

Zoonosis Update

West Nile virus

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West Nile virus was first identified in Africa in 1937, and subsequently, Africa, Europe, Australia, and Asia were recognized as regions in which the virus was endemic.¹ In 1999, concurrent outbreaks of encephalitis among crows, humans, and horses in New York State triggered an investigation by human and veterinary health officials that led to the initial detection of WNV in the western hemisphere.^{2,3} West Nile virus is now the leading cause of human arboviral encephalitis in the United States.⁴ It is found throughout the western hemisphere, including North America, Central America, South America, and the Caribbean.¹

Etiology

West Nile virus (family, Flaviviridae; genus, Flavivirus) is a member of the serologically related Japanese encephalitis antigenic complex; members of that complex are mosquito-borne and include Japanese encephalitis, Murray Valley encephalitis, Kunjin, and St Louis encephalitis viruses.^{5,6} The flaviviruses have characteristics in common: size range (40 to 60 nm), symmetry (enveloped, icosahedral nucleocapsid), and type of nucleic acid (positive-sense, single-stranded RNA [approx 10,000 to 11,000 bases]).⁵

Ecology and Transmission

Sylvatic transmission—The enzootic cycle of WNV involves the transmission of the virus among wild birds and infected *Culex* mosquitoes.⁷ Wild bird species vary in their host competence, as evidenced by the duration and magnitude of viremia in affected birds and in their consequent ability to transmit the infection to mosquitoes. Only a small proportion of WNV-positive birds detected through surveillance efforts are likely to be competent hosts for WNV. Passerines (ie, jays, finches, grackles, sparrows, and crows) appear to be important reservoirs, given that they can act as a source of infection for mosquitoes for prolonged peri-

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Supported in part by grants from the Centers for Disease Control and Prevention and the University of Arizona.

The authors thank Drs. Laura Kramer and Susan Wong for laboratory support and Dr. Dennis White and Bryon Backenson for human and mosquito surveillance data.

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ABBREVIATIONS

WNV	West Nile virus
WNF	West Nile fever
WNE	West Nile encephalitis
WNND	West Nile neuroinvasive disease
PRNT	Plaque reduction neutralization test
RT	Reverse transcriptase
RAMP	Rapid analyte measurement platform

ods under experimental conditions and that the geographic distributions of many of those species are wide.⁸⁻¹⁰ Results of field studies^{11,12} indicate that the American robin (*Turdus migratorius*) is an important reservoir; although relatively uncommon, these birds are frequently a source of blood meals for important *Culex* spp. Conversely, selected avian species from the orders Psittaciformes (eg, Monk parakeets and budgerigars), Galliformes (eg, chickens and Japanese quail), and Columbiformes (eg, rock doves) that have been evaluated appear to be incompetent reservoirs of WNV because the extent of the WNV-associated viremia in these birds is typically insufficient to provide a source of infection for mosquitoes.^{8,13}

On the basis of their ability to become infected after feeding on infected hosts and to transmit infection to susceptible hosts, it is apparent that mosquito species vary in their vector competence.^{10,14,15} Surveillance data and experimental transmission studies have revealed that *Culex quinquefasciatus*, *Culex pipiens*, *Culex restuans*, *Culex salinarius*, and *Culex tarsalis* are the principal vectors of WNV in the United States.^{4,16} Other mosquito species, such as *Culex nigripalpus*, *Aedes albopictus*, *Aedes vexans*, and *Ochlerotatus triseriatus*, may be of secondary importance.¹⁷ The host preferences of individual mosquito species are also important determinants of transmission dynamics. For instance, *Culex* spp typically feed on birds, whereas *Aedes* and *Ochlerotatus* spp prefer to feed on mammals.^{18,19} Although certain *Culex* spp appear to play major roles in the enzootic cycle of WNV, opportunistic feeding by these species and transmission by secondary vectors are routes by which mammalian hosts can become infected.

