JAMA | Review

West Nile Virus
A Review

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IMPORTANCE West Nile virus (WNV), a neurotropic flavivirus spread by *Culex* species mosquitoes, is the leading cause of mosquito-borne disease in the contiguous US. From 2014 to 2023, a mean of 1300 WNV neuroinvasive disease cases and 130 deaths were reported annually in the US.

OBSERVATIONS Almost all WNV infection occurs via mosquito bites, but transmission can rarely occur via blood transfusion, organ transplantation, and transplacental, perinatal, breastmilk, percutaneous, and conjunctival exposure. Since 2018, large WNV outbreaks have been reported in Europe, Tunisia, Israel, and the US. In 2021, the largest county-level US outbreak occurred in Arizona, with 1487 disease cases and 101 deaths reported. Based on seroprevalence surveys, approximately 80% of human WNV infections are asymptomatic, 20% cause a febrile illness (West Nile fever), and less than 1% cause neuroinvasive disease (eg, meningitis, encephalitis, acute flaccid myelitis). Mortality of patients with neuroinvasive disease is approximately 10% overall but is 20% in individuals 70 years or older and 30% to 40% in patients with hematologic malignancies, solid organ transplants, and those receiving B-cell–depleting monoclonal antibodies. Among patients hospitalized for WNV disease, 30% to 40% are discharged to long-term care facilities, and more than 50% have long-term sequelae such as fatigue, weakness, myalgia, memory loss, and depression. WNV transmission during solid organ transplantation was identified in 14 clusters in the US and Italy from 2002 to 2023. Since WNV screening of the US blood supply began in 2003, 14 cases of WNV transmission through blood transfusion have been reported. For patients with fever or neurologic symptoms during summer and fall months, WNV should be considered; IgM testing of serum and/or cerebrospinal fluid is recommended, followed by confirmatory neutralizing antibody testing in cases of possible exposure to cross-reacting flaviviruses, atypical presentation or death, or suspected unusual transmission modes such as organ transplantation. Reverse transcription–polymerase chain reaction testing is often more sensitive than IgM testing in patients with severe immunocompromise. There are no evidence-based therapies or human vaccines for WNV disease. Preventive methods include personal protective behaviors, such as using Environmental Protection Agency–registered mosquito repellents, wearing protective clothing, and limiting outdoor exposure from dusk to dawn, and community mosquito control measures.

CONCLUSIONS AND RELEVANCE WNV causes approximately 1300 neuroinvasive disease cases and 130 deaths annually in the US. People who are older or immunocompromised are at higher risk of severe disease and death. Since there are no therapies or human vaccines, prevention relies on personal protective measures, WNV surveillance, and mosquito control interventions.

Multimedia

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Twenty-five years since its emergence in the US, West Nile virus (WNV) has become the leading cause of domestic mosquito-borne disease. Recent large WNV outbreaks have occurred in Europe, the US,[1] Tunisia,[2] and Israel. Despite development and expansion of vector control programs since 1999 when WNV was first detected in the US, WNV disease incidence has not decreased and remains high in the central and western regions, where local and regional outbreaks continue to occur.[1,3,4] From 2014 to 2023, a mean of 1300 WNV neuroinvasive disease cases and 130 deaths were reported annually. Milder winters, longer summers, and higher levels of precipitation can increase the distribution, propagation, and longevity of vectors, increasing the likelihood and magnitude of outbreaks.[1,4-6] However, WNV outbreaks remain difficult to predict using environmental factors such as temperature and precipitation[7,8] and can occur suddenly after years of low activity in a region.[1,4]

Aging of US and European populations and more frequent use of immunosuppressive therapies increase the risk of severe disease and death from WNV infection.[9-11] No evidence-based therapies or approved human vaccines for WNV currently exist, and long-term symptoms and disability following WNV disease occur among more than 50% of patients after hospitalization.[12] This review summarizes current evidence regarding epidemiology, diagnosis, treatment, and prevention of WNV disease.

Methods

A PubMed search was conducted using the search term *West Nile virus* from January 1, 2000, through May 9, 2025, limited to full-text and English-language publications. The search retrieved 8117 articles. We focused on the most recent articles and those from the start of the US epidemic; of those, 95 were included, consisting of 23 public health surveillance and investigation reports, 18 review articles, 11 observational studies, 11 case series/reports, 5 nonhuman studies, 5 systematic reviews, 5 blood donor studies, 4 seroprevalence surveys, 4 modeling studies, 3 clinical laboratory studies, 3 randomized clinical trials, 1 systematic review and meta-analysis, 1 case-control study, and 1 survey. Data from US patients with disease onset from 1999 through 2023 were obtained from ArboNET (the national arboviral diseases surveillance system of the US Centers for Disease Control and Prevention) and organ transplant investigations. Non-US surveillance data were obtained from ministries of health, the World Health Organization, and the European Centre for Disease Prevention and Control websites.

Virus and Transmission

WNV is a single-stranded positive RNA virus in the *Flaviviridae* family. Although genotypic analysis suggests at least 9 distinct lineages of WNV, only lineage 1 and 2 have previously been associated with human disease.[13] In 2023, the first human infection with lineage 3 was documented in the US in a patient co-infected with lineage 1.[14]

WNV is maintained in an enzootic cycle involving mosquito-bird-mosquito transmission.[15] Certain passerine (perching) birds are the primary amplifying hosts because they develop sufficient viremia to infect mosquitoes.[16] Species in the *Corvidae* family (eg, crows, jays, ravens) are the most susceptible to illness and death, and disease outbreaks among birds can precede human outbreaks.[17,18] In the US, WNV transmission is driven primarily by the mosquito species *Culex pipiens* in northern regions, *C quinquefasciatus* in southern regions, and *C tarsalis* in western regions.[19] Humans, horses, and most other vertebrates are generally considered dead-end hosts because they have low levels and brief periods of viremia, so are unlikely to infect mosquitoes.[20,21]

