West Nile Virus has become endemic in all 48 contiguous United States as well as all Canadian provinces since its discovery in North America in New York City in 1999.1 It has produced the 3 largest arboviral neuroinvasive disease outbreaks ever recorded in the United States, with nearly 3000 cases of neuroinvasive disease recorded each year in 2002, 2003, and 2012.

Evidence Review

This review is intended to provide a general overview of West Nile virus to the practicing physician or public health practitioner. Relevant background information was obtained by searching the PubMed electronic database through February 5, 2013, using the search term West Nile virus. Surveillance data from patients with disease onset from 1999 through 2012 and reported by May 15, 2013, were gathered from the national ArboNET surveillance system conducted by the Centers for Disease Control and Prevention.
ciently infect mosquitoes feeding upon them and thus are competent amplifier hosts. A relatively small subset of the bird community may significantly influence transmission dynamics and certain passerine species such as the American robin (Turdus migratorius) are important amplifiers despite their low abundance relative to other West Nile virus–susceptible birds. Humans are unlikely to infect mosquitoes because they only develop a low-level serum viremia and thus are considered dead-end hosts.

When conditions favor substantial viral amplification within the passerine–Culex transmission cycle, increasing numbers of infected mosquitoes present a human infection risk by mid to late summer. The complex and interrelated factors that promote viral amplification and hence human outbreaks are not well quantified and vary among the diverse ecological conditions present in North America. Warmer temperatures correlate with increased human incidence at national or regional (multistate) scales. Increased ambient temperature shortens the incubation time from infection to infectiousness in mosquitoes and increases viral transmission efficiency to birds, both critical factors for arboviral amplification. At smaller scales, urban and agricultural land covers, rural irrigated landscapes, increased temperature, increased rainfall, decreased rainfall, and several socioeconomic factors such as housing age and community drainage patterns, per capita income, and density of poorly maintained swimming pools relate to higher incidence in some locations. Nevertheless, considerable challenges remain in predicting how, when, and where these factors will combine to produce the focal, intense outbreaks that now characterize West Nile virus ecology in the United States.

Virology and Pathogenesis

West Nile virus is 1 of more than 70 viruses of the family Flaviviridae of the genus Flavivirus. Serologically, West Nile virus is a member of the Japanese encephalitis serocomplex, which includes Japanese encephalitis virus and an endemic North American flavivirus, St Louis encephalitis virus. West Nile viruses can be designated into at least 5 phylogenetic lineages. Only lineage 1 and 2 West Nile viruses have been associated with significant outbreaks in humans.

Figure 1. Schematic of Pathogenesis of West Nile Virus Infection

Lineage 1 can be further subdivided into 3 sublineages: isolates from the western hemisphere, Africa, the Middle East, and Europe constitute lineage 1a; Kunjin virus from Australasia represents lineage 1b; and lineage 1c consists of viruses from India. The initial North American isolates (East Coast genotype) identified in 1999 in New York City have been most closely related to a lineage 1a West Nile virus isolated from Israel in 1998. Since approximately 2002, the East Coast genotype has largely been displaced by a new genotype (WN02 genotype) encompassing several conserved amino acid substitutions that may have increased the efficiency and rapidity of viral transmission in North American mosquito vectors.

Mosquito salivary components introduced at the site of infection in vertebrates modulate initial infection of target cells such as keratinocytes and skin-resident dendritic cells through several mechanisms including focalized suppression of immune effector cell trafficking to the site of inoculation. Infected dendritic cells or keratinocytes migrate to draining lymph nodes from which a serum viremia is generated that then relays infection to visceral organs and potentially to the central nervous system (Figure 1).

West Nile virus is capable of replicating and eliciting pathology in the brain (ie, neurovirulence); however, a critical prerequisite to generating neuroinvasive disease in humans is the virus’ capacity to gain access to the central nervous system (ie, neuroinvasiveness). Postulated West Nile virus neuroinvasive mechanisms include (1) direct viral crossing of the blood-brain barrier due to cytokine-mediated increased vascular permeability; (2) passage through the endothelium of the blood-brain barrier; (3) a Trojan horse mechanism in which infected tissue macrophages are trafficked across the blood-brain barrier; and (4) retrograde axonal transport of the virus to the central nervous system via...
infection of olfactory or peripheral neurons (Figure 2). Regard-
less of how the virus enters the central nervous system, murine
modelsofinfectionhaveshownpersistentviralreplicationinvari-
ous tissues, including the central nervous system, suggesting a
potential etiology for long-term neurological sequelae observed
in patients with neuroinvasive disease.21