Most mammals do not appear to have a role in the enzootic transmission of WNV largely because the viremia that develops following infection is inadequate for subsequent transmission of the virus to mosquitoes during feeding. Such dead-end hosts may or may not develop clinical signs of disease. Two dead-end hosts that are notable for their susceptibility to clinical disease resulting from WNV infection are horses and humans. There is also evidence that the extent of viremia that develops in tree squirrels (*Sciurus* spp),

eastern chipmunks (*Tamias striatus*), and eastern cottontail rabbits (*Sylvilagus floridanus*) may be sufficient to provide a source of infection for mosquitoes.^{20–22} Additional studies are needed to explore the potential role of these species in the maintenance and transmission of WNV and to identify other competent host species. For example, alligators (*Alligator mississippiensis*) can develop viremia to a degree that suggests at least low competence for infection of feeding mosquitoes.^{23,24} In Russia, the lake frog (*Rana ridibunda*) appears to be a competent reservoir.¹⁶

Other routes of transmission—Non-mosquito-borne transmission of WNV to animals and humans also occurs. In 2002, transplacental infection in a human infant born with severe brain abnormalities was reported.²⁵ Results of subsequent surveillance efforts suggest that transplacental transmission is extremely rare.^{25,26} Transplacental transmission of WNV occurs in experimentally infected mice.²⁷ Possible WNV transmission via breastfeeding from a woman who had become infected as a result of a blood transfusion was reported in 2002.²⁸ However, a subsequent study²⁹ of WNV-infected women during the breastfeeding period revealed no conclusive evidence of transmission via breastfeeding, suggesting that it rarely occurs. There have been reports^{30–32} of WNV-associated disease in humans following blood transfusion, organ transplantation, and possibly dialysis.

Results of several studies^{8,21,23,33–36} of experimentally infected animals indicate the potential for direct transmission of WNV. Experimentally infected American and fish crows shed infectious WNV in their feces.³³ Among experimentally infected birds in 1 study,⁸ cloacal shedding of WNV was detected in 17 of 24 species and oral shedding of WNV was detected in 12 of 14 species, including several passerine species. In that same study, birds of 4 species (ring-billed gulls, blue jays, black-billed magpies, and American crows) that were infected as a result of mosquitoes feeding subsequently directly transmitted WNV to their uninfected cagemates. Shedding of WNV in feces or other bodily secretions by infected Eastern chipmunks and tree squirrels suggests the potential for direct transmission by those species.^{20,21} Infection with WNV via the oral route (ingestion) in golden hamsters, alligators, cats, and some raptors has been reported.^{23,34–36} In the wild, fecal shedding of WNV was detected among birds in an American crow roost in New York State following a period of bird deaths during winter, when no mosquito activity was detected; this suggested lateral transmission was possible through contact or fecal contamination.³⁷ Theoretically, companion animals such as dogs or cats could be infected with WNV following ingestion or contact with an infected bird or small mammal. Additional studies are needed to determine whether direct transmission plays a role in the sylvatic propagation of WNV and, if so, to further characterize that role.

The evidence of fecal and oral shedding of WNV by infected animals suggests the potential for zoonotic transmission. Handlers of sick or dead birds or rodents should take appropriate precautions to avoid exposure to potentially infectious material. There is a need for additional studies to examine the viability of WNV in

fecal material or other bodily secretions in the environment and the potential for zoonotic transmission through contact with, ingestion of, or aerosol exposure to such material. It appears that occupational exposure to WNV is possible. An outbreak of WNV among turkey-farm workers may have resulted from aerosol exposure.³⁸ In addition, laboratory workers have acquired WNV infection through percutaneous inoculation.³⁹

Epidemiology

Surveillance—In 2000, the CDC developed an electronic-based surveillance and reporting system (ArboNET) to track state and local agency reports of WNV infection among humans, horses, and other mammals; birds; and mosquitoes.⁴⁰ National guidelines for WNV surveillance, prevention, and control have been developed by the CDC and partnering institutions.¹⁷ A standardized surveillance case definition for human neuroinvasive and non-neuroinvasive domestic arboviral disease was last updated by the Council of State and Territorial Epidemiologists in 2004.⁴¹ The case definition includes both clinical and laboratory criteria. Health-care workers are to report human cases of WNV infection to their local health department as part of the National Notifiable Diseases Surveillance System.¹⁷ In the United States, 4,269 humans with WNV infection were reported in 2006, of which 2,774 (65%) were cases of non-neuroinvasive WNV.⁴² Of more than 23,500 human cases reported in the United States since the appearance of WNV in New York City in 1999 through November 2006, 904 (4%) were fatal.⁴³

