West Nile Virus in the Americas

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In the summer of 1999, physicians at Flushing Hospital Medical Center in New York City attended several patients with an acute neurologic illness of unknown etiology.1 On August 12, a 60-year-old man was admitted with a 3-day history of fever, weakness, and nausea. He developed confusion, proximal muscle weakness, urinary retention, and respiratory insufficiency requiring mechanical ventilation. Three days later, an 80-year-old man was admitted with a 1-week history of fever, headache, weakness, and diarrhea. He developed flaccid paralysis and died. From August 18 through September 2, four more patients with acute onset of encephalitis and two with meningitis were admitted. Subsequent investigation revealed that these patients were infected with the West Nile virus (WNV), documenting the first autochthonous WNV transmission in the Western Hemisphere and heralding its establishment as the principal cause of arboviral disease in the United States and Canada.1,2

The 1999 New York City outbreak caused an estimated 8200 human infections, resulting in approximately 1700 cases of West Nile fever (WNF).3 WNV infection was diagnostically confirmed in 62 ill persons, 59 of whom were hospitalized with neurologic disease and seven of whom died.2 Although human cases were documented only in the New York City area, avian and equine mortality from WNV was noted over a much wider area including Connecticut, New Jersey, New York, and Maryland (Fig. 1).

ORIGIN OF WEST NILE VIRUS IN NORTH AMERICA

WNV was first isolated from the blood of a febrile woman in the West Nile district of Uganda in 1937. The virus was recognized as the cause of usually self-resolving illness
in humans and animals in Africa, Asia, Australia, Europe, and the Middle East.\(^4\) Sporadic cases of encephalitis and occasional small outbreaks were reported, but epidemics of neuroinvasive disease during the 1990s in Algeria, Romania, Tunisia, and Russia suggested a new epidemiologic pattern of outbreaks of unusual severity.\(^5\) Viral genetic analysis indicated that these outbreaks were caused by closely related new genetic variants of apparently increased pathogenicity.\(^6\) A substantial human epidemic with concomitant avian mortality struck Israel in 2000.\(^7\) The Israel outbreak was unusual in that avian mortality from WNV was previously rare. The virus strain implicated in the Israel outbreak and avian epizootic was closely related to the recent outbreak strains but contained an additional mutation in the NS3 helicase gene, which greatly increased the virus’ avian mortality.\(^8\)

The means of importation of WNV to the New York City area is unknown; however, the virus was most likely introduced by an infected mosquito or bird, because humans and horses develop insufficient viremia to efficiently infect mosquitoes. The genetic sequences of WNV isolates obtained from ill patients and a dead flamingo in New York were closely homologous to sequences from a patient who died from WNV in Tel Aviv in 1999 and from a dead goose found in Israel following an epizootic in 1998, indicating that the New York strain probably originated from the Middle East or Eastern Europe.\(^4,9,10\)

**GEOGRAPHIC SPREAD IN NORTH AMERICA**

Following the New York City epidemic, the Centers for Disease Control and Prevention (CDC) in conjunction with local and state health departments established an intensive monitoring program (ArboNet) to document the virus’ geographic spread and focus local prevention efforts.\(^11–13\) The unusual avian mortality produced by the North American WNV strain provided an unprecedented opportunity to monitor the spread of an exotic arbovirus in its natural hosts.

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**Fig. 1.** WNV in the United States, 1999–2007. The incidence of human neuroinvasive disease is indicated by county.
Both bird migration and random bird dispersion are likely to have spread WNV across North America. The clearest indication of the role of bird migration occurred in 2000 when dead bird surveillance indicated northward viral spread to New Hampshire and Vermont in the spring and southward spread to North Carolina in the fall (Fig. 1); however, the virus’ rapid westward dispersion to Lake Erie in 2000 and to California and Washington State by 2002 is more difficult to explain simply based on bird migration.