Distribution and Human Disease Incidence
West Nile virus has an extensive distribution throughout Africa, the
Middle East, southern Europe, western Russia, southwestern Asia,
and Australia (Kunjin subtype of West Nile virus), which derives from
its ability to infect numerous mosquito and bird species. Until the
early 1990s, human outbreaks, mainly associated with mild febrile
illnesses, were reported infrequently from Israel and Africa. Since
then, new viral strains with likely African origin have increased hu-
mankind incidence in parts of Russia and southern and eastern
Europe, with large outbreaks of increased clinical severity occur-
ing in Romania, Russia, Israel, and Greece.15,23 In the western hemi-
sphere, West Nile virus spread from its 1999 discovery location in
New York City1 to the Pacific Coast by 200323,24 and Argentina by
2005.23 Although West Nile virus now circulates in many countries
in the western hemisphere, for unknown reasons only the United
States and Canada have experienced substantial human disease
incidence.24

Most patients with West Nile virus-related illnesses are unrec-
nogized clinically. A follow-up study of asymptomatic, viremic blood
donors who subsequently developed West Nile fever showed that
38% sought medical care and 2% were hospitalized for symptoms
attributable to the infection; however, only 5% of those seeking
medical care were correctly diagnosed.4 Thus, incidence trends are
best monitored by the incidence of neuroinvasive disease because
reporting of these cases is comparatively complete. Nevertheless,
even during a well-publicized outbreak, only 40% of patients with
clinically compatible meningitis or encephalitis were tested for West
Nile virus.25

A total of 16,196 patients with West Nile virus neuroinvasive dis-
ease with onsets from 1999 through 2012 and 1549 deaths have been
recorded in the United States. Although the number of patients with
neuroinvasive disease fluctuates annually, some regions experience
persistently higher incidence (Figure 3). Ninety-four percent of patients
with West Nile virus infection have symptom onsets in July through Sep-
tember (Figure 4).23 Extrapolations from neuroinvasive disease case
reporting in the United States suggest that through 2010 approximately
3 million persons were infected, of whom 780,000 developed West
Nile fever.26 In Canada, West Nile virus was first detected in southern
Ontario in 2001 and by 2009 the virus’ distribution had extended west-
ward to British Columbia. Through October 2012, 975 patients with
neuroinvasive disease have been reported in Canada.

Transmission to Humans
Mosquito bites account for nearly all human infections. West Nile
virus can also be transmitted via transfused platelets, red blood cells,
and fresh frozen plasma5 as well as through heart, liver, lung, and
kidney transplants.27 Transmission via organ transplant has oc-
curred from donors without detectable viremia, suggesting viral se-
questration in organs shortly after viremia has cleared.

One possible transplacental transmission following a second tri-
mester infection resulted in an infant with chorioretinitis, lissen-
cephaly, and cerebral white matter loss. Fortunately, fetal abnor-
malities due to intrauterine infection are uncommon: none of 72 live
infants born to 71 women infected during pregnancy had malfor-
mations linked to West Nile viral infection or had conclusive labo-
atory evidence of congenital infection.28 Nevertheless, 3 neo-

Figure 2. Potential mechanisms for neuroinvasion of West Nile virus include:
(1) direct infection of the vascular endothelium and subsequent entry to the central
nervous system, (2) viral passage through the vascular endothelium due to disruption of
the blood-brain barrier integrity by vasoactive cytokines, (3) a Trojan horse mechanism
through which infected monocytes are trafficked into the central nervous system, or
(4) retrograde axonal transport to the central nervous system following
infection of peripheral neurons.
Infection and Illness

It is not known what proportion of persons develop West Nile virus infection following an infected mosquito bite. Persons with a genetic defect in the OAS1 gene (HGNC:8086), which modulates host response to exogenous viral RNA, are more likely to have anti-West Nile virus antibodies than persons without this defect, suggesting that immune response function determines who becomes infected after exposure. Among persons who become infected, approximately 25% develop West Nile fever and 1 in 150 to 250 develops neuroinvasive disease. Risk factors for developing West Nile fever following infection are poorly defined. A follow-up study of asymptomatic, viremic blood donors indicated that increasing viral load and female sex, but not age, subsequently increased the risk of developing West Nile fever. A smaller follow-up study of viremic blood donors suggested that younger persons were more likely to develop West Nile fever. In contrast, advancing age profoundly increases the risk of neuroinvasive disease, particularly encephalitis. The risk may approach 1 in 50 among persons aged at least 65 years, a rate 16 times higher than that for persons aged 16 to 24 years. In addition, a history of cancer, diabetes, hypertension, alcohol abuse, renal disease, and chemokine receptor CCR5 deficiency as well as male sex may increase the risk of neuroinvasive disease. Persons infected through transplant of infected organs are at extreme risk of developing neuroinvasive disease; however, conflicting data exist regarding risk among previous organ recipients infected via mosquito bite.
Clinical Illness