In 1999, cases of WNV infection among humans were reported only from New York State, but there was evidence of WNV infection in birds, other mammals, and mosquitoes in Connecticut, New Jersey, and Maryland.⁴⁰ Evidence of WNV was later detected in the south of the United States and then in progressively westward states, with initial detection usually in species other than humans.⁴⁰ By 2006, human cases had been reported in all states in the continental United States, with evidence of transmission to humans or other species in 1,402 counties.⁴

After humans, horses constitute the majority of mammals identified with WNV infection, representing 97% of the 1,121 nonhuman mammal cases reported in 2006.⁴ From 1999 through 2006, the CDC also received a small number of reports of WNV infection in bats, a chipmunk, a skunk, squirrels, and a domestic rabbit.^{4,44} In surveillance studies,^{45–50} serologic evidence of WNV exposure was detected in a broad range of wild and domestic mammalian hosts, including dogs, cats, deer, feral swine, coyotes, foxes, opossums, raccoons, skunks, bats, squirrels, and other rodent species.

As the major reservoir (amplifying) hosts for WNV, birds are a core component of surveillance.¹⁷ Dead-bird surveillance involves reporting of dead birds by the general public to health, agriculture, or mosquito- and vector-control agencies. To optimize their use of resources, some agencies may restrict collection of dead birds to 1 or more corvid species (ie, crows, jays, and magpies) or to certain periods of the year. As of April 2007, > 300 bird species have been identified as positive for WNV infection through ArboNET, including 11

additional species identified in 2006.^{4,44} In 2006, ArboNET received reports of 4,106 dead WNV-infected birds from 43 states, with corvids accounting for 80% of those cases.⁴ Dead birds can serve as so-called neon needles in a haystack, offering a relatively inexpensive passive indicator of WNV activity in an area.⁵¹ For example, 404 counties from 38 states reported infected birds but no instances of human disease in 2006.⁴

Live-bird surveillance involves observation of captive sentinel flocks (eg, poultry, pigeons, or birds in zoologic collections) or free-ranging wild birds.¹⁷ Sentinel chicken flocks are often used by local agencies for arboviral surveillance because they are attractive hosts for *Culex* spp, develop a measurable antibody response following infection but no clinical signs, and are cost-effective to use in such a manner.^{13,52} An advantage of captive flocks over wild birds is that serologic activity in the former can establish the timing and location of arboviral transmission. Birds can also be assessed for antibodies against mosquito salivary gland antigens to evaluate the sensitivity of flocks for detection of arboviral activity.⁵³ West Nile virus infections in captive populations, such as those present at zoologic institutions, have been valuable disease indicators.⁵⁴ Unusually high morbidity and mortality rates among birds at the Wildlife Conservation Society's Bronx Zoo was one of the initial indicators of introduction of WNV into the United States.⁵⁵

Mosquito surveillance is a core component of arboviral surveillance, although it is not universally implemented because it requires active, ongoing collection efforts. Adult mosquitoes are pooled and examined to estimate minimum infection rates ([number of pools positive for WNV/total number of mosquitoes tested] × 1,000) and are identified and counted by species to estimate mosquito abundance (number of mosquitoes collected/trap night).¹⁷ As of April 2007, 62 mosquito species were identified as positive for WNV infection through data obtained via ArboNET.⁵⁶ In 2006, reports were received of WNV-positive mosquito pools in 38 states and the District of Columbia, of which 73% included *Culex* spp that are presently thought to be the principal vectors of WNV transmission in the United States.⁴ Unidentified or other *Culex* spp accounted for 26% and other non-*Culex* spp accounted for 1% of the WNV-positive mosquito pools.

The arboviral transmission season coincides with the availability of mosquito vectors, which are seasonally abundant. In the temperate portions of the United States, the incidence of WNV disease typically peaks between July and October⁵⁷; in 2006, the peak detection of WNV-infected birds and horses occurred in August.⁴ However, the transmission season has lengthened as WNV has moved into the western United States, with onset of WNV-related human illness detected as early as April and as late as December.¹⁶

Risk factors—The most important risk factor for acquisition of WNV infection is exposure to infected mosquitoes.¹⁶ During the 1999 outbreak in New York City, human cases were clustered in areas with large amounts of vegetation, indicating favorable mosquito habitats.⁵⁸ A study⁵⁹ of an outbreak in Chicago in 2002

revealed that humans with WNV infection were more likely to live in areas with greater amounts of vegetation, older housing, low population density, predominance of older Caucasian residents, and proximity to dead birds (although differences in efforts by mosquito-control agencies influenced the effects of these variables). The observed decrease in human cases of St Louis encephalitis and western equine encephalomyelitis in California since the 1960s coincided with the advent of television and air conditioning, the uses of which encourage people to remain indoors.⁶⁰

