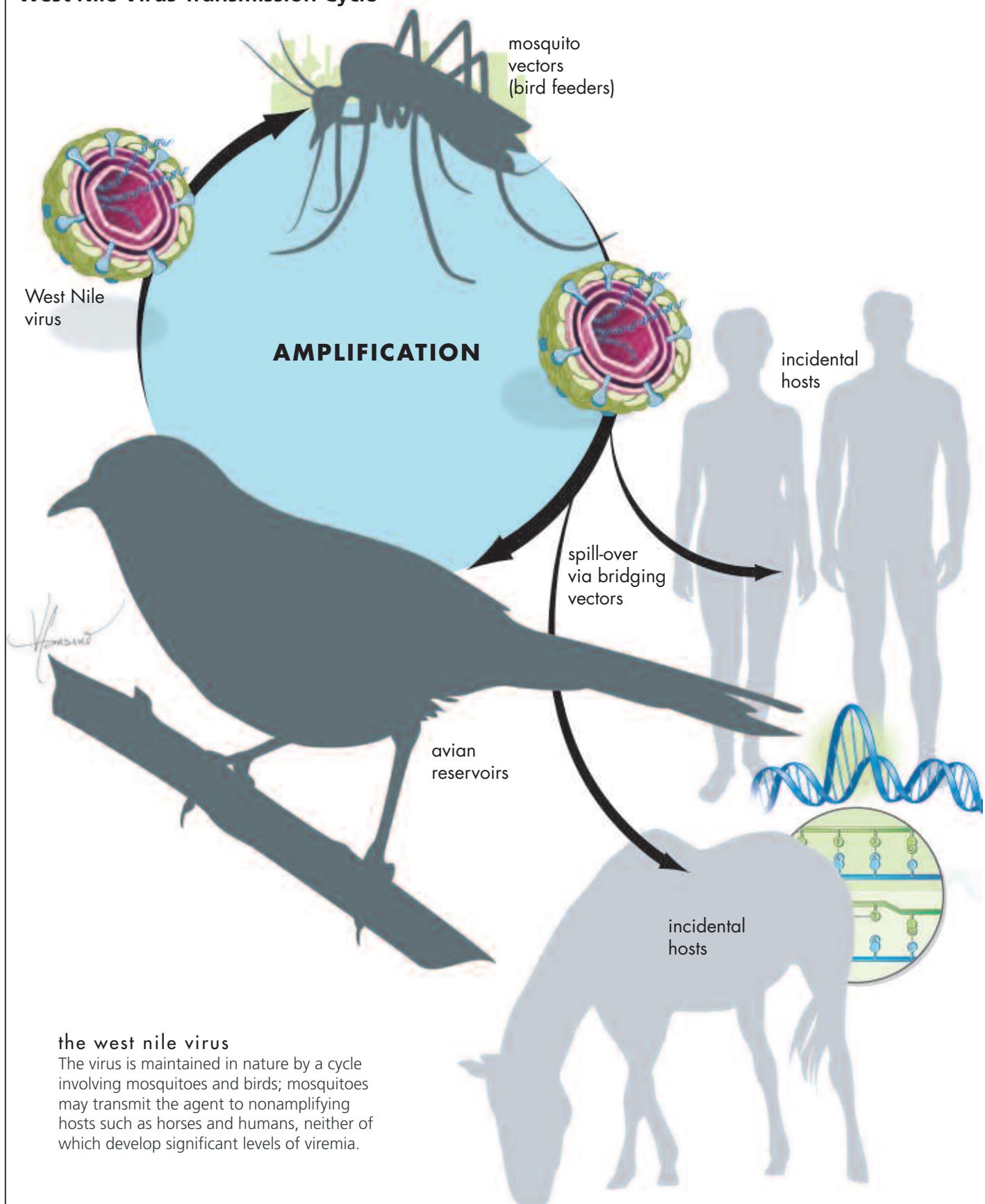
Diagnosis

The primary laboratory diagnostics algorithm for case investigations of WNV infection involves the testing of serum for the presence of WNV-reactive IgM antibody by using either in-house or com-

Table 1: Precautionary Measures Recommended to Reduce Risk of Mosquito-borne Disease Infections

Avoid outdoor activities between dusk and dawn, when mosquitoes are most active.
Wear light-coloured long pants and long-sleeve shirts.
Use mosquito repellent containing DEET.
Dispose of stagnant water where mosquitoes might breed.
Ensure house screens on windows and doors are in excellent condition to prevent insect intrusions.

