

Epidemiology and pathogenesis of West Nile virus infection

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INTRODUCTION — West Nile (WN) virus, a flavivirus that is a member of the Japanese encephalitis virus antigenic complex, emerged from obscurity in 1999 when the first incursion of the virus in North America caused 62 cases of encephalitis and seven deaths in New York [1]. Since that time, the virus has dramatically spread, and during 2005, WN virus activity was detected in 48 states and the District of Columbia. WN virus causes both sporadic infection and outbreaks that may be associated with severe neurologic disease.

EPIDEMIOLOGY — WN virus is one of the most widely distributed of all arboviruses with an extensive distribution in the Old World, throughout Africa, the Middle East, parts of Europe and the former Soviet Union, South Asia, and Australia [2]. The virus had not been detected in North America before the 1999 New York City outbreak. It is unknown how WN virus got to the United States; however, the circulating strain is genetically identical to a virus identified in Israel, suggesting importation from the Middle East [3,4].

Patterns of illness — Since the virus' first discovery in the blood of a febrile woman in the West Nile district of Uganda in 1937, infrequent human outbreaks were mostly reported in groups of soldiers, children, and healthy adults in Israel and Africa [5-8]. These outbreaks were associated with only minor illness in the majority of patients; some case fatalities were associated with increasing age. In one of the largest outbreaks reported, thousands of self-limited and relatively mild clinical cases, consisting of fever, rash, and polyarthralgias occurred in South Africa, resulting in an epidemic attack rate of 55 percent [9].

However, since the mid-1990s, outbreaks of WN virus infection associated with severe neurologic disease have occurred in Romania (1996), Russia (1999), Israel (2000), the United States (2002-2005), and Canada (2002, 2003) [10-14]. In each of these outbreaks, mortality among patients with meningitis and encephalitis was approximately 10 percent and occurred more often in elderly patients.

However, serologic surveys in Romania and the United States indicate that severe complications are infrequent, with only approximately 1 in 150 infections resulting in meningitis or encephalitis [11,15-17]. Clustered serologic sampling during an outbreak of 59 cases in Queens, New York City demonstrated that an estimated 2.6 percent of the surrounding population was infected during this time [15]. Approximately one-third of these participants reported a recent febrile illness compared to only 11 percent of seronegative controls. By extrapolation, the more than 8000 cases of invasive neurologic disease reported in the United States through 2005, would imply that at least 1.2 million persons have been infected.

Incidence in the United States — Despite extensive spread of the virus in nature, only 21 human cases of WN virus infection were reported in the United States in 2000 and 66 in 2001 [18]. However, in 2002, a multistate outbreak throughout the Midwest involved more than 4000 persons [10]. At the peak of the outbreak in 2003, WN virus was reported in all but three states in the continental United States, for a total of 9862 cases (2866 with neuroinvasive disease) [19]. In 2005, as of December 1, forty-two states reported 2744 cases of human WN virus illness (1165 with neuroinvasive disease), 85 of which were fatal cases [20]. The state with the leading number of cases was California (n=854). ([See "Laboratory testing of donated blood"](#), section on West Nile virus).

Human illness has been reported in the United States from April to December with the peak incidence in late summer or early fall [17]. It is likely that sporadic cases occur throughout the year in southern states. The seasonal variation is due to the fact that mosquitoes emerge in the spring in temperate climates, which begins viral amplification in the bird-mosquito-bird cycle. Viral amplification peaks in early fall; the risk of infection then decreases in humans when female mosquitoes begin diapause and infrequently bite.

Incidence in Canada — The epidemiology and ecology of WN virus in Canada reflects that of the northern United States. The first human cases were reported in 2002, with 426 reported illnesses and 20 deaths reported from Quebec and Ontario. In 2003, 1494 cases were reported, of whom 217 had neuroinvasive disease and 10 died. In 2004, only 26 cases were reported, of whom, 13 had neuroinvasive disease. As of February 2006, 229 cases were reported, of whom 49 had neuroinvasive disease, with 12 deaths; human cases of WN virus infection without travel history were reported from Alberta, Saskatchewan, Manitoba, Ontario, and Quebec.