Identification of high-risk areas through disease prediction models offers the potential for targeted prevention and control measures. Dead-crow density (number of dead crows/square mile) was highly associated with the number of human cases by county in New York State and other areas.^{61,62} Persons living in towns near areas of current or recent dead-crow clusters were at increased risk of infection.^{63,64} As the number of dead-crow reports decline because of a decrease in the susceptible population (either through deaths or selection for disease resistance) or reduced public interest, indicators such as the proportion of birds that yield positive results for WNV infection⁶⁵ may be of increased value despite inherent delays associated with submission of bodies and testing. With regard to WNV infection, clusters of equine cases have not been identified as a timely predictor of human cases.⁶⁶

In a study⁶⁷ to identify risk factors for complications of WNV disease in humans, those with WNE were more likely to have a history of advanced age, alcohol abuse, and diabetes mellitus, compared to patients with West Nile meningitis or non-neuroinvasive WNE. Advanced age, immunosuppression, requirement of mechanical ventilation, and history of stroke were all associated with death in patients with WNE.⁶⁷ Advanced age is also a predictor of poor prognosis among humans with non-neuroinvasive WNE.⁶⁸ However, all ages are at risk of WNV infection; in the period of January through August 2007, ages of reported cases ranged from 2 to 96 years.⁶⁹ In 2002, 105 cases of WNND (which includes WNE and meningitis) and 45 cases of WNF among children (< 19 years old) in the United States were reported.⁷⁰ Host immunity also appears to play a role in risk of developing WNV infection.⁷¹ Approximately 1% of the Caucasian population is homozygous for a defective CCR5 allele (CCR5Δ32) and appears to be at higher risk of developing fatal WNV infection.⁷² Results of experimental research involving mice indicate that WNV-associated death was more likely if the mice lacked receptors for α/β -interferon.⁷³

A study³ of 23 horses with WNV encephalitis in New York State revealed that horses that died or were euthanatized were similar in age to horses that survived. However, a larger study⁷⁴ of an outbreak of WNV encephalomyelitis in Texas revealed that older horses were at greater risk of death or euthanasia. In that latter outbreak, collapse, recumbency, and lack of WNV vaccination in the previous 12 months were all predictive of nonsurvival of horses with WNV disease. In a serologic study⁷⁵ of dogs and cats during an outbreak of WNV infection among humans in Louisiana, factors such as residing exclusively outdoors and not receiv-

ing heartworm medication were associated with seropositivity in pet dogs. In addition, stray dogs were more likely to be seropositive, compared with owned dogs, and dogs were more likely to be seropositive for WNV than cats; no risk factors for seropositivity in cats were identified.

Clinical Features

Birds—Avian infections can be clinically inapparent or fatal, with considerable variability among species. Signs of WNV-associated neurologic disease include sudden onset of recumbency, mild ataxia, abnormal head posture, circling, swimming in circles, tetraparesis, tremors, nystagmus, seizures, and disorientation; additionally, signs of depression, mental dullness, anorexia, rapid weight loss, impaired vision, and sudden death may be evident.^{54,76,77} The case fatality rate in American crows appears to be close to 100%.⁸ In dead birds, affected organs include the spleen and liver (evidence of enlargement, necrosis, and hemorrhage), heart (evidence of myocardial degeneration, inflammation, and pericardial lesions), pancreas (pancreatitis), and adrenal gland (chronic inflammation).^{54,76,78} Less frequent pathologic signs are pulmonary and intestinal hemorrhage, lymphoplasmacytic enteritis, renal congestion and nephritic foci, ovarian necrosis, and disseminated intravascular coagulation.^{54,76} Pathologic changes in neural tissue include gross brain hemorrhage, degeneration or necrosis of Purkinje cells, and lymphoplasmacytic encephalitis with glial nodules. Histopathologic ocular abnormalities include pectenitis (ie, fibrinous material coating the pecten [a group of specialized blood vessels in the vitreous body of the avian eye]).^{54,76,77}

