

West Nile Virus

Lyle R. Petersen, MD, MPH

Anthony A. Marfin, MD, MPH

Duane J. Gubler, ScD

WEST NILE VIRUS (WNV) emerged from relative obscurity in 1999 when the first incursion of the virus into North America caused an outbreak of meningoencephalitis leading to 7 deaths in the New York City area.¹ By 2002, human and veterinary surveillance documented geographic spread westward to the Pacific Coast. In the same year, WNV caused the largest arboviral meningoencephalitis outbreak ever recorded in North America.²

Virology

West Nile virus is a single-stranded RNA virus of the family Flaviviridae, genus *Flavivirus*, within the Japanese encephalitis virus antigenic complex. This complex includes several viruses associated with human encephalitis: St Louis encephalitis virus in the Americas, Japanese encephalitis virus in East Asia, and Murray Valley encephalitis virus and Kunjin virus (a subtype of WNV) in Australia.^{3,4} Two lineages of WNV exist. Only viruses belonging to lineage 1 are associated with human disease; viruses in lineage 2 consist of African isolates maintained in enzootic cycles. The WNV variant circulating in North America is from lineage 1, which is genetically nearly identical to a strain previously circulating in Israel, suggesting Middle Eastern origin.^{3,4} How WNV was imported to North America

is unknown. The virus has undergone little genetic evolution since its initial isolation in 1999.⁴

Ecology

The virus is maintained in a bird-mosquito-bird cycle, with passerine birds serving as the primary amplifying hosts. In temperate regions, this cycle begins in spring when mosquitoes first emerge and lasts until early fall when female mosquitoes enter diapause (physiologic dormancy) and infrequently bite. As with St Louis encephalitis virus, mosquitoes from the genus *Culex* are the principal maintenance and amplifying vectors.^{2,4} When significant amplification within the passerine-*Culex* cycle occurs, other mosquitoes that act as bridge vectors that bite both humans and birds may become infected by mid to late summer. Although many of the 37 North American mosquito species shown to harbor WNV as of spring 2003 have been reported to infrequently bite humans,² it is unclear whether most human infections have resulted from bites of the primarily ornithophilic *Culex* species or from bites of potential bridge vectors (eg, *Aedes* and *Ochlerotatus* species).^{3,4}

Significant avian mortality from WNV has been reported only in the United States, Canada, and Israel.^{3,4} As of spring 2003, avian mortality has been documented in 162 native and captive species in North America. Mortality varies by species, but approaches 100% among laboratory-infected American crows (*Corvus brachyrhynchos*).⁵ Certain common bird species, such as house sparrows (*Passer domesticus*), are frequently infected during epizootics, develop high-level viremia for several days, and thus are likely to be impor-

tant amplifying hosts.⁵ Humans and horses are unlikely to be important amplifying hosts since viremia in these organisms is short lived and low grade.^{3,4,6}

West Nile virus can be isolated from the feces and oral secretions of birds, and bird-to-bird transmission can occur in the laboratory.⁵ Although birds can become infected following ingestion of infected mosquitoes, birds, and rodents, the importance of oral transmission in nature is unknown.

Epidemiology

West Nile virus was first isolated in 1937 from a resident of the West Nile district of Uganda.⁴ West Nile virus is distributed extensively throughout Africa, the Middle East, parts of Europe, western Russia, southwestern Asia, and Australia (Kunjin virus subtype).^{3,4} From 1937 to the early 1990s, human outbreaks, mainly associated with mild febrile illnesses, were reported infrequently in Israel and Africa.^{3,4} However, recent outbreaks in Romania (1996),⁷ Russia (1999),⁸ Israel (2000),^{9,10} and the United States and Canada (2002)^{2,11} have involved hundreds to thousands of humans causing severe neurologic disease and have coincided with emergence of new, closely related WNV strains.^{3,4}

Despite the known rapid geographic expansion of the virus in the United States (FIGURE), reported cases

See also p 511 and Patient Page.

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Author Affiliations: Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, US Public Health Service, Department of Health and Human Services, Fort Collins, Colo.