The incubation period for clinical illness generally ranges from 2 to 14 days, but prolonged incubation periods of up to 21 days have been observed among immunocompromised patients. West Nile fever can range from a mild infirmity lasting a few days to a debilitating illness lasting weeks to months. Symptoms are of sudden onset and often include headache, malaise, fever, myalgia, chills, vomiting, rash, fatigue, and eye pain (Box 1). Fever may be low-grade or absent. A rash, which often appears around the time of defervescence, tends to be morbilliform, maculopapular, and nonpruritic, and predominates over the torso and extremities, sparing the palms and soles.

West Nile meningitis, similar to that of other viral meningitides, is characterized by abrupt onset of fever and headache along with meningeal signs and photophobia. Headache may be severe, and associated gastrointestinal disturbance may result in dehydration (Box 2). West Nile encephalitis ranges in severity from a mild, self-limited confusional state to severe encephalopathy, coma, and death. Extrapyramidal disorders are frequently observed, and features of Parkinsonism may be seen. Patients with West Nile encephalitis frequently develop a coarse tremor, particularly in the upper extremities. The tremor tends to be postural and may have a kinetic component. Myoclonus, predominantly of the upper extremities and facial muscles, may occur and may be present during sleep. Cerebellar ataxia, increased intracranial pressure, cerebral edema, and seizures have been described but are uncommon.

West Nile virus-associated paralysis most commonly results from destruction of the anterior horn cells of the spinal cord. Asymmetric weakness usually develops rapidly within the first 48 hours after symptom onset, although patients with extensive spinal cord involvement develop a more symmetric dense quadriplegia. Central facial weakness, frequently bilateral, may occur. Respiratory failure requiring emergent endotracheal intubation may result from diaphragmatic and intercostal muscle paralysis. Sensory loss or numbness is generally absent though some patients experience intense pain in the affected limbs just before or during the onset of weakness. Other causes of weakness associated with West Nile virus infection include Guillain-Barré syndrome and other demyelinating neuropathies, motor axonopathy, axonal polyneuropathy, involvement of ventral spinal roots, myasthenia gravis, and brachial plexopathies.

Other manifestations described in the setting of West Nile virus infection include multifocal choroiditis, vitritis, myocarditis, pancreatitis, fulminant hepatitis, rhabdomyolysis, stiff-person syndrome, and autonomic instability.

Clinical Outcome

Full recovery is the norm for patients with uncomplicated West Nile fever or meningitis; however, initial symptoms, particularly extreme fatigue, may be prolonged. West Nile fever may precipitate death among persons of advanced age or with underlying medical conditions. Outcomes of West Nile encephalitis are variable and may not correlate with severity of initial illness. Patients hospitalized with West Nile virus encephalitis frequently require assistance with daily activities following acute care discharge and often report substantial functional and cognitive difficulties for up to a year following acute infection. Only 37% of patients in the 1999 New York City outbreak achieved full recovery at 1 year and 53% of patients.

Box 1. Characteristics of West Nile Fever

| Abrupt onset, usually July through September |
| Occurs in approximately 25% of those infected by mosquito bite |
| All ages affected, but no strong age predilection |
| Symptoms present in more than 50% of patients |
| Headache, generalized weakness, morbilliform or maculopapular rash (often at time of defervescence), fever (often low grade), myalgia |
| Less common symptoms: |
| Joint pain, chills, painful eyes, vomiting or diarrhea, lymphadenopathy |
| Diagnosis most readily made by detection of West Nile virus-specific IgM antibody in serum, although a convalescent-phase sample may be required because the antibody often is not present at the time of clinical presentation |
| Treatment is supportive |
| Illness duration days to weeks, generally with complete recovery, although prolonged fatigue may occur |