Although almost all WNV transmission occurs via mosquito bites, less common routes of transmission include transfusion of blood products,[22] organ transplantation,[23] and transplacental,[24] perinatal,[25] breastmilk,[26] percutaneous,[27] and conjunctival[28] exposure. WNV transmission by blood transfusion was first identified in the US in 2002,[22] and nationwide screening of all blood donations with nucleic acid amplification testing started in 2003, diminishing the risk of transmission.[29,30] Since 2003, 14 cases of WNV transmitted by blood transfusion have been reported, the last occurring in 2016.[31]

During 2002-2023, WNV transmission by solid organ transplantation resulted in 14 identified disease clusters, 12 in the US and 2 in Italy, involving 32 infected recipients.[23,32] Although living tissue donors in the US are screened for WNV on a seasonal basis (June 1-October 31), no US policy for screening organ donors for WNV currently exists. Only 18 of 46 (39%) surveyed organ procurement organizations performed WNV screening as of 2020.[33]

WNV can be transmitted during pregnancy, and 1 case of transplacental transmission associated with fetal abnormalities has been reported.[24] However, in a prospective cohort study of 28 women infected with WNV during the first, second, and third trimesters of pregnancy, no adverse outcomes in the infants were observed compared with an uninfected cohort.[34] In another cohort of 77 women infected with WNV during pregnancy, none of the 72 infants followed up had conclusive evidence of congenital WNV infection; among 3 infants who developed WNV disease within 1 week of delivery, the timing of symptoms in the mothers suggested peripartum transmission.[25]

Transmission via puncture wounds with sharp instruments contaminated with WNV-infected animal brain tissue in 2 laboratory personnel and face/eye exposure to infected body fluid and brain of an injured crow in a field worker have been documented.[27,28]

Epidemiology

WNV is widely dispersed globally. First isolated from a patient from the West Nile subregion of Uganda in 1937, WNV was previously associated with relatively mild febrile illness in parts of Africa until the 1990s, when it began to emerge as a cause of severe neurologic disease in North Africa, Europe, Israel, North America, and Australia.[15]

In 2018, Europe experienced its largest WNV outbreak on record, driven by lineage 2, with 2083 locally-acquired WNV cases reported in European Union/European Economic Area Member States and European Union neighboring countries. Most European cases have been reported from Italy, Greece, and Romania, but the geographic range of WNV began to expand northward into Germany in 2018[35] and the Netherlands in 2020,[36] likely associated with increases in temperatures, precipitation, and intensity of agricultural land use.[37,38] Although few comparative analyses of strain type and human virulence have been performed, a new WNV lineage 1 strain detected in Italy in 2021 was associated with more severe disease in humans and more rapid expansion in birds and mosquitoes than the circulating WNV lineage 2 strain.[13] Recent WNV outbreaks in

Tunisia were reported in 2018 and 2023[2] and in Israel in 2024, with more than 930 reported cases and 73 deaths.

In the US, WNV is the most prevalent and widespread endemic arbovirus, with cases reported from all 48 contiguous states, the District of Columbia, and Puerto Rico. In 2023, 1789 human WNV neuroinvasive disease cases associated with 190 deaths (11%) were reported to ArboNET. The number of cases of nonneuroinvasive disease is unknown because patients are less likely to seek medical care, and clinicians may not consider WNV in the differential diagnosis.[39,40] Using seroprevalence estimates of 140 to 250 WNV infections for every neuroinvasive disease case reported[9,41,42] and 26% of infections leading to clinical disease (febrile or neuroinvasive),[43] an estimated 4.3 to 7.6 million WNV infections and 1.1 to 2.0 million resulting disease cases (≈46 000-83 000 disease cases per year) occurred in the US from 1999 to 2023, with only 3% to 6% of total disease cases reported. Therefore, reported cases of neuroinvasive disease are a more reliable indicator of WNV incidence.

From 2014 to 2023, cumulative WNV neuroinvasive disease incidence per 100 000 population in the US has remained highest in the western and central regions, with most cases occurring July to October (**Figure 1**). In 2021, 51% of WNV disease cases reported nationally were from Maricopa County, Arizona, which experienced the largest US outbreak on record in a single county, including 1487 reported human disease cases (956 neuroinvasive disease) and 101 deaths.[1] Extreme weather patterns, including increases in rainfall and higher winter temperatures, have been associated with outbreaks in the southwest.[1,4] However, WNV outbreaks in the US have been difficult to predict on the basis of climatic variables; the strongest predictor nationally or regionally is the occurrence of historical neuroinvasive disease cases, emphasizing the need to understand geographic patterns of human disease to focus preseason vector surveillance and control interventions.[4,7,8]

Host Susceptibility to Disease

Although individuals of any age can develop neuroinvasive disease, advanced age is the strongest risk factor, with incidence increasing with each decade of life.[11,17,44,45] Among those infected with WNV, about 2% of persons 65 years or older develop neuroinvasive disease vs 0.1% to 0.4% of persons younger than 65 years.[9] Mortality of patients with neuroinvasive disease is 10% overall but increases with age, from 2% for those younger than 50 years to 21% for those 70 years or older.[11] Age-related impairment in immune responses, such as defects in receptor signaling, innate and adaptive immunity, and regulation of blood-brain barrier permeability, likely contribute to increased risk of neuroinvasive disease and mortality.[46,47]

Other risk factors for severe disease include male sex, diabetes, hypertension, chronic kidney disease, cancer, and immunosuppression.[9,48] Patients with hematologic malignancies and recipients of stem cell and solid organ transplants have a high risk of neuroinvasive disease and death.[23,49-51] Among 14 WNV clusters from solid organ transplant transmission, 32 of 38 total recipients (84%) were infected with WNV, 24 of 32 infected recipients (75%) developed encephalitis, and 9 of 24 patients with encephalitis (38%) died.[23] Severe WNV disease may occur among patients receiving B-cell depleting chimeric anti-CD20 monoclonal antibodies, such as rituximab and ocrelizumab.[10,52,53] Among 38 patients with WNV neuroinvasive disease who were receiving anti-CD20 therapies, 29% died, and long-term disability occurred in many survivors.[10,52,53] In 1 study, incidence of WNV neuroinvasive disease among patients with multiple sclerosis receiving ocrelizumab was estimated to be 201 per 100 000 population, compared with 0.78 per 100 000 in the general population of the region.[53]

Host genetic factors such as polymorphisms in genes involved in antiviral activity can increase susceptibility to disease.[47,54] In addition, the presence of anti–type I interferon (IFN) antibodies are associated with worse outcomes and were present in 40% of 348 patients with WNV neuroinvasive disease compared with approximately 1% of uninfected people.[55]

Infection with WNV is generally believed to confer lifelong protection from reinfection for most people, based on a lack of documented reinfections with WNV, although sustained infection or reinfection may occur in patients with immunocompromising conditions.