Corresponding Author and Reprints: Lyle R. Petersen, MD, MPH, Division of Vector-Borne Infectious Diseases, PO Box 2087, Foothills Campus, Fort Collins, CO 80522 (e-mail: LRPetersen@CDC.GOV).

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were infrequent (62 cases in 1999, 21 in 2000, 66 in 2001) until a large outbreak, mostly occurring in the Ohio and Mississippi River basins, resulted in more than 4000 reported cases in 2002.² The geographic distribution of cases during 2002 was strikingly similar to that of a large outbreak of St Louis encephalitis virus in 1975.¹² In Canada, WNV was first detected in birds in Ontario in 2001; in 2002, its epizootic activity extended to 5 provinces, with approximately 400 human cases in Ontario and Quebec.¹¹ Coincident with the peak transmission within the bird-mosquito-bird cycle, approximately 85% of human infections occur in August and September; however, human illness has been reported in the United States from May to December.²⁻⁴

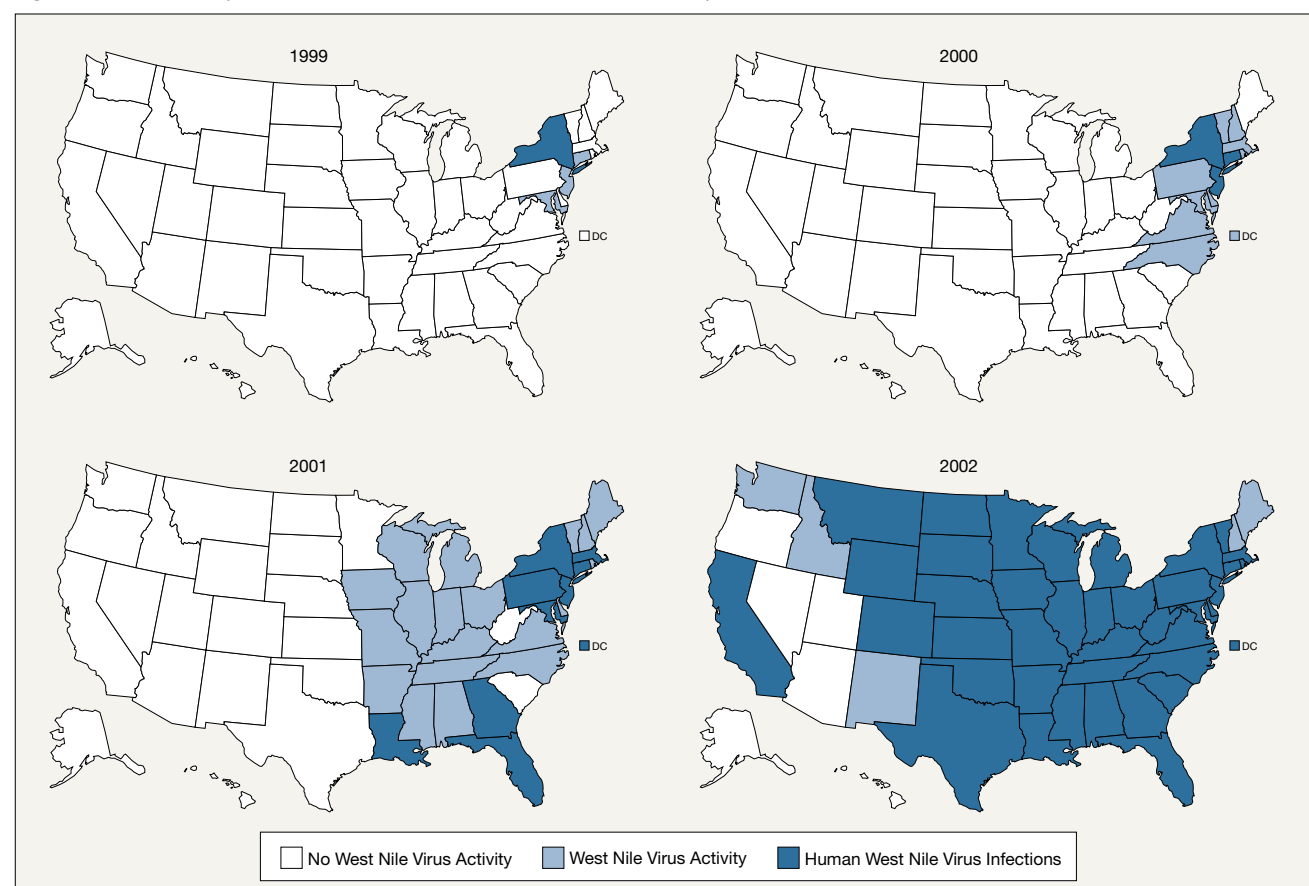
Transmission to Humans

Nearly all human infections with WNV have resulted from mosquito bites; however, several novel modalities of transmission were recognized in 2002. For example, a pregnant woman was infected with WNV while in her second trimester, which was followed by transplacental transmission to the fetus.¹³ The infant, delivered at term, had chorioretinitis, severe neurologic impairment, and serum IgM antibody, and cerebrospinal fluid (CSF) positive for WNV. Three infants, whose mothers acquired WNV during pregnancy, were not infected (Daniel O'Leary, DVM, oral communication, 2003, US Centers for Disease Control and Prevention [CDC]). Probable transmission via breast milk had occurred when a lac-

tating mother acquired WNV through blood transfusion.¹⁴ West Nile virus RNA was detected in her breast milk. Her infant remained asymptomatic but developed IgM antibodies to WNV. West Nile virus is a known but uncommon occupational hazard for laboratory workers; 2 such infections acquired via percutaneous inoculation were reported in 2002.¹⁵

West Nile virus was transmitted to 4 recipients of organs from a single donor who had been infected from a blood transfusion contaminated with WNV 1 day before organ recovery.¹⁶ Subsequently, WNV transmission was documented in 23 recipients of transfused platelets, red blood cells, or fresh frozen plasma (Lisa Pealer, PhD, written communication, 2003, CDC). The risk