Horses and other nonhuman mammals—In horses, WNV infection is associated with signs of depression, abnormal gait, ataxia (primarily hind limb), muscle tremors, knuckling over at the metacarpo- or metatarsophalangeal joints (fetlocks), and recumbency.^{3,74} In 1 case series,³ fever was detected in approximately 33% of affected horses. Of 1,299 horses investigated during a 2002 outbreak in Texas, 434 (33.4%) did not survive; of those nonsurvivors, 308 (71.0%) were euthanized.⁷⁴

West Nile virus infection does not appear to cause extensive illness in dogs or cats.⁴⁴ Via ArboNET, there were no reports of dogs or cats with WNV disease in 2006 and only 5 reports^{4,79} of infected dogs in 2005. However, there are case reports^{80,81} of acute encephalitis, polyarthritis, and myocarditis associated with WNV infection in dogs. West Nile virus was isolated from a dog in Africa in 1982⁴⁴ and from a dead cat that had neurologic disease in 1999.⁷ In 4 dogs and 4 cats that were experimentally infected with WNV via mosquito bites, the only clinical signs observed were fever and lethargy among 3 of the cats.³⁵ In another study,³⁵ no clinical signs were evident in 4 cats following exposure to WNV via the oral route. Even dogs treated with high doses of glucocorticoids developed no clinical signs of WNV disease following experimental infection with the virus, although the extent of viremia in the glucocorticoid-treated group was significantly greater than that detected in the untreated group.⁸² Additionally, serologic evidence of WNV infections in dogs, cats, and

horses that had no clinical signs of disease has been reported.^{3,46,75}

Humans—West Nile virus infection in humans can have either a neuroinvasive or non-neuroinvasive form. According to the surveillance case definition, a human case of WNND must have fever, the absence of a more likely clinical explanation, and at least 1 of the following⁴¹: acutely altered mental status (eg, disorientation, obtundation, stupor, or coma), other acute signs of central or peripheral neurologic dysfunction (eg, paresis or paralysis, nerve palsies, sensory deficits, abnormal reflexes, generalized convulsions, or abnormal movements), or pleocytosis (high WBC concentration in CSF) associated with illness that is clinically compatible with meningitis (eg, headache or stiff neck). Among WNND patients, it is estimated that approximately 40% have meningitis and 60% have encephalitis.⁷¹ A reported complication in approximately 13% of patients with WNND is acute, asymmetric flaccid paralysis (similar to that associated with poliomyelitis), which results from WNV infection of spinal motor neurons.⁸³ Less frequent complications include myocarditis, acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome), and respiratory failure and death resulting from infection of the brainstem and cranial portion of the cervical spinal cord.^{83,84} In an overview⁷¹ of studies of the pathologic features of WNND in humans, no gross abnormalities of the brain were reported. Histopathologic findings include glial nodules; perivascular cuffing with mononuclear cells; neuronal loss; neuronophagia; focal areas of brain necrosis; inflammation in the spinal cord (especially anterior horn), brainstem, cortex, and cerebellum (often greater in the brainstem); and lymphocytic infiltrates of cranial or spinal nerves.⁷¹

For every reported human WNND case, it is estimated that there are 140 persons with asymptomatic or mildly symptomatic infections⁸⁵; of those, it is estimated that 30 are individuals with non-neuroinvasive WNE.^{41,85} One study⁷¹ estimated that more than 1 million people have been infected in the United States from 1999 through 2006. Among 98 affected humans with non-neuroinvasive WNE, in addition to fever, the most common clinical signs in 1 study⁸⁶ were fatigue (96%), headache (71%), muscle weakness (61%), and difficulty concentrating (53%). A generalized, maculopapular rash may also develop 5 to 12 days after onset of illness.⁸⁷

Diagnosis

In humans and other animals, there are many potential causes of encephalitis, including bacterial, viral, parasitic, and noninfectious causes. West Nile virus encephalitis may be suspected on the basis of clinical signs and history; however, laboratory testing is required for a confirmed diagnosis and to rule out important differential diagnoses. Specimens that can be tested for WNV include CSF, serum, blood, tissues, oral and cloacal swabs, and feather pulp. The laboratory diagnostic methods used for serologic and virologic diagnosis of WNV are similar for humans and other animals (with species-specific differences where war-