Despite marked geographic expansion of WNV epizootic activity in 2000 and 2001, human disease incidence remained low until 2002 when an epidemic concentrated in the mid-West, Gulf region, and Great Plains caused over 2900 cases of neuroinvasive disease resulting in at least 280 deaths (Fig. 1) (Table 1). A similarly large epidemic occurred in the western plains and Rocky Mountain States the following year. From 2004 through 2007, continued intense transmission occurred in the western plains and Rocky Mountain states, as well as in Arizona, California, Louisiana, and Mississippi (Figs. 1 and 2). The higher incidence of WNV disease in the western United States probably results from the prominence of *Culex tarsalis* as a highly efficient WNV vector mosquito in these areas. Serological surveys in North America indicate that fewer than 10% of residents of outbreak areas become infected, but in some western regions, convenience samples have found prevalence of WNV-specific antibody as high as 20%. Through 2007, more than 11,000 cases of WNV neuroinvasive disease (WNND) and more than 1000 deaths from WNV had been reported in the United States (CDC, unpublished data) (Table 1). Based on an estimated ratio of 140 WNV infections for every case of WNND and assuming that WNF develops in 20% of infected people, WNV has infected more than 1.5 million people and caused more than 300,000 cases of WNF in the United States from 1999 through 2007 (Fig. 3). Within the United States, WNV transmission has been documented in all of the continental states and Puerto Rico, and cases of human disease have been reported from all states except Maine, Alaska, and Hawaii (see Fig. 1). The persistence of WNV transmission in eastern states 9 years after it was first detected suggests that WNV will remain endemic in most of the continental United States for the foreseeable future.

Analysis of WNV isolates in the United States indicates slowly evolving genetic divergence in different geographic regions, suggesting the absence of strong selective pressure. west Nile virus in the Americas

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<th>Year</th>
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*Abbreviation: Culex tarsalis West Nile Virus neuroinvasive disease.*

* Other clinical syndrome or syndrome unspecified.
Nevertheless, a distinct genetic variant emerged in 2001 (WN02 strain), which subsequently displaced the original New York 1999 strain by 2004. When compared with the 1999 virus, this newly emergent genotype is transmitted earlier and more efficiently in *Culex* mosquitoes. Genetic analysis suggests that all contemporary circulating viruses derive from the WN02 strain.


Fig. 2. Cumulative incidence of WNND in humans by county, 2002–2007.

Fig. 3. Human infections with WNV in the United States, 1999–2007. The actual number of reported infections represents a small fraction of the estimated number of infections because national surveillance focuses on complete reporting of only neuroinvasive disease cases. The estimated number of infections is based on a ratio of 1:140 for neuroinvasive disease cases to total infections. Approximately 20% of infections results in WNF.
By 2001, WNV had spread south to islands in the Caribbean Sea, probably carried by migrating birds late in 2000. By 2002, WNV had infected horses and chickens on Guadeloupe, birds in the Dominican Republic, and horses in Mexico. By 2003, WNV had spread to El Salvador, Guatemala, Belize, Cuba, Puerto Rico, and the Bahamas, and by 2004 to Haiti, Trinidad, Colombia, and Venezuela. By early 2005, WNV had infected birds in Argentina. Surprisingly little human WNV disease has been reported in Latin America and the Caribbean, with only isolated instances of human illness reported from Mexico, Cuba, Haiti, the Bahamas, and Argentina. Several hypotheses may explain the lack of epidemics south of the United States: (1) the spread of WNV through migrating birds might select for attenuated viral strains if more virulent strains impair bird migration; (2) previous flavivirus infection such as dengue virus might provide some cross-protection against severe WNV disease; (3) ecologic conditions in tropical regions might select for less virulent virus strains; and (4) insensitive surveillance and nonspecific laboratory tests could impair the detection of WNV disease. Another possibility is that continuous avian host availability for ornithophilic mosquitoes in tropical areas might decrease the likelihood that infected mosquitoes would feed on humans. Whether any of these hypotheses, either singly or in combination, explains the low incidence of reported WNV disease in Latin America awaits further research. Epidemics of related flaviviruses, such as the Japanese encephalitis and St. Louis encephalitis viruses (SLEV), also have been less common in the tropical reaches of their distributions. Evidence of attenuation was found in a WNV isolate obtained from a dead raven in Mexico, but eight other isolates from Mexico did not show the attenuating feature, and an experiment with thrush and catbirds suggested that WNV infection would not impair their migration. Although previous flavivirus infection does not protect against heterotypic flavivirus infection, it might modulate disease severity. The possibility that dengue virus infection, which is widespread in the American tropics, or infection with yellow fever, SLEV, Ilheus, Roccio, or other more rarely circulating flaviviruses might protect against severe WNV illness deserves further investigation. Monitoring WNV transmission in the United States and Canada has required considerable investment in sophisticated laboratory diagnostics and surveillance. Because most Latin American and Caribbean nations do not have such systems, WNV disease might not be detected or may be misdiagnosed as dengue or another infectious disease. Intensive WNV surveillance in Guatemala yielded evidence of WNV transmission to birds and horses but conclusively has not yet detected WNND in humans (E. Dueger and N. Komar, personal communication, CDC unpublished data, 2008). In Puerto Rico, ecologic surveillance identified WNV transmission throughout the island, and three viremic blood donors were identified through routine WNV screening. The virus’ genetic sequence was identical to strains circulating in the continental United States, yet an intensive effort failed to find WNND in humans.