Pathophysiology

WNV infection most often is caused by cutaneous inoculation of viral particles from saliva of infected mosquitoes (**Figure 2**). Following inoculation, the virus replicates in epidermal keratinocytes and dendritic (antigen-presenting) cells, which migrate to draining lymph nodes, where the virus replicates and spreads to the bloodstream and subsequently to visceral organs. In susceptible persons, the virus can invade the central nervous system.[54,56]

Infection with WNV typically leads to activation of an early innate immune response involving proinflammatory cytokines, particularly type I IFNs, which limit viral replication. Other proinflammatory cytokines, such as tumor necrosis factor and interleukin 1β, innate cell-mediated responses, chemotactic cytokines (chemokines), and complement, control WNV during early infection.[57] Although proinflammatory cytokines are important for controlling viral replication, they can cause worsening disease from inflammation-induced damage.[57] Activation of the adaptive immune response, including humoral (B cell) and T-cell–mediated responses, allows for clearance of WNV and prevents damage caused by inflammation.[54]

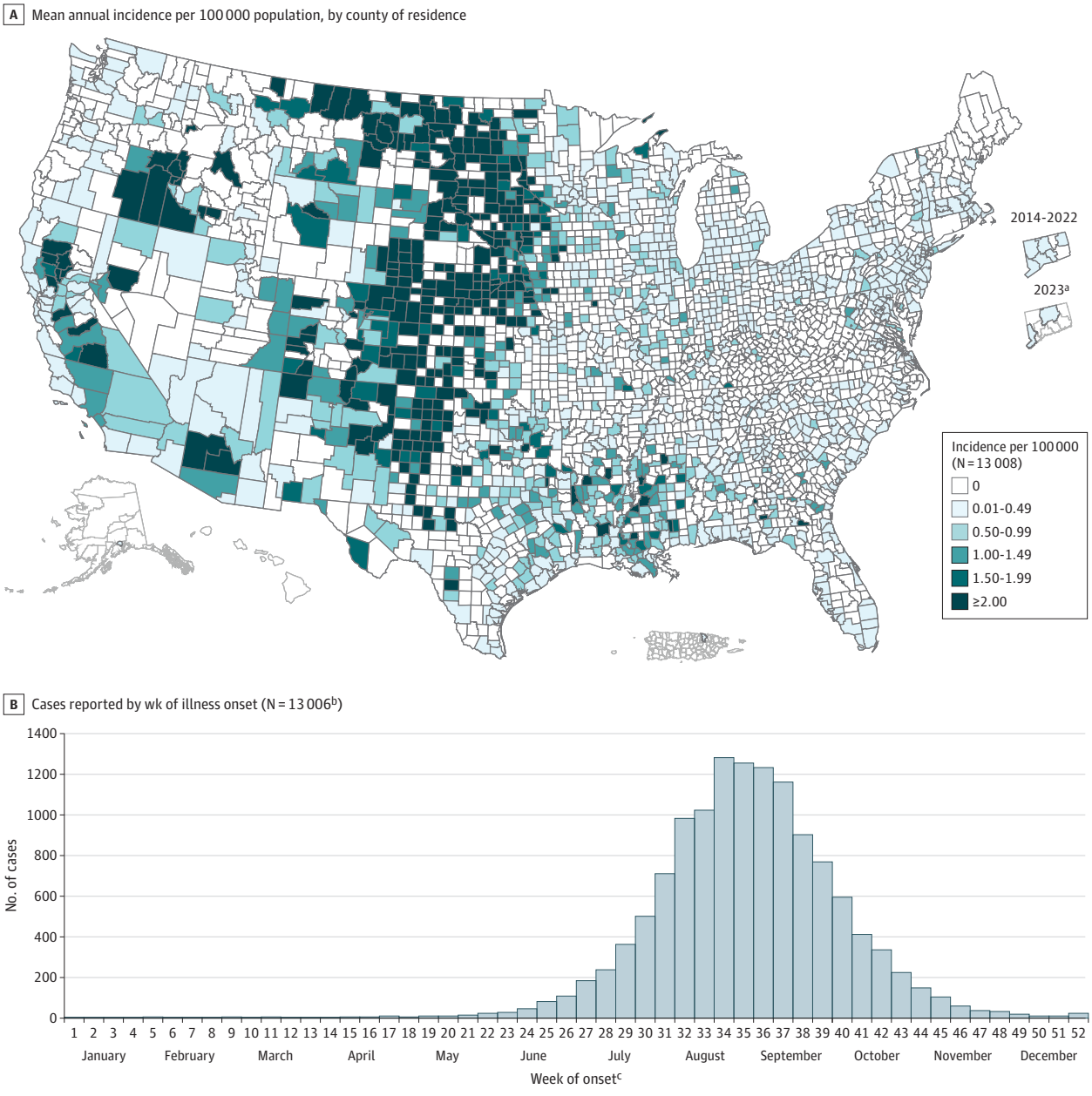
Neuroinvasion is mediated by several possible routes, including penetration of endothelial cells, cytokine-mediated damage to the blood-brain barrier, migration of infected immune cells across tight junctions ("Trojan Horse" mechanism), or axonal transport from olfactory or peripheral nerves.[54] WNV infects neurons and causes cell death, with tropism for extrapyramidal structures, including the brainstem, basal ganglia, thalami, and cerebellum.