Incidence in Latin America and the Caribbean — WN virus was first detected south of the United States border in 2001, when a resident of the Cayman Islands developed WNV encephalitis [21]. Subsequently, serologic studies in birds and horses suggested that WN virus has circulated in the Dominican Republic [22], Jamaica [23], Guadeloupe [24], El Salvador [25], Colombia [26], and widely in Mexico [27,28].

However, viral isolation have been infrequent and documented avian and equine morbidity are scant [28]. The reasons for the discrepancy between the serologic evidence indicating widespread WN virus circulation in the Caribbean, Central America, and Mexico and the lack of substantial avian, equine, or human morbidity remain a mystery.

Transmission — Nearly all human infections of WN virus are due to mosquito bites. Birds are the primary amplifying hosts, and the virus is maintained in a bird-mosquito-bird cycle [29,30]. Humans, horses, and dogs, serve as incidental hosts and are not felt to be important for transmission since viremia is both short-lived and low-grade. ([See "Birds as amplifying hosts" below](#)).

Mosquitoes that transmit WN virus are usually of the *Culex* species, which vary by geographic area. The major mosquito vectors in Africa and the Middle East are *Cx*.

univittatus and *Cx. pipiens molestus*, and in Asia, *Cx. tritaeniorhynchus*. WN virus has been recovered from ticks in Russia, but it is not clear what role they play in maintaining or disseminating the virus.

Surveillance has identified 60 mosquito species infected with the WN virus in North America. However, WN and the St. Louis encephalitis viruses appear to share the same maintenance vectors. (See "[St. Louis encephalitis](#)"). *Cx. pipiens pipiens* (northern house mosquito) and *Cx. restuans* are the maintenance vectors in the Northeast, while *Cx. pipiens quinquefasciatus* (southern house mosquito) and *Cx. tarsalis* are the main maintenance vectors in the southern and western United States, respectively. It remains unknown which mosquito species primarily transmit WN virus to man [\[31\]](#).

Birds as amplifying hosts — Wild birds develop prolonged high levels of viremia and serve as amplifying hosts but generally remain asymptomatic [\[32\]](#). Nevertheless, dead bird surveillance has noted 308 species of native and captive birds in the United States. Significant avian mortality has only been noted in Israel, the United States, and Canada, in which similar strains of the virus have circulated [\[5,33\]](#). High mortality has been noted among American crows and other North American corvids (ravens, jays, and other crows). In 2002, approximately 60 percent of dead birds with WN virus infection were crows [\[10\]](#); however, this probably reflects the fact that crows are readily identifiable and have high mortality, rather than their importance as maintenance hosts.

Crows are amplifying hosts and also herald disease activity in humans. In many communities with intense epizootics, all of the dead birds collected in late summer have WN virus infection. There is a higher incidence of West Nile infection in residents of high crow-mortality areas relative to those outside of these areas [\[34\]](#). Furthermore, clusters of dead crows can predict an increased risk for one to two weeks prior to appearance of human cases, suggesting that dead crow sightings are a valuable crude indicator of virus activity and may be useful for public health alerts [\[35\]](#).

Other routes of transmission — Transmission has also been described via transfused blood [\[36-38\]](#), transplanted organs [\[39,40\]](#), transplacental transmission [\[41\]](#), occupational transmission via percutaneous exposure [\[42\]](#) conjunctival exposure [\[43\]](#), and in a dialysis center by unidentified means [\[44\]](#). Transmission via breast milk is also likely [\[45\]](#).

In 2002, transmission via donated organs was first documented when fever and mental status changes occurred in recipients of organs from a common donor [\[39\]](#). The investigation revealed that the organ donor had become infected from a blood transfusion shortly before the organs were harvested. Serum from the day the organs were harvested was positive for WN virus by nucleic acid testing and culture. All four recipients of organs from this patient developed febrile illnesses and three had encephalitis. Three patients had serologic evidence of WN virus infection; the fourth patient, who died, had extensive WN virus infection of brain tissue by immunohistochemical staining and PCR testing.