Figure. States With Reported West Nile Virus Activity From 1999-2002, Reported as of May 2003



In 2002, California reported only a single human case. All other states that reported human disease cases also reported West Nile virus infections in birds, horses, or mosquitoes.

of blood-borne transmission was estimated to be as high as 21 per 10 000 donations in some cities at the peak of the 2002 epidemic.¹⁷

Clinical Illness

Most individuals infected with WNV remain asymptomatic. Serologic survey data indicate that the rates of WNV infection are similar by age; however, the frequency and severity of clinical illness increases as age increases.^{1,7,18} When clinical illness occurs, the incubation period generally ranges from 2 to 14 days,^{3,4} but prolonged incubation periods of up to 21 days have been observed among patients following organ transplantation.¹⁶

West Nile fever is a mild illness, typically lasting 3 to 6 days. Symptoms are of sudden onset and often include malaise, anorexia, nausea, vomiting, eye pain, headache, myalgia, and rash.^{3,4,19,20,21} Upper respiratory tract symptoms including rhinorrhea, cough, and sore throat may occur, but a cause-and-effect relationship has not been proven.^{15,18,19,20} Lymphadenopathy and the erythematous macular, papular, or morbilliform eruption that can involve the entire body were common symptoms in earlier outbreaks, but are now less frequently reported.^{1,3,4,19} The proportion of infected patients developing West Nile fever has not been determined precisely. A household-based, serologic survey in New York City suggested that approximately 20% of infected individuals develop West Nile fever.¹⁸ Among patients seeking treatment at hospitals and clinics in Czechland, approximately 40% of patients with serologic evidence of WNV infection also had West Nile fever.²²

Despite the increased clinical severity during recent outbreaks, less than 1% of individuals infected with WNV developed severe neurologic disease (eg, encephalitis, meningitis, or acute flaccid paralysis [AFP]).^{7,18,21} In recent outbreaks, encephalitis-meningoencephalitis was reported more commonly than meningitis alone.^{1,7,10} More than 90% of patients with severe neurologic disease have had fever, often accompanied by

severe weakness, gastrointestinal tract symptoms, and headache.^{1,7,23,24} Movement disorders may occur, such as tremor, myoclonus, and parkinsonian features including rigidity, postural instability, and bradykinesia.^{6,23-25}