Clinical Presentation

Most WNV infections do not result in clinically apparent disease. Seroprevalence surveys indicate that approximately 80% of WNV infections are asymptomatic, 20% cause a self-limited febrile illness (West Nile fever), and 0.4% to 0.7% lead to neuroinvasive disease (**Figure 3**).[9,41,42] The typical incubation period of WNV disease following a mosquito bite is 2 to 6 days (up to 14 days)[15] but can be longer for patients with immunocompromise, including stem cell and organ transplant recipients infected by blood transfusion (median, 13.5 days [range, 10-16 days])[22] and patients infected during organ transplantation (median, 15 days [range, 7-46 days]).

Among 98 patients with WNV disease without neurologic signs or symptoms (WNV fever), the most common symptoms were fatigue (96%; median duration, 36 days), fever (81%; median, 5 days), headache (71%; median, 10 days), myalgia (62%; median, 14 days), muscle weakness (61%; median, 28 days), and rash (57%; median,

Figure 1. West Nile Virus Human Neuroinvasive Disease Incidence and Cases, 2014-2023



[a]Connecticut data transitioned to planning regions in 2023. These data could not be combined with historic country data from 2014 to 2022.

[b]Two neuroinvasive disease cases had missing onset dates and were not included in the figure.

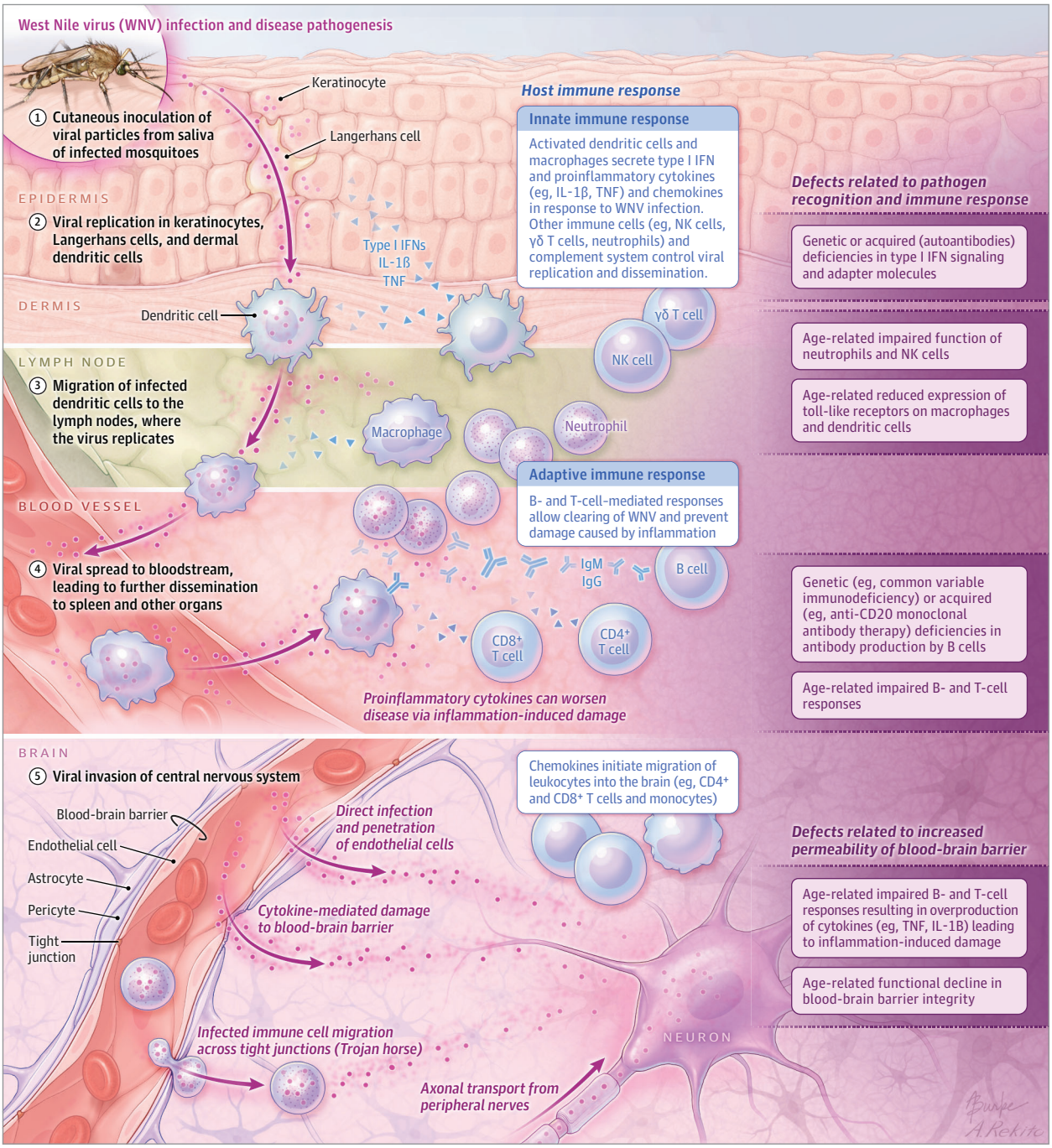
[c]Epidemiological weeks can vary depending on the year.

Source: ArboNET (US national arboviral surveillance system [https://www.cdc.gov/west-nile-virus/data-maps/historic-data.html]).

7 days). Other symptoms included arthralgia (37%; median, 14 days), vomiting (28%; median, 3 days), and diarrhea (27%; median, 5 days).[58] Frequency of rash ranges from 14% to 60%, and it is most commonly maculopapular, typically appearing on the trunk and extremities (**Figure 4**).[59] WNV-associated rash is indistinguishable from other viral exanthems, drug eruptions, or hypersensitivity reactions.