In 2005, transmission via donated organs occurred from a donor who apparently had a mosquito-borne WN virus infection one to two weeks before fatal injury [43]. Serum from the day of organ harvesting was positive for WN virus-specific IgG and IgM antibodies, but was negative for WN virus RNA. Two organ recipients developed encephalitis, one had WN virus nucleic acid and IgG antibodies in serum but remained asymptomatic, and another remained asymptomatic and had no serologic evidence of WN virus infection.

Subsequent investigations of possible WN virus transmission via blood transfusion have demonstrated transmission through transfused red blood cells, platelets, and fresh frozen plasma [36]. ([See "Laboratory testing of donated blood"](#)).

The likelihood of WN virus transmission via donated organs or blood reflects the underlying infection incidence in the general population from which blood and organ donors are drawn. Mathematical modeling indicated that the risk of transmission via transfused blood was as high as 21 per 10,000 units in some metropolitan areas during the 2002 epidemic [46]. The fact that these modes of transmission were identified in 2002 reflects that many persons were infected with the virus in that year.

PATHOGENESIS — The pathogenesis of severe infection with WN virus is not well understood. During feeding, the mosquito injects virus-laden saliva into the host. Virus may infect fibroblasts, vascular endothelial cells, or cells of the reticuloendothelial system. Viremia develops, which may lead to central nervous system infection [47]. The pronounced risk of neurologic infection in the elderly suggests a role for risk factors such as immune senescence.

Immunosuppression may increase the likelihood of severe illness as illustrated by the following observations:

Mice genetically deficient in B cells had increased WN viral loads in the central nervous system (CNS), and the infection was lethal at lower doses of virus than in controls [48]. Host genetic factors have also been postulated to increase susceptibility for severe disease.

In a review of WN virus encephalitis in 11 solid organ transplant recipients, the clinical presentation and laboratory findings were similar to those in immunocompetent patients but the degree of neurologic damage was at the severe end of the spectrum [49]. Other reports, based upon a small number of cases and extrapolation to a larger population, suggest that neuroinvasive disease is approximately 40 times more likely to develop in transplant recipients than in the general population [50,51].

The virus can be detected in the blood during the acute phase of the illness, and the mechanism for bloodborne CNS invasion is probably similar to other flaviviruses, such as St. Louis encephalitis virus. Characteristics of WN virus and its receptors may also

determine its predilection for CNS invasion as illustrated by the following observations in animal models:

The degree of neuroinvasiveness of particular strains of WN virus was affected by specific amino acid substitutions in the envelope protein [\[52\]](#).

Mice deficient in toll-like receptor 3 have decreased viral RNA production and inflammation in the central nervous system with subsequent decreased neuronal injury compared to mice with wild-type receptors [\[53\]](#).

Macrophage depletion led to higher levels of viremia and accelerated development of encephalitis and death compared to control mice [\[54\]](#).

Pathologic observations in a few human cases of fatal encephalitis showed scattered microglial nodules and mononuclear perivascular inflammatory infiltrates most common in the posterior thalamus, basal ganglia, and brain stem and destruction of spinal anterior horn cells [\[55,56\]](#). WN virus was used in the 1950s as an experimental treatment for cancer; virus was isolated in the spleen, lymph nodes, liver, and lungs in patients who died within approximately four weeks after inoculation, consistent with widespread dissemination of infection [\[57,58\]](#).

SUMMARY

WN virus is one of the most widely distributed of all arboviruses with an extensive distribution in the Old World, throughout Africa, the Middle East, parts of Europe and the former Soviet Union, South Asia, and Australia. The virus had not been detected in North America before the 1999 New York City outbreak. ([See "Epidemiology" above](#)).

Wild birds develop prolonged high levels of viremia and serve as amplifying hosts but generally remain asymptomatic.

Nearly all human infections of WN virus are due to mosquito bites; mosquitoes that transmit WN virus are usually of the *Culex* species, which vary by geographic area.

Other less common routes include transfused blood and transplanted organs.

The risk of neuroinvasive disease is increased in the setting of increased age and immunosuppression. ([See "Pathogenesis" above](#)).

The clinical manifestations, diagnosis and treatment of WN virus is discussed elsewhere. ([See "Clinical manifestations, diagnosis, and treatment of West Nile virus infection"](#)).