Figure 2:
West Nile Virus Transmission Cycle



mercial enzyme-linked immunosorbent assays (ELISA).^{3,16,23} If the IgM ELISA is positive it may be necessary to evaluate cross-reactivity with other flaviviruses by performing a viral neutralization assay to document cases. A convalescent serum sample obtained 10–15 days after the first is helpful in confirming WNV infection through the demonstration of a fourfold rise in specific neutralizing antibody titer. IgM antibody to WNV may persist for >1 year in some patients, which may cause diagnostic misinterpretation when testing individuals with compatible illness who live in jurisdictions that experienced

epidemics the previous year.²⁴ As a result the demonstration of seroconversions or the use of IgG avidity assays may be necessary to identify individuals who give positive serology results but were exposed during the previous season.²⁵

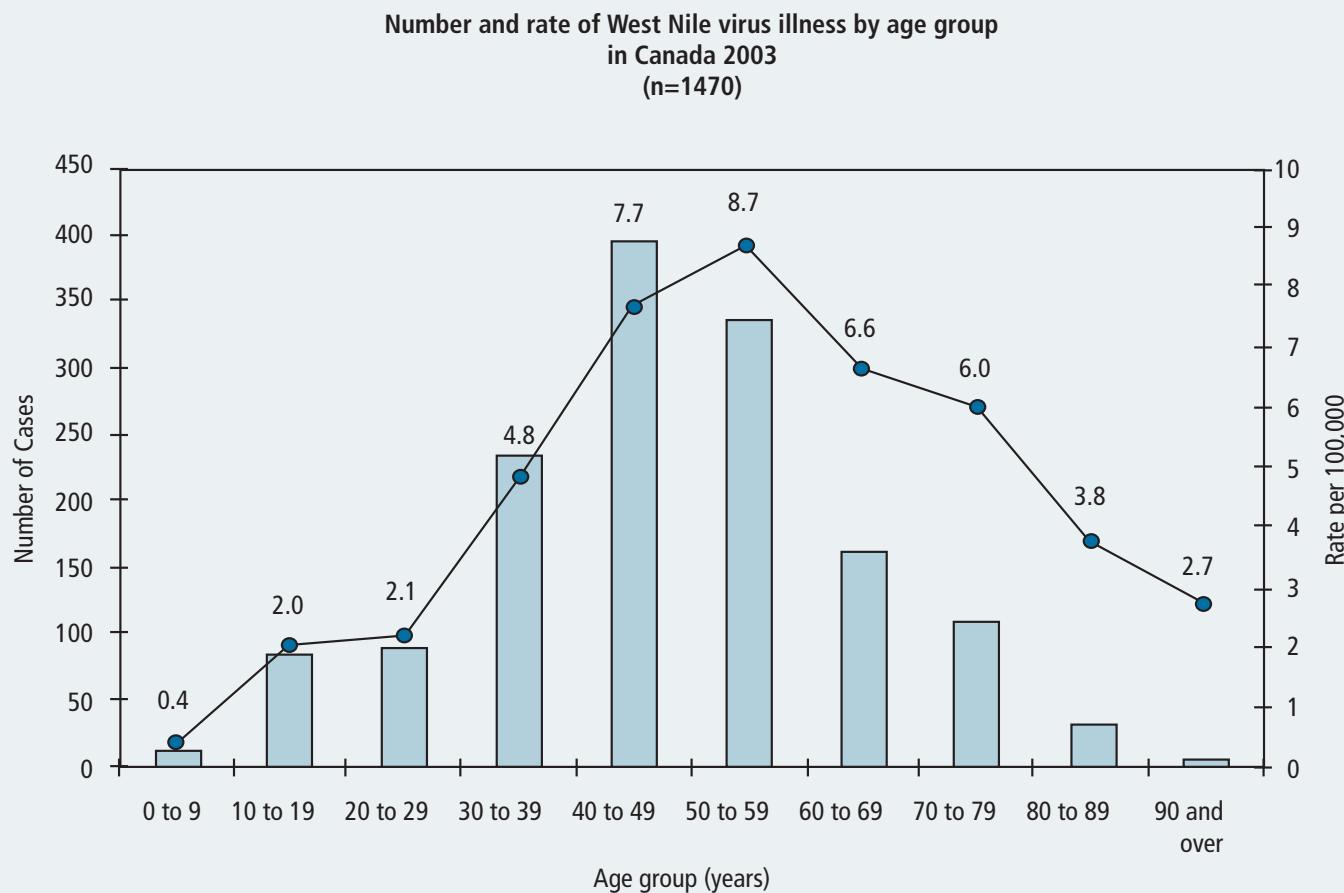
Laboratories can also test cerebrospinal fluid for the presence of WNV nucleic acid (e.g., polymerase chain reaction) and although the sensitivity of these tests is low (50% or less), a positive result confirms WNV infection of the central nervous system.²⁶ Since IgM may also persist in cerebrospinal fluid the detection of viral RNA is an additional labora-

tory criterium for identifying current cases of WNV disease. Serum samples taken early during the acute phase of infection may be negative by IgM serology but positive by a nucleic acid detection test (NAT); therefore, a combination of IgM ELISA and WNV NAT diagnostics may be warranted to ensure the most sensitive testing algorithm.