WNV neuroinvasive disease can present as meningitis, encephalitis/meningoencephalitis, and/or acute flaccid myelitis. WNV meningitis is characterized by headache, stiff neck, and photophobia, often with gastrointestinal symptoms such as nausea, vomiting, and diarrhea.[60] Patients with WNV encephalitis can develop confusion, stupor, or coma. Movement disorders, such as tremors, myoclonus, parkinsonism, and cerebellar ataxia, are associated with severe WNV encephalitis. Seizures occur in 3% to 6% of patients with WNV encephalitis.[60] Acute flaccid myelitis (sometimes called WNV poliomyelitis) is caused by viral infection of lower motor neurons of the spinal cord (anterior horn cells) and typically presents within 24 to 48 hours of illness onset, often concurrently with meningitis or

Figure 2. West Nile Virus Pathogenesis and Predisposing Factors for Neuroinvasive Disease

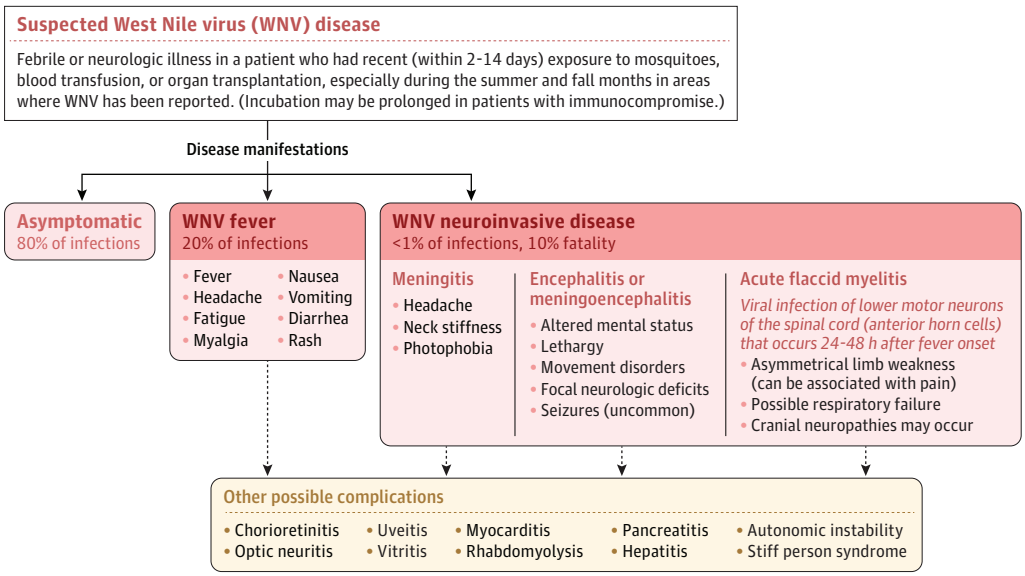


Following the bite of an infected mosquito, West Nile virus replicates in epidermal keratinocytes and immune cells. Infected immune cells migrate to draining lymph nodes, where the virus replicates further and disseminates to the bloodstream and visceral organs. Central nervous system invasion can occur by several potential mechanisms. Viral infection leads to activation of the innate immune system with secretion of cytokines, important for early control of viral replication. Activation of the adaptive immune system is important for viral clearance and regulation of inflammation. Genetic and acquired immune deficiencies and age-related effects can increase the risk of severe West Nile virus disease and neuroinvasion. IFN indicates interferon; IL, interleukin; NK, natural killer; TNF, tumor necrosis factor.

encephalitis.[60,61] Patients typically present with acute onset of asymmetric limb weakness, ranging from monoplegia to generalized quadriplegia. Absence of reflexes and lack of sensory symptoms are characteristic, although patients can have severe pain in the affected limbs. Cranial neuropathies causing facial weakness can also occur. Dysarthria and dysphagia may precede diaphragmatic and intercostal muscle paralysis, leading to respiratory failure and prolonged ventilatory dependence.[60,61]

Other less common neurologic manifestations of WNV infection include brachial plexus neuropathy, transverse myelitis,

Figure 3. West Nile Virus Clinical Disease Manifestations



Source: https://www.cdc.gov/west-nile-virus/hcp/diagnosis-testing/diagnostic-testing-algorithm.html

myasthenia gravis, and demyelinating neuropathies.[15,61] Acute demyelinating polyradiculoneuropathy, known as Guillain-Barré syndrome (GBS), can occur and is characterized by ascending, symmetric weakness and sensory and autonomic dysfunction. Symptoms begin 1 to 8 weeks following acute WNV infection. Guillain-Barré syndrome can be distinguished from acute flaccid myelitis based on clinical, cerebrospinal fluid (CSF), and electrodiagnostic studies.

Other clinical manifestations of WNV disease include ocular disease (eg, chorioretinitis, anterior uveitis, vitritis, optic neuritis)[62] and, rarely, myocarditis, pancreatitis, hepatitis, rhabdomyolysis, stiff person syndrome, and autonomic instability.[15]

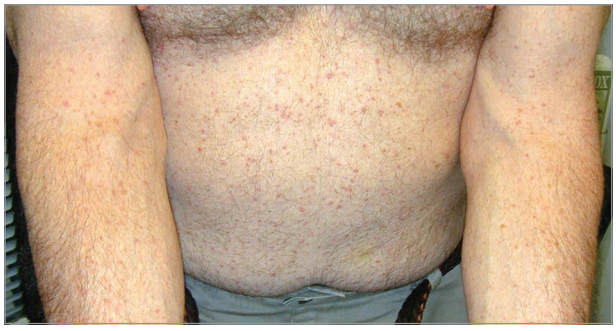
Laboratory Findings

Among 250 patients with serologically confirmed WNV neuroinvasive disease, CSF demonstrated a similar pleocytosis in cases of meningitis and encephalitis (mean, 226 white blood cells/mm^3 [range, 1-7950]).[63] Mean neutrophil percentage was 43% (range, 0%-98%) and declined in most patients with subsequent lumbar puncture. Glucose level is generally normal, and protein levels are elevated. Patients with encephalitis tended to have higher protein concentrations (mean, 101 mg/dL [range, 32-295]) than those with meningitis (mean, 76 mg/dL [range, 21-207]).[63] In cases of GBS, CSF typically has elevated protein levels without pleocytosis (cytoalbuminologic dissociation).[60]