**MOSQUITO-BORNE TRANSMISSION**

WNV is transmitted to humans through the bite of infected mosquitoes that acquire the virus after feeding on vertebrate amplifying hosts, usually birds. In the United States, the principal mosquito vectors are *Culex tarsalis, C quinquefasciatus, C pipiens, C restuans*, and *C nigripalpus*; other species may contribute to localized foci of
transmission. Birds, particularly corvids (crows, magpies, and jays), house sparrows, house finches, and grackles, appear to be highly competent reservoirs for WNV. Humans and horses generally develop insufficient WNV titers in the blood to infect mosquitoes, but squirrels, chipmunks, and rabbits may develop sufficiently high viremia to infect mosquitoes, raising the possibility that small mammals might contribute to WNV transmission cycles.4,14,41,42 Alligators may also serve as competent reservoirs in the southeastern United States.43

In temperate climates, the virus overwinters in hibernating (diapause) adult female Culex mosquitoes, probably in some birds and possibly in rodents.41,44,45 In springtime, overwintering mosquitoes emerge and bite birds, which initiates a mosquito-bird-mosquito amplification cycle that persists until fall when female mosquitoes enter diapause and stop biting. The intensity of WNV transmission to humans depends on the abundance and feeding behavior of infected mosquitoes and on local ecologic determinants of human exposure to mosquitoes. Departure of avian hosts at the end of nesting season in temperate climates leads to shifts in mosquito feeding toward mammals.46

Ambient temperature influences the abundance of vector mosquitoes, the extrinsic incubation period of viral replication in mosquitoes (duration from virus acquisition to when the mosquito is capable of transmitting the virus during subsequent blood meals), the ability of an infected mosquito to transmit infection (vector competence), and patterns of human behavior. Summer temperatures accelerate the enzootic amplification cycle, which increases likelihood of human exposure to infected mosquitoes. WNV disease incidence in North America increases in early summer and peaks during late summer or early fall (Fig. 4). In temperate areas of the United States, regional increases in WNV transmission have been correlated with above average temperatures, although this pattern is not as evident in southern latitudes.47,48 One study along the Front Range of the Rocky Mountains in Colorado found that C. tarsalis #Fig. 4. Number of neuroinvasive disease cases by week of symptom onset, 2002–2007.
abundance was variably correlated with the mean temperature, cooling degree days, humidity, precipitation, and snowfall.49 In the United States and Canada, the WNV incidence is highest in rural and suburban settings, presumably because of human proximity to enzootic transmission cycles and infected vector mosquitoes. In New York City, the risk of WNV disease was correlated with areas of higher vegetation.50 In Chicago and Detroit, inner suburban urban areas with moderate vegetation, housing built from 1940 to 1960, and moderate population density had higher WNV disease incidence.51 A nationwide study comparing viremic with uninfected blood donors showed that residents of rural areas were 3.4 times more likely to be infected than residents of suburban or urban locations.52 In Saskatchewan, Canada, residents of rural areas were approximately six times more likely than urban dwellers to have WNV antibodies.20 In states experiencing outbreaks, the county WNV incidence was correlated with farming activity as determined by total crop sales.53 A calculated measure of the intensity of exposure to WNV-infected mosquitoes in Illinois was highest in areas along two rivers, possibly related to the presence of wetlands and forest preserves.54