ranted). According to the surveillance case definition, arboviral disease can be confirmed in a human on the basis of 1 of the following criteria^{17,41}: 4-fold or greater change in serum virus-specific antibody titer between acute-phase (collected 0 to 8 days after illness onset) and convalescent-phase (collected 14 to 21 days after the acute-phase sample) serum specimens; isolation of virus from or identification of specific viral antigen or genomic sequences in samples of tissue, blood, CSF, or other body fluid; detection via antibody-capture ELISA of virus-specific IgM antibodies in CSF; detection via antibody-capture ELISA of virus-specific IgM antibodies in serum and detection via another serologic assay (ie, PRNT or hemagglutination inhibition) of virus-specific IgG antibodies in the same sample or in a specimen obtained later. Probable cases are those with stable (2-fold or less change between titers in acute- and convalescent-phase specimens) but high titer of virus-specific serum antibodies; or virus-specific serum IgM antibodies detected via antibody-capture ELISA but with no available results of a confirmatory test for virus-specific serum IgG antibodies in the same sample or in a specimen obtained later.

Serologic testing methods are most commonly used for diagnosis of WNV infection in humans and other animals. Assessment of paired acute- and convalescent-phase serum samples is useful for detection of seroconversion to WNV.¹⁷ Typically, WNV-specific IgM antibodies can be detected in human and chicken sera within 8 days of infection.^{17,88} Detection of IgM antibody in a single acute-phase serum specimen provides evidence of recent WNV infection; however, WNV infection cannot be ruled out on the basis of a negative result from 1 acute-phase specimen. Sera can be tested via IgM-capture ELISA and IgG-capture ELISA; results are classified as positive, negative, or equivocal. Plaque reduction neutralization testing is used to confirm positive and equivocal ELISA results or to differentiate between other cross-reactive flaviviruses (eg, St Louis encephalitis virus, which is of importance in assessment of human, bird, and mosquito specimens⁸⁹). If neutralizing antibodies are present, the PRNT result provides a titer with which to quantify the degree of the antibody response. The equine WNV vaccine stimulates production of neutralizing antibodies, thereby confounding the interpretation of PRNT results for vaccinated horses suspected of being infected with WNV.⁹⁰ A competitive ELISA has been developed for more rapid detection of WNV neutralizing antibodies in horse sera.⁹¹ A recombinant WNV envelope protein-based fluorescent microsphere immunoassay that was developed to titrate anti-WNV antibodies in equine sera provides results that are essentially identical to those derived via PRNT for recently vaccinated and unvaccinated horses.⁹²

By use of the IgM-capture ELISA, anti-WNV antibody can be detected in CSF samples as early as the day of illness onset.¹⁷ Virus can also be detected in acute-phase CSF samples via RT-PCR assay or via viral isolation procedures. The advantage of the RT-PCR assay is that it can rapidly detect nucleic acid that is of insufficient quantity or quality for detection via cell culture–virus isolation methods. However, the RT-PCR

procedure is susceptible to cross contamination and test results are often equivocal.⁹³ West Nile virus antigen can also be detected in whole blood samples by use of the RT-PCR technique, and this method has been used in horses and birds.^{94,95} Virus isolation is infrequently performed because it is a more involved procedure that requires specialized biocontainment facilities equipped for work with live virus.

Tissues, including brain, spinal cord, heart, liver, and kidneys, from animals that have died or been euthanized can be submitted for WNV testing. Viral detection methods include cell culture, RT-PCR assay, and immunohistochemistry. An antigen-capture ELISA is a cost-effective alternative for WNV detection in avian tissue specimens collected for surveillance purposes.⁹⁶

The cost and delays associated with specimen shipping and laboratory testing has prompted the development of rapid screening methods that can be performed in-house by local agencies conducting surveillance activities. A dipstick wicking assay^a is available that requires no specific storage or training requirements and provides results within 15 minutes. This method is highly sensitive and specific for detection of WNV in mosquitoes and in avian oral, cloacal, and tissue swabs.^{97,98} The RAMP assay and dipstick wicking assay both use immunochromatographic test strips with labeled antibodies to detect antigen, but the RAMP assay requires an electronic reader and provides results within 1.5 hours. Compared with the dipstick wicking assay, the RAMP assay is more sensitive for detection of WNV in oral swabs obtained from selected avian species and interpretation of results is less subjective, but false-positive results may occur.⁹⁹