Imaging and Electrodiagnostic Studies

Brain magnetic resonance imaging findings may be normal in patients with neuroinvasive disease or show abnormalities on diffusion-weighted images or hyperintensity on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images.[64,65] In patients with encephalitis, the brain stem and/or deep gray matter, including basal ganglia, thalami, mesial temporal structures, and cerebellum can demonstrate hyperintensity on FLAIR and T2-weighted imaging. Patients with acute flaccid myelitis can have hyperintensity on FLAIR and T2-weighted imaging and enhancement on contrast-enhanced T1-weighted imaging in the anterior horns or around the conus medullaris and cauda equina.[64] Worse clinical outcomes may occur in patients with signal intensity abnormalities, meningeal involvement, and intraspinal abnormalities vs normal magnetic resonance imaging findings or isolated diffusion restriction.[64] Electroencephalographic abnormalities such as generalized slowing and triphasic sharp waves may be present and are generally nonspecific in patients with WNV encephalitis.[60]

Figure 4. Diffuse Maculopapular Rash on Chest, Abdomen, and Arms of a Patient With West Nile Virus Disease

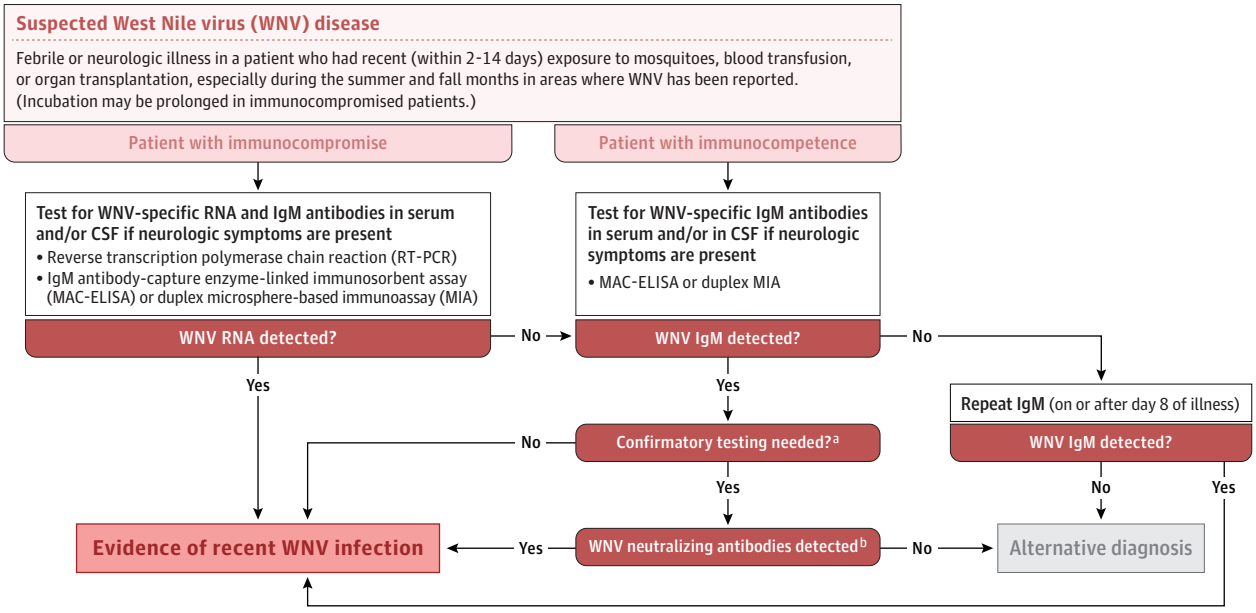


Electromyography and nerve conduction studies can help differentiate acute flaccid myelitis from GBS. In patients with acute flaccid myelitis, a motor axonopathy and/or anterior horn cell process with preservation of sensory nerve potentials is seen, in contrast to the demyelinating sensorimotor neuropathy observed with GBS.[61]

Assessment and Diagnosis

WNV disease should be considered in the differential diagnosis for any person with an acute febrile or neurologic illness who has had recent exposure to mosquitoes, blood transfusion, or organ transplantation, especially during the summer and fall months in areas where the virus has been reported. In patients who are immunocompetent,

Figure 5. West Nile Virus Diagnostic Algorithm



CSF indicates cerebrospinal fluid.

[a]Indications for confirmatory testing by plaque reduction neutralization test: possible exposure to cross-reactive flaviviruses (eg, St. Louis encephalitis virus, Powassan virus, dengue virus); atypical or unusually severe presentation or death; suspected unusual route of transmission (eg, organ transplant, blood transfusion, laboratory); presentation outside of the typical WNV transmission season (ie, July-October).

[b]WNV-specific neutralizing antibody titers 4-fold or greater than for other flaviviruses tested.

Source: https://www.cdc.gov/west-nile-virus/hcp/diagnosis-testing/diagnostic-testing-algorithm.html

testing for WNV-specific IgM antibodies in serum and/or CSF using either the IgM antibody-capture enzyme-linked immunosorbent assay or duplex microsphere-based immunoassay is the most sensitive approach to detecting acute WNV infection.[66] If results of initial IgM testing are negative during the acute phase of illness, repeat IgM testing on or after day 8 is recommended, because IgM antibodies can be detected by day 8 of illness in more than 98% of patients[67] (**Figure 5**). Because IgM antibodies do not cross an intact blood-brain barrier, detection of IgM in a nonbloody CSF specimen usually indicates central nervous system infection. A caveat in interpreting IgM results is the prolonged persistence of WNV IgM antibodies described in several longitudinal studies. Although the mean time to IgM negativity among 22 viremic blood donors was approximately 5 months,[20] studies of patients with WNV disease reported persistence of IgM antibodies in serum for more than 16 months in 23% to 60% of patients[68,69] and in CSF as long as 6 months after onset.[70] IgM testing can be performed at commercial or public health laboratories. IgG testing is not helpful to diagnose acute WNV disease, because a positive result in the absence of IgM antibodies suggests a prior WNV or related flavivirus infection.