Treatment

No approved antiviral treatments or therapeutics exist for WNV infected patients, and therefore only supportive therapy can be instituted such as pain control for

Figure 3: Age Profile of Human Cases of West Nile Virus by Classification in Canada 2003



- This figure shows all cases together, divided into 10-year age groupings for 2003 data
- The mean age of the WNFS cases was 46 years, with a range of 3 to 92
- The mean age of the WNNS cases was 9 years higher at 55 years, with a range of 0–92 years
- The line graph shows rate per 100,000, by age group, for all cases

Source: This figure courtesy of Dr. Peter Buck, Zoonoses section, Foodborne, Waterborne, and Zoonotic Infections Division, Public Health Agency of Canada.

Key Points

West Nile virus (WNV) is now endemic throughout much of North America and poses a significant seasonal health threat.

WNV is mainly transmitted by mosquitoes but other routes of infection such as blood and organ transplant transmission have been documented.

Approximately 80% of WNV infections are asymptomatic, but older adults and immunocompromised individuals are at higher risk for serious disease.

Specific treatments and vaccines are not currently available; personal protective procedures are key to avoid exposure to this virus.

headaches, rehydration for nausea/vomiting, and controlling seizures. Antivirals such as ribavirin and IFN-2b inhibit replication of the virus in vitro; however, there have been no controlled clinical trials using either agent.²⁷ Other potential antivirals include inhibitors of viral genome replication such as small inhibitory RNAs (siRNA) and phosphorodiamidate morpholino oligomers (PMOs).^{28,29} A phase 1 clinical trial to assess the safety and efficacy of PMO compounds is currently being performed.

A number of human case reports indicate that treatment with intravenous immunoglobulin (IVIG) may aid in recovery from infection.³⁰ However, because the precise timing of infection in a human being is usually undetermined and most individuals do not go to their clinician prior to severe illness, administration of antibodies may be of limited use as a therapeutic. Nevertheless, as a prophylaxis, IVIG could prove useful for individuals at high risk of infection due to a needle stick exposure. Recent animal studies have also indicated that there may potential for IVIG immunotherapeutics, and a large clinical trial in the United States is currently underway.

Vaccines

There has been progress made in the development of WNV vaccines, and a number of candidates are in various stages of development and testing.³¹ An experimental recombinant WNV vaccine candidate was constructed by inserting the premembrane (prM) and envelope (E) genes from a North American WNV isolate into an infectious clone of the Yellow

Fever 17D vaccine virus.³² This hybrid virus elicits a strong and potentially long-lasting humoral immune response in rodent models, and additional trials involving nonhuman primates have shown promise.³² Other vaccine candidates include recombinant DNA vaccines expressing the prM and E or capsid proteins, and a recombinant E protein subunit preparation.³¹ It is possible that several of these vaccines will be effective; however, 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 may be difficult to select human populations for vaccination and to assess the practical aspects of a human vaccine. Since older adults are at highest risk for serious disease the initial use of vaccines may be most appropriate for immunizing older individuals in high-risk areas.

Prevention

Although various modes of transmission have been identified, the major risk factor for exposure is the bite of an infected mosquito. Numerous U.S. and Canadian jurisdictions have implemented mosquito control programs as part of preventive measures against WNV.³³ However, personal protective measures continue to be emphasized as a strategy for reducing human risk in areas with WNV-infected mosquitoes (Table 1). Recently published serosurveys and risk behaviour analyses found that individuals who practiced at least two personal protective behaviour traits (e.g., minimizing outdoor activities during peak mosquito-feeding times, wearing long sleeves and pants, using

mosquito repellent) decreased risk of exposure by approximately 50%.³⁴

A number of compounds have been assessed as repellents; however, the most effective repellent for use on the skin against mosquitoes is N,N-diethyl-m-toluamide (DEET).³⁵ DEET or permethrin also can be applied directly to clothing to repel mosquitoes.

Conclusion

WNV has been responsible for large outbreaks of febrile and neurological disease in North America, and it is apparent that it will be a pathogen of concern in the Americas for years to come. Although all age groups can be affected, older adults and immunocompromised individuals are at most risk for serious illness. Research continues on the assessment of potential therapeutics for WNV disease; however, no specific treatments currently exist. Preventative and control measures are paramount for decreasing the risk of infection.



No competing financial interests declared.

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