Box 2. Characteristics of West Nile Neuroinvasive Disease

| Abrupt onset, usually July through September |
| Occurs in less than 1% of those infected via mosquito bite |
| All ages affected, although very strong predilection with advancing age |
| Clinical Syndromes |
| Meningitis characterized by clinical signs of meningeal inflammation, including nuchal rigidity, Kernig or Brudzinski sign, or photophobia or phonophobia |
| Encephalitis characterized by depressed or altered level of consciousness, lethargy or personality change lasting more than 24 hours |
| Acute flaccid paralysis characterized by acute onset of limb weakness with marked progression over 48 hours, which is usually asymmetric, areflexic or hyporeflexic, and without sensory abnormalities |
| Five-fifths of persons with acute flaccid paralysis occur in conjunction with encephalitis or meningitis |
| May be commonly accompanied by other symptoms and signs |
| Nausea and vomiting, myalgia, chills, rash (less commonly reported than patients with West Nile fever), arthralgia, ataxia, visual disturbance, tremors, myoclonus, bulbar dysfunction (dysarthria, dysphagia) |
| Diagnosis most readily made by detection of West Nile virus-specific IgM antibody in cerebrospinal fluid or serum; in immunocompromised patients, development of IgM antibody may be delayed or absent, and nucleic acid amplification tests may be required |
| Cerebrospinal fluid generally shows normal glucose, elevated protein, pleocytosis (>5 leukocytes/μL) |
| Treatment is supportive |
| Illness duration weeks to months; long-term functional and cognitive difficulties common in patients with encephalitis, paralysis, or both |
in Idaho reported symptoms lasting at least 6 months, mostly fatigue, muscle aches, and difficulties with memory and concentration.

Although some studies have documented neurocognitive deficits on standardized testing for as long as 1 year after acute illness, others have failed to confirm this finding. Nevertheless, self-reported fatigue, somatic, and cognitive complaints lasting months or years are common among persons recovering from West Nile virus illness. Neuropsychiatric symptoms, including depression, anxiety, and apathy, have been reported.

One investigator reported West Nile virus RNA in urine in patients up to 7 years following acute illness and implied an association with chronic renal failure; however, 2 other studies failed to substantiate this finding.

Among patients with acute flaccid paralysis due to poliomylitis-like syndrome, roughly one-third recover strength to near baseline, one-third have some improvement, and one-third have little or no improvement. Little functional improvement has been documented 6 months after onset.

Case fatality rates among patients with neuroinvasive disease generally approximate 10%. Advanced age is the most important risk factor for death, ranging from 0.8% among those aged less than 40 years to 17% among those aged at least 70 years. Encephalitis with severe muscle weakness, changes in the level of consciousness, diabetes, cardiovascular disease, hepatitis C virus infection, and immunosuppression are possible risk factors for death. Patients discharged from the hospital following acute West Nile virus illness experience a 2- to 3-fold increase in long-term, all-cause mortality compared with age-adjusted population norms, although not all of this increase may be attributable to West Nile virus.

**Diagnosis**

Detection of IgM antibody in serum or cerebrospinal fluid (CSF) using the IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) forms the cornerstone of West Nile virus diagnosis in most clinical settings. Because IgM antibody does not cross the blood-brain barrier, its presence in CSF indicates CNS infection. At least 90% of patients with encephalitis or meningitis have demonstrable IgM antibodies in CSF within 8 days of symptom onset. The West Nile virus–specific IgM antibody may not be detected initially in serum or plasma; 1 study showed that only 58% of patients with West Nile fever had a positive MAC-ELISA result at clinical presentation. Nevertheless, MAC-ELISA testing of acute- and convalescent-phase sera will provide definitive diagnosis. Testing for IgG antibodies has no utility in the acute clinical diagnostic setting.

Recent vaccination with yellow fever or Japanese encephalitis vaccines or recent infection with a related flavivirus (eg, St Louis encephalitis or dengue) may produce a positive West Nile virus–IgM antibody test result. The plaque-reduction neutralization test can help distinguish serologic cross-reactions among the flaviviruses, but the test is only available in reference laboratories. In 1 study, 17% of patients had demonstrable West Nile virus–specific IgM antibodies a year after initial infection; thus, persistent IgM antibody from a previous infection may be unrelated to current illness.

Nucleic acid amplification testing has utility in certain clinical settings as an adjunct to MAC-ELISA. Among patients presenting with West Nile fever, 1 study showed that 45% of cases were identified with nucleic acid testing; 58% with serology, or 94% with a combined approach of these 2 methods. Nucleic acid amplification testing may prove useful in immunocompromised patients when antibody development is delayed or absent and its use in blood donor screening in the United States and Canada has nearly eliminated the risk of West Nile virus transfusion transmission.