If a WNV IgM test result is positive, confirmatory testing for WNV-specific neutralizing antibodies by plaque reduction neutralization test (PRNT) of serum or CSF should be considered in certain patients. PRNT is not commercially available but can be performed at US Centers for Disease Control and Prevention and some state public health laboratories. PRNT is recommended if the patient was possibly exposed to another circulating flavivirus (eg, St. Louis encephalitis, Powassan, dengue[71] viruses) or was recently (eg, within 6 months) vaccinated against another flavivirus (eg, yellow fever virus, Japanese encephalitis virus), if disease presentation is atypical or leads to death, if non–mosquito-borne transmission is suspected (eg, solid organ transplantation, blood transfusion, laboratory), or if the patient presents outside of the usual arboviral season (typically June to October or longer in warmer regions). WNV infection is confirmed if neutralizing antibody titers are at least 4-fold greater than those for other related flaviviruses tested. At least a 4-fold change in titer between paired acute and convalescent specimens also confirms a recent WNV infection.

In patients who are immunocompetent, reverse transcription polymerase chain reaction (RT-PCR)[72] is of limited diagnostic value because viremia is only detected early in the course of disease and is usually resolved before neurologic symptoms develop.[41,67,73] Sensitivity of RT-PCR for diagnosing acute WNV disease varies by specimen type; among 105 patients with serologically confirmed acute WNV disease, RT-PCR sensitivity was 26% (20/77) for serum, 20% (7/35) for plasma, and 17% (11/66) for CSF.[73]

In patients with immunocompromising conditions, RT-PCR and other molecular methods, such as metagenomic sequencing, may be more sensitive than serologic testing and are often required to diagnose acute WNV disease in patients receiving B-cell inhibiting monoclonal antibody therapy because of an inability to mount a humoral immune response.[10,52,53]

Tissues obtained on biopsy or autopsy can identify histopathologic changes consistent with WNV infection and detect WNV antigens by immunohistochemical staining or RNA by RT-PCR. In patients with encephalitis, histopathologic changes include microglial nodules and perivascular lymphocytic inflammation, predominantly in the brain stem, basal ganglia, thalami, and cerebellum;

leptomeningeal inflammation is present in patients with meningitis or meningoencephalitis.[74] See the **Box** for commonly asked questions about testing for WNV.

Treatment

No specific therapies have been proven effective against WNV disease, and supportive care is recommended. Patients with encephalitis require close monitoring in an intensive care unit setting for development of elevated intracranial pressure, seizures, or inability to protect the airway. Patients with acute flaccid myelitis should be monitored closely for symptoms or signs of acute neuromuscular respiratory failure (eg, development of dysarthria and dysphagia),[60] by history, physical examination, and bedside pulmonary function testing.

Limited data from case reports, case series, observational studies, and phase 1 and 2 clinical trials are available on efficacy of various therapeutics to treat patients with WNV disease (eTable in the Supplement). Treatments assessed include passive antibody transfer (polyclonal intravenous immunoglobulin [IVIG], IVIG containing high titers of WNV neutralizing antibodies, and WNV recombinant humanized monoclonal antibodies),[75,76] IFN,[77] corticosteroids,[78,79] and ribavirin.[80] Reports were generally inconclusive (case reports or underpowered) or showed no benefit. See the Box for commonly asked questions about treatment.

Prognosis

Among patients hospitalized with WNV disease, 30% to 40% are discharged to a long-term care or rehabilitation facility.[4,81,82] A systematic review of 29 studies (12 cohort, 4 cross-sectional, 13 case series) including 2135 patients examining long-term sequelae following WNV disease reported that at least one-half of patients experienced long-term symptoms and functional disabilities.[12] The review noted heterogeneity in studies with variable patient populations, study designs, follow-up periods, and outcome assessments.

The most common physical sequelae in patients with WNV disease were muscle weakness (7%-73% of patients with WNV neuroinvasive disease 3-18 months after discharge; 12%-24% of patients with WNV fever 1-6 months after discharge), fatigue (48%-75% for WNV neuroinvasive disease at 8-18 months; 48% for WNV fever at 30 days), and myalgia (19%-49% for WNV neuroinvasive disease at 6-12 months; 12%-13% for WNV fever at 1-6 months).[12] The most common cognitive and psychological sequelae were memory loss (25%-49% for WNV neuroinvasive disease at 3-18 months), depression (23%-41% for WNV neuroinvasive disease at 12-16 months), and difficulty concentrating (34%-48% for WNV neuroinvasive disease at 13-18 months; 13% for WNV fever at 30 days).[12] Approximately 9% to 29% of patients with WNV neuroinvasive disease had difficulties with activities of daily living at 1 to 18 months after discharge.[12]

Patients with acute flaccid myelitis commonly have prolonged weakness and other neurologic deficits from spinal motor neuron damage such as tremors and myoclonus, although outcomes vary. In a cohort of 27 patients with WNV acute flaccid myelitis, two-thirds had some improvement in strength at 1-year follow-up, with most improvement occurring within the first 4 months after illness.[83]

Prevention

Prevention of WNV disease is important because of the absence of effective treatment (**Table**). Nonhuman surveillance of WNV, including dead birds, mosquitoes, sentinel chickens, and equines have been evaluated as early indicators of WNV activity and human disease risk. Early in the US epidemic, bird surveillance had the highest success in predicting human infections, followed by mosquitoes.[18,93] However, more recently, WNV-positive mosquitoes have become the most frequent first indicator of WNV activity,[1,4] since decreases in dead bird reports, avian host factors, and reductions in bird surveillance programs have limited the utility of dead bird surveillance.[93]