Weakness from AFP is asymmetric, affects the upper and lower limbs, and can occur without overt meningoencephalitis.²³⁻³² In addition to weakness, most WNV-associated AFP is characterized by hypoflexia or areflexia, acute bowel or bladder dysfunction, and absence of pain or acute sensory abnormalities; results of CSF samples are often characterized by an elevation of protein levels and pleocytosis. Although initial reports attributed AFP to Guillain-Barré syndrome,^{26,27} recent evidence suggests that most WNV-associated AFP is caused by the destruction of the spinal anterior horn cells, resulting in a poliomyelitis-like syndrome.^{24,25,28-32} Axonal and demyelinating neuropathy also has been described.²⁴

Descriptions of other neurologic manifestations associated with WNV infection include cranial nerve abnormalities,^{24,25} optic neuritis,³³ and seizures.²⁴ Several ocular manifestations, including multifocal choroiditis,³⁴ vitritis,³⁵ and chorioretinitis,^{13,35} as well as myocarditis, pancreatitis, and fulminant hepatitis also have been described.³

Clinical Outcome

Case-fatality rates ranged from 4% to 18% among patients hospitalized during recent outbreaks.^{1,7,10,24} During the outbreak in the United States in 2002, patients with meningoencephalitis had a case-fatality rate of 9%. Advanced age is the most important risk factor for death. Among persons older than 70 years, case-fatality rates were 15% and 29% among hospitalized patients in Romania⁷ and Israel,¹⁰ respectively, and 21% among those with meningoencephalitis in the United States in 2002 (Daniel O'Leary, DVM, oral communication, 2003, CDC). Encephalitis with severe muscle weakness, change in the level of consciousness, and history of diabetes and immunosuppression are

possible risk factors for death and poor neurologic outcome.^{1,10,16}

Substantial morbidity may follow hospitalization for WNV. At discharge, fewer than half of patients hospitalized in New York and New Jersey in 2000 had returned to their previous functional level, and only one third were fully ambulatory.⁴ Only 28% of surviving Canadian patients in one series were discharged home without assistance and most had persistent neurologic deficits 30 days after discharge.²⁴ In Louisiana, 8 months after patients were hospitalized for WNV, parkinsonism, tremor, and gait or balance abnormalities remained common neurologic findings.²⁵ Of interest, severe initial encephalopathy did not necessarily portend poor outcome.²⁵ Patients who were followed 1 year after infection during the 1999 outbreak in New York City were reported to have frequent persistent symptoms, such as fatigue, memory loss, and difficulty walking.³⁶ Patients with AFP due to the poliomyelitis-like syndrome have shown to have very limited recovery.^{25,30}

Pathogenesis

Following a mosquito bite, the initial viral replication is thought to occur in the skin and regional lymph nodes and produces a primary viremia that seeds the reticuloendothelial system.³⁷ A secondary viremia then occurs which may seed other organs and the central nervous system (CNS).³ In otherwise healthy individuals, WNV can be isolated from serum samples several days before illness onset, but viremia rapidly disappears after symptom onset along with concomitant development of IgM, IgG, and neutralizing antibodies.^{3,4} Viremia can occur without subsequent illness.¹⁷ Individuals who are immunocompromised may develop prolonged periods of viremia, which have been documented to continue up to 31 days after infection with WNV, and may have delayed development of IgM antibody and symptoms.^{6,16}

The pathogenesis of severe infection with WNV is poorly understood, but the pronounced risk of neurologic infec-

tion and death in elderly individuals suggests a role for age-related factors such as immune senescence or changes to the blood-brain barrier. Studies in mice indicate a critical role of the early antibody response in containing viral replication and limiting the dissemination of WNV in the CNS.³⁸ Three of 4 patients who were infected with WNV via transplanted organs developed meningoencephalitis, indicating that administration of immunosuppressive drugs may place patients at very high risk for CNS disease.¹⁶ Recipients of blood transfusions contaminated with WNV appeared to be more likely to develop severe neurologic disease if they had underlying hematologic or advanced solid-organ malignancies or had undergone previous organ, stem cell, or bone marrow transplantation (Lisa Pealer, PhD, written communication, 2003, CDC). Studies in mice have indicated that WNV strains differ in severity of neurovirulence.³⁹