A study in Ohio found that children were more likely to spend time outdoors and were more likely to become infected with WNV, but, as reflected in national surveillance data, they were less likely than adults to develop WNND.19,55 People of lower socioeconomic status and particularly those who are homeless may be at higher risk of WNV infection.56,57

NON-MOSQUITO TRANSMISSION

WNV can also be transmitted through blood transfusions, transplanted organs, and from mother to fetus transplacentally.58–60 WNV transmission has also been reported through percutaneous exposure and inhalation in laboratories, conjunctival exposure while handling dead birds, in a dialysis center by unidentified means, and at a turkey farm, possibly by aerosol.61–65 Transmission via breast milk has also been reported but appears to be rare.66

Transfusion-associated WNV transmission was first detected during the 2002 WNV epidemic in the United States when 23 transfusion recipients were infected through receipt of platelets, red blood cells, or fresh frozen plasma from 16 viremic blood donors.59 Mathematical models indicated that the risk of transfusion-associated WNV transmission during the 2002 epidemic ranged from 2.1 to 4.7 cases per 10,000 donors in high incidence states.67 Since 2003, the United States and Canadian blood supplies have been screened using WNV nucleic acid amplification (NAT) tests. Blood centers conduct NAT testing on minipools of 6 to 16 specimens depending on test kit manufacturer. From 2003 through 2007, WNV NAT screening identified approximately 2000 NAT-positive blood donors, with as many as 1 in 150 donors being positive in some outbreak areas,68 however, many NAT-positive donations also have WNV-specific IgM antibody, which seems to confer a much lower transfusion transmission risk, because all but 1 of 32 documented transfusion transmissions to date occurred from donors lacking WNV IgM antibody.59,69 Universal pooled blood donation screening has not eliminated WNV transfusion transmission. Through 2007, nine “breakthrough” transmissions have occurred from donations without WNV IgM antibody and with virus levels below the limit of detection by minipool screening.69,70 To minimize the risk of breakthrough transmissions, blood centers switch to individual donation testing in areas experiencing outbreaks.

In 2002, transmission via donated organs was first documented when WNV infection developed in four recipients of organs from a common donor.60 Serum from the day of
organ harvest was positive for WNV by NAT and culture. A second transmission occurred in 2005 in which WNV infection developed in three of four organ recipients.71 Serum from the day of organ harvest was positive for WNV-specific IgG and IgM antibodies but was negative for WNV RNA, suggesting that transmission can occur from virus sequestered in organs in the absence of detectable viremia in serum.

Intrauterine transmission of WNV was first documented in 2002 when a woman who had WNV encephalitis (WNE) during the 27th week of pregnancy delivered a term infant with chorioretinitis, cerebral lesions, and laboratory evidence of congenitally acquired WNV infection.72 A follow-up study of 77 women infected with WNV during pregnancy found that 71 women delivered 72 live infants, and most of these infants were born healthy.58 Congenital WNV infection could not be proven in any of the infants, but three infants had evidence of WNV infection that could have been congenitally acquired. One had WNV meningitis at 10 days of age, one had a neonatal rash and was positive for anti-WNV IgM at 1 month of age, and one had WNE with underlying lissencephaly detected at 17 days of age.58 A study of 549 infants born at a community hospital in Colorado whose mothers were pregnant during a WNV outbreak in the community found evidence of WNV infection in 4% of the mothers and none of the infants.17 Birth outcomes of the infants born to mothers who had evidence of WNV infection during pregnancy were similar to outcomes of infants whose mothers had no evidence of WNV infection.17