When local human or nonhuman surveillance indicates early evidence of WNV activity, public health professionals and clinicians should increase messaging to raise awareness and recommend personal protective behaviors, such as avoiding outdoor exposure from dusk to dawn, using screens on windows and doors, removing standing water, wearing protective clothing, and using Environmental Protection Agency–registered insect repellents. However, adherence to these measures is often low; a systematic review (17 survey studies on WNV knowledge, attitudes, perceptions, and practices) reported that use of personal protective measures varied by an individual's concern about WNV, age, and educational level; repellent use ranged from 29% to 73%, with the lowest use reported among persons older than 60 years (29%) and pregnant women (33%).[84]

Community mosquito-control activities, such as application of compounds that target developing and adult mosquitoes (ie, larvicides and adulticides), can prevent WNV outbreaks or reduce the size of outbreaks once they occur. However, few studies have evaluated the effectiveness of these activities on public health outcomes, and local mosquito surveillance thresholds (ie, vector indices) for initiating control activities before human cases occur need to be defined.[3,4,94] Effective use of vector indices has also been hampered by the short interval (eg, 1-2 weeks) between recognition of

Box. Commonly Asked Questions About West Nile Virus

Who Should Be Tested for WNV and What Testing Should Be Performed?

WNV disease should be considered in the differential diagnosis for any person with an acute febrile or neurologic illness who has had recent exposure to mosquitoes, blood transfusion, or organ transplantation, especially during the summer and fall months in areas where the virus has been reported. For patients who are immunocompetent, WNV IgM antibody testing of serum or CSF should be performed to diagnose a recent WNV infection. For patients who are immunocompromised, WNV IgM and RT-PCR testing should be considered, particularly in patients receiving B-cell inhibiting monoclonal antibody treatment.

Are There Any Treatments for WNV Disease?

There are no treatments proven effective for WNV disease, and management is supportive.

How Should Patients Be Counseled About Preventing WNV Infection in Areas With Elevated Risk?

Patients can decrease their risk of WNV infection by avoiding outdoor exposure from dusk to dawn, wearing protective clothing, using EPA-registered insect repellents, and controlling mosquitoes indoors and outdoors by using screens on windows and doors and removing standing water.

CSF indicates cerebrospinal fluid; EPA, Environmental Protection Agency; RT-PCR, reverse transcription polymerase chain reaction; WNV, West Nile virus.

Table. West Nile Virus Prevention Measures

Prevention measure	Anticipated effectiveness	Limitations	Comments
Personal protective behaviors (eg, using EPA-registered repellent, avoiding outdoor exposure from dusk to dawn, removing standing water, using screens on windows and doors, wearing long sleeves and pants)	Varies by user, number of personal protective behaviors used, environmental conditions, and other factors[84,85]	Low adherence by public	Currently available; need improved messaging focused on people most susceptible to severe WNV disease (older persons and those with immunocompromise)
Community mosquito control (application of insecticides to kill adult mosquitoes [adulticides] and larvicide)	Evidence that adulticides decrease WNV entomologic indicators (eg, measures of infected *Culex* spp mosquitoes); limited evidence that larvicides decrease WNV entomologic indicators in drainage systems and other larval habitats; limited data that adulticides are safe and reduce likelihood of WNV disease cases[86-89]	Negative public perceptions of using pesticides; lack of uniform mosquito control program infrastructure in US; delays in adulticide application because of time lags in identification and reporting of human cases; lack of defined thresholds for initiating mosquito control activities	Currently available; need to define mosquito surveillance thresholds for initiating mosquito control activities; improve messaging to the public about safety of use of adulticides; assess alternative mosquito control strategies (eg, mosquito sterilization, genetically modified mosquitoes)
Human WNV vaccine	Seven vaccine candidates assessed in phase 1 or 2 human clinical trials; safety and/or immunogenicity demonstrated for several vaccines[90]	Perceived lack of profitability hinders further investments in research and development; geographical and temporal variability are challenging for designing traditional phase 3 clinical trials	Not currently available; need to conduct sales forecast analysis; identify immune correlate of protection for potential alternative licensing pathway
Prophylactic WNV monoclonal antibodies for people at high risk of severe WNV disease	Efficacy data limited to preclinical animal studies[91,92]	Perceived lack of profitability hinders further investments in research and development; geographical and temporal variability are challenging for designing traditional phase 3 clinical trials	Not currently available; need to identify immune correlate of protection; develop a target product profile

Abbreviations: EPA, Environmental Protection Agency; WNV, West Nile Virus

an elevated vector index and onset of human disease cases, followed by the time needed to diagnose and report cases to public health authorities.[4] See the Box for commonly asked questions about preventing WNV infection.

Future Directions

Although serum and CSF have been the main specimen types used to diagnosis WNV infection, validating molecular assays for additional specimen types, such as urine and whole blood, should be considered, because these specimens have a higher sensitivity (87% and 58%, respectively).[73] At least 7 different WNV vaccine candidates have been studied in phase 1 or 2 clinical trials.[90,95] Development of phase 3 efficacy trials has been limited by the unpredictable nature of WNV outbreaks, which makes it challenging to select geographic areas and prepare for trials before WNV activity is detected. Alternative pathways for licensure may be needed to have an approved human WNV vaccine.[90,95] Additional barriers to vaccine development include potential safety concerns and cost of a vaccine program without commercial incentive or partnership. Prophylactic WNV monoclonal antibody administration has been investigated in preclinical studies but is not currently available for human use.[91,92]

Limitations

This review has several limitations. First, some relevant studies may have been missed. Second, few clinical trials were available on treatment and prevention of WNV disease, precluding more specific recommendations. Third, WNV surveillance data likely underestimate infection risk, because ArboNET is a passive surveillance system.

Conclusions

WNV causes approximately 1300 neuroinvasive disease cases and 130 deaths annually in the US. People who are older or immunocompromised are at higher risk of severe disease and death. Since there are no therapies or human vaccines, prevention relies on personal protective measures, WNV surveillance, and mosquito control interventions.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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