Total leukocyte counts in peripheral blood typically are normal or slightly elevated. Examination of CSF of patients with neuroinvasive disease shows normal glucose, elevated protein (generally <150 mg/dL) and moderate pleocytosis (generally <500 cells/μL) usually with a predominance of lymphocytes; however, neutrophils may predominate in early infection. Imaging studies are usually normal, but focal lesions in the pons, basal ganglia, thalamus, and anterior horns and enhancement of the leptomeninges, the periventricular areas, or both are occasionally seen. These lesions may appear hyperintense on T2-weighted magnetic resonance and fluid-attenuated inversion recovery images.

**Treatment and Prevention**

Treatment of West Nile virus infection remains supportive. Several investigated therapeutic approaches include immune γ-globulin, West Nile virus–specific neutralizing monoclonal antibodies, corticosteroids, ribavirin, interferon α-2b, and antisense oligomers. Investigated therapeutic approaches include immune γ-globulin, West Nile virus–specific neutralizing monoclonal antibodies, corticosteroids, ribavirin, interferon α-2b, and antisense oligomers. Preliminary analysis suggested that universal West Nile virus vaccine coverage would not be cost-effective; however, the cost-effectiveness of vaccination of specific target groups such as elderly individuals has not yet been established. Because humans are dead-end hosts, a human vaccination program would not influence viral amplification in nature.

West Nile virus prevention relies in part on methods to reduce the numbers of West Nile virus–infected mosquitoes. Community-based mosquito control programs using integrated pest management principles proactively identify the sources of vector mosquitoes and use several methods such as elimination of breeding sites, larviciding, and targeted adult mosquito control to prevent adult mosquito populations from achieving levels that increase human infection risk.

When increasing human case incidence or surveillance of vector mosquito populations indicates an impending human epidemic, the immediate goal is to reduce rapidly the number of infected adult mosquitoes by widespread ultra-low volume application of organophosphate or synthetic pyrethroid insecticides. Organophosphates irreversibly block the enzyme acetylcholinesterase; pyrethroids open sodium channels of neuronal membranes, paralyzing the mosquito, and are usually combined with piperonyl butoxide,
preventing the mosquito’s microsomal oxidase enzymes from metabolizing pyrethroids.

Although the efficacy of these control measures is difficult to measure, strategically timed early-season control of adult mosquitoes in the Coachella Valley of California using ultra-low volume insecticide applications decreased subsequent West Nile virus transmission. In addition, aerial ultra-low volume insecticide application decreased infected mosquito abundance and reduced human-case incidence during a West Nile virus outbreak in the Sacramento area. Human health risks associated with ultra-low-volume organophosphate or synthetic pyrethroid use appear negligible, largely because the timing of application and low volume of pesticide used result in minimal human exposure.

Insect repellent use has been associated with reduced West Nile virus risk. Unfortunately, few people report regular repellent use even during well-publicized outbreaks. Commercially available insect repellents containing DEET, IR3535, oil of lemon eucalyptus, and picaridin are registered by the US Environmental Protection Agency on the basis of their excellent safety profiles and proven efficacy in reducing or preventing mosquito biting. Many other commercially available unregistered products, such as those containing citronella oil, cedar oil, geranium oil, peppermint oil, and soybean oil, have unproven efficacy.

Future Perspectives

The resurgence of West Nile virus in 2012 after several years of decreasing incidence in the United States suggests that West Nile virus will continue to produce unpredictable local and regional outbreaks. These outbreaks are associated with considerable long- and short-term morbidity from West Nile virus neuroinvasive disease and West Nile fever, respectively. Thus, sustainable, community-based surveillance and vector management programs are critical, particularly in metropolitan areas with a history of West Nile virus and large human populations at risk. Community response plans must include provisions for rapidly implementing large-scale adult mosquito control interventions when surveillance indicates such measures are necessary. Further evaluation of target populations and cost-efficacy of a vaccine will help determine the need for continued human vaccine development. Practical pathways and paradigms for testing and approval of vaccines and therapeutics adapted to the sporadic outbreak nature of West Nile virus are required. These measures will not only help address the risks associated with West Nile virus but will add to our preparedness for all domestic and exotic mosquito-borne pathogens.

ARTICLE INFORMATION

Author Contributions: Dr. Petersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition of data: All authors.

Analysis and interpretation of data: Nasci, Petersen.

Drafting of the manuscript: All authors.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdn608@northwestern.edu.

REFERENCES