CLINICAL MANIFESTATIONS

Data from serologic surveys in North America and Europe and from blood donor screening in the United States indicate that about 70% to 80% of WNV infections are asymptomatic, 20% to 30% result in WNF, and less than 1% result in WNND.3,73 The incubation period for WNV disease ranges from 2 to 14 days but can be longer in people who are immunocompromised. Older people are more likely to develop WNND and appear less likely to develop WNF.11,73 The reported incidence of WNND is higher in males than females. In an analysis of 880 patients with WNV disease reported to the California Department of Public Health, male sex, age greater than 64 years, and a history of diabetes were risk factors for developing WNND.74 A study of 172 patients with WNV disease in Houston found that those with WNE were more likely to be older and have a history of hypertension or cardiovascular disease than patients without WNE.75 A survey of 656 patients with WNV disease in Colorado found that those with WNE were more likely to have histories of hypertension, diabetes, cancer, kidney disease, and chemotherapy.76 Patients who have received solid organ transplants appear to be about 40 times more likely to develop WNND than people who have not received transplants.77,78 In addition to apparently increasing the risk of WNND, diabetes mellitus may be a risk factor for WNV chorioretinitis.79–81 Persons homozygous for a deletion in the CCR5 gene (CCR5Δ32) were shown to be at increased risk for symptomatic infection and death from WNV.82

Symptoms and signs of WNF include fever, headache, malaise, fatigue, weakness, muscle pain, difficulty concentrating, nausea, vomiting, diarrhea, abdominal pain, and rash.83 WNND presents as WNE, meningitis, or flaccid paralysis, singly or in combination, sometimes with tremor, myoclonus, and parkinsonian features such as rigidity, postural instability, and bradykinesia.84–86 Patients with WNV meningitis tend to have nuchal rigidity, photophobia, phonophobia, and pleocytosis in the cerebrospinal fluid.86,87 WNE is characterized by an altered mental status or lethargy with or without focal neurologic signs or movement disorders.86,87 WNV paralysis often has an acute onset and is typically asymmetrical in one or more limbs, sometimes without fever or
other manifestations of WNV disease. Chorioretinitis may be frequent in patients with WNV infection, particularly those with underlying diabetes. Rare manifestations of WNV infection include hepatitis, pancreatitis, myocarditis, rhabdomyolysis, orchitis, diabetes insipidus, stiff person syndrome, and hemorrhagic fever.

Patients with WNF usually recover without severe sequelae, but many experience fatigue, weakness, and aching that can last for weeks or months. WNF is rarely fatal but can provoke hospitalization and has rarely been associated with cardiac arrhythmias and respiratory failure. WNV meningitis frequently leads to hospitalization, but the prognosis is similar to that of WNF. Severe sequelae are infrequent; however, persistent fatigue, weakness, and difficulty with concentration and memory for months after acute illness are common.

Patients with WNE are usually hospitalized and have a higher risk of severe complications than patients with WNF or WNV meningitis. The case fatality rate for WNE ranges from 12% to 20% and increases with age. Survivors often have persistent neurologic sequelae such as parkinsonism, tremors, and ataxia, although some recover completely. WNV paralysis may result in neuromuscular respiratory failure, which carries a mortality above 50%. Most people who recover from WNV paralysis have persistent weakness, but recovery of strength can occur during the first 8 months after the onset of paralysis, and even patients with severe quadriparesis can completely recover. No proven specific treatment for WNV disease exists. Patients with profound weakness following WNV paralysis may benefit from physical or occupational therapy.

PREVENTION

Prevention efforts have focused on encouraging personal protection such as wearing repellent and on reducing the abundance of vector mosquitoes. A study in Ontario found that people who practiced at least two personal protective strategies (wearing repellent, wearing protective clothing, or avoiding outdoor exposure to mosquitoes) were about half as likely to have been infected with WNV than people who did not practice at least two protective strategies. A study comparing two adjacent communities in Colorado found that the incidence of WNV disease was better correlated ecologically with the practice of personal protection strategies than with the level of local mosquito control efforts. A comparison of health risks from pesticides used to kill adult mosquitoes with the health risks from WNV infection found that the health risks of WNV infection outweighed the risks from pesticide use, suggesting that, depending on its anticipated effectiveness, appropriately managed adult mosquito control is a reasonable public health response to epidemics of WNV disease. Emergency aerial pesticide spraying is highly effective in curtailing ongoing WNV epidemics.