Pathological observations in cases of fatal encephalitis showed scattered microglial nodules and perivascular inflammatory infiltrates.^{24,40} Involvement of the basal ganglia, thalamus, and pons may account for the clinical findings of tremor and parkinsonism.²⁵ Pathological findings in 1 case of AFP included focal loss of anterior horn neurons, with gliosis, occasional presence of macrophages, neuronophagia, and perivascular lymphocytes.³²

Diagnosis

Results from peripheral blood samples show that total leukocyte counts are mostly normal or elevated.^{3,4,25} Examination of CSF samples of patients with meningoencephalitis or AFP show pleocytosis usually with a predominance of lymphocytes and elevated protein levels.^{3,4,24,25} Computed tomographic findings of the brain typically show no evidence of acute disease.^{1,3,4,10,24,25} Findings from magnetic resonance imaging scans are normal in most patients, but can show focal lesions in the pons, basal ganglia, and thalamus, and enhancement of the leptomeninges, the periventricular areas, or both.^{3,25}

The diagnosis of WNV infection in most clinical settings should be made using serologic methods, particularly by detection of IgM antibody in serum or CSF samples using the IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA).^{3,4} Since IgM antibody does not cross the blood-brain barrier, its presence in CSF indicates infection of the CNS; at least 90% of patients with meningoencephalitis have demonstrable IgM antibody in CSF samples within 8 days of symptom onset.³⁶ The MAC-ELISA testing of sera or CSF can be obtained through local and state health departments. Prompt reporting of cases of WNV infection will facilitate activities of local public health control services.

Individuals recently vaccinated for yellow fever virus or Japanese encephalitis virus or individuals recently infected with a related flavivirus (eg, St Louis encephalitis virus or dengue virus) may have a positive WNV IgM antibody test result.^{3,4} The plaque-reduction neutralization test can help distinguish false-positive results of MAC-ELISA or other assays as well as to help to distinguish serologic cross-reactions among the flaviviruses. IgM antibody may persist in serum for longer than 500 days; therefore, persistent IgM antibody from a previous infection may be unrelated to the current illness.⁴¹ A 4-fold or higher increase in WNV-specific neutralizing antibody titer in acute- and convalescent-phase serum samples is considered confirmatory of acute infection.⁴

Although the low sensitivities of viral isolation, nucleic acid amplification, or antigen detection assays preclude their use for routine clinical diagnosis, nucleic acid amplification tests will be introduced for blood donor screening in 2003. These tests also may prove useful in immunocompromised patients when antibody development is delayed or absent.^{16,24}

Treatment and Prevention

Treatment of WNV infection is supportive. No controlled studies to date have assessed the efficacy of ribavirin,

interferon, gamma globulin, steroids, antiseizure medications, or osmotic agents in the treatment of WNV encephalitis. An inactivated WNV vaccine is available for horses, but human vaccines are unlikely to be available for several years. Personal protection to avoid mosquito exposure, including using repellants containing diethyltoluamide or permethrin, is a mainstay of prevention.^{3,4} Draining standing water where mosquitoes are likely to breed and instituting community mosquito control programs are recommended.

Future Perspective

In North America, WNV and St Louis encephalitis virus share similar avian hosts and amplifying mosquito species.^{3,5} These ecologic similarities suggest that the 2 viruses may share a common epidemiologic pattern. The wide distributions of WNV in Asia and Africa^{3,4} and St Louis encephalitis virus in North and South America¹² suggest that WNV will spread widely in the Americas. In the United States, St Louis encephalitis virus produces sporadic cases of infection as well as local and regional outbreaks that are difficult to predict, resulting in highly variable annual incidence rates ranging from a handful of cases to nearly 2000 cases that occurred during the 1975 epidemic.^{3,12} However, WNV produces extremely high-level viremia in common bird species,⁵ many mosquito species harbor WNV,² and human infections continue to occur in subsequent years after its introduction in an area. These facts suggest that WNV has greater epidemic potential than St Louis encephalitis virus and is likely to challenge clinicians and public health officials for years to come.

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All true knowledge contradicts common sense.
—Mandell Creighton (1843-1901)