If WNV continues to cause epidemic disease in the Americas, a safe and effective vaccine could be the optimal prevention tool. The introduction of a vaccine against WNV for use in horses appears to have substantially reduced the incidence of equine WNV disease in the United States. Although universal vaccination against WNV is not likely to result in societal financial savings, vaccination could well be targeted toward populations and individuals at highest risk for WNND. A live chimeric vaccine using the widely used yellow fever 17-D vaccine as a backbone with insertion of the premembrane and envelope proteins of WNV has been evaluated in a phase 1 safety and immunogenicity trial in 45 humans. Adverse events were similar between vaccine and placebo recipients, and the vaccine elicited neutralizing antibody against WNV in 35 of 36 volunteers tested 12 months after vaccination. In a phase 1 safety and immunogenicity trial, a single-plasmid DNA vaccine against WNV was administered to...
15 human volunteers.\textsuperscript{101} The vaccine produced no serious adverse effects and elicited neutralizing antibody to WNV in all 12 subjects who received three doses. Several other WNV vaccines are in various stages of development.\textsuperscript{102}

FUTURE OUTLOOK

The dramatic spread of WNV across the Western Hemisphere has produced a new public health problem of substantial impact. Unlike in the Old World where outbreaks are separated by years or decades of little or no WNV activity, epidemics continue to arise each summer in North America. It remains unknown whether this pattern of recurrent outbreaks will persist. The long-standing North American experience with SLEV, a related flavivirus which uses the same vertebrate hosts and mosquito species as WNV in its amplification cycle, may be foretelling. SLEV produces focal or regional outbreaks spaced many years apart (Fig. 5); however, important biologic differences exist between WNV and SLEV. WNV produces substantially higher viremia levels in birds, which is a critical element in infecting vector mosquitoes and thereby promoting enzootic WNV transmission cycles.\textsuperscript{103,104} House finches infected with WNV were protected against developing SLEV and WNV viremia; however, finches infected with SLEV were protected against WNV mortality but still developed WNV viremia.\textsuperscript{104} Currently circulating WNV strains may be more likely than SLEV to be intensely transmitted in enzootic cycles and may even be suppressing SLEV transmission.\textsuperscript{14}

WNV outbreaks in temperate areas are more commonly reported during periods of above average summertime temperatures, and improved models of the effects of climate and weather on WNV transmission might be used to target prevention strategies.\textsuperscript{47–49} Nevertheless, it remains unclear whether long-term global increases in temperature will provoke an increased WNND incidence because of the multiple interacting effects of increased temperature on vector survival, the distribution of vectors and vertebrate amplifying hosts, and patterns of human behavior.

It also remains unknown whether the unexplained paucity of avian, equine, and human morbidity and mortality in the Western Hemisphere south of the United States

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Fig. 5. Reported number of SLEV (solid line) and WNV (dashed line) neuroinvasive disease cases by year, 1932–2007.
will persist. The scarcity of large WNV outbreaks in the tropics of the Old World sug-
gests that seasonal temperature variations affecting bird and mosquito populations
may promote outbreaks, possibly by temporal and geographic alignment of the pres-
ence of highly susceptible nesting birds with springtime mosquito population
increases. Similarly, SLEV causes few outbreaks in tropical America. It is yet to
be determined whether WNV will produce large outbreaks as it becomes established
in temperate areas of South America.

More than 100 arboviruses are known to cause human illness, many of which are not
extant in the New World. Two previously imported flaviviruses, dengue and yellow fever
viruses, remain important scourges in tropical America and at one time were consider-
able public health problems in the continental United States. After mosquito control
programs in the early twentieth century nearly eliminated these pathogens from most
countries in the Americas, public health priorities shifted and arbovirus surveillance,
prevention, and research programs withered. Meanwhile, dengue returned to most
of Latin America and the Caribbean with vengeance, partly due to importation of
more pathogenic strains from Asia. These experiences indicate that it is only a ques-
tion of time until globalization brings the next exotic arbovirus to the Americas. WNV
warns us of the unpredictable public health consequences of such an importation.

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