Treatment

Currently, treatment of humans and other animals with WNV disease is supportive. A review of data did not find a clear-cut benefit at this time for postexposure treatment of animals (including humans) with interferon, ribavirin, human immunoglobulin, corticosteroids, or antisense oligomers.⁷¹ In horses, supportive treatment includes administration of anti-inflammatory drugs, vitamins, and fluids; antimicrobials are given in an attempt to minimize development of coinfections.⁷⁴ Similar approaches to supportive treatment have been described for dogs, cats, and birds.^{76,81,100}

Prevention and Control

With regard to WNV, an important focus of prevention is environmental control of mosquito vectors. These measures include removal of any potential mosquito breeding sites, such as containers or old tires that collect standing water. Depending on state regulations, ponds or water tanks can be stocked with mosquito fish (*Gambusia affinis*) that feed on mosquito larvae. Local mosquito- and vector-control agencies often provide the public with mosquito fish free of charge as well as consultation on mosquito-control issues. These agencies are tasked with monitoring mosquito populations at the community level and with the control of larval and adult mosquitoes through the use of larvicides and pesticides, respectively.

Mosquito avoidance and repellents are another line of defense against infection. By remaining indoors during dawn and dusk, humans and other animals will avoid exposure to *Culex* mosquitoes during their peak feeding periods. The use of fans and mosquito traps can also reduce mosquito exposure. Topical application of insect repellents containing permethrin, pyrethrins, or butoxypropyl glycol are effective for repelling mosquitoes when used on dogs and horses.^{100,101} It is important to select a product that has been approved for use in the intended species. Products approved for topical use in humans, such as N, N-diethyl-m-toluamide (DEET) or oil of lemon eucalyptus (p-menthane-3,8 diol) should not be used on other animals because of the potential for toxic effects.¹⁰⁰

Given the potential severity of WNV infection in horses, the American Association of Equine Practitioners recommends vaccination of all horses in North America.⁹⁰ There are several commercially available vaccines for equine use that contain either killed virus or modified-live recombinant virus. The initial administration of vaccine is followed by a booster in 3 to 6 weeks. Vaccine manufacturers recommend subsequent boosters be administered 2 to 3 times annually in areas in which the virus is endemic and in areas of ongoing epidemics. Foals can be vaccinated starting at 3 to 4 months of age, and even earlier in foals from nonvaccinated mares.⁹⁰ Vaccination is recommended in advance of the mosquito season to allow sufficient time for development of neutralizing antibodies. Although vaccination may not fully prevent clinical disease, it does reduce the risk of severe disease and death associated with WNV infection, even when vaccination is not performed sufficiently in advance of mosquito-related WNV transmission activity.^{74,102} There is no evidence of adverse effects resulting from vaccination of pregnant mares.¹⁰³

Vaccination has been used experimentally in animals from zoologic collections.¹⁰⁴ There are efforts to develop a human vaccine, but no licensed vaccine currently exists.⁷¹

Public Health Implications

The role of animals in the discovery of WNV in the United States provides yet another example of how animals act as sentinels for emerging diseases. It also highlights the vital role that veterinarians play in recognition of emerging diseases, many of which affect humans. Given the extreme susceptibility of certain species to signs of WNV infection (eg, crows) and their increased opportunity for potential mosquito exposure, animals can be sensitive indicators of WNV activity.

The total impact of human WNV infection in the United States has not been estimated, to our knowledge. But with the relatively long duration and severity of clinical signs, the health-care, personal, and workplace costs are likely to be high. In 1 study⁸⁶ of 98 humans with WNF infection, 31% were hospitalized, 79% missed work or school, 84% had to limit household activities, 91% had to limit activities outside their homes, 91% had to reduce level of exercise, and 48% reported difficulty walking. Sixty-three percent required > 1 month (median, 60 days) for their status to return to normal.

In a survey that was conducted 13 months after diagnosis of WNF or WNND in 49 people in North Dakota, many respondents still reported poor physical health (49%), fatigue (49%), depression (24%), and moderate-to-severe disability (8%).¹⁰⁵ Neuropsychologic testing also revealed abnormalities of motor skills, attention, and executive function. Patients who were never hospitalized and those that were hospitalized were equally likely to experience longer-term adverse outcomes. A recent overview of long-term outcomes has highlighted the need for future studies to monitor parkinsonism and postpolio syndrome as clinical conditions associated with WNV infection.⁴³

Overview

Given the recent emergence of WNV in North America, much remains to be learned about disease associated with the virus. Without doubt, veterinary practitioners are most likely to encounter equine and avian cases, but occasional reports of infection in other species have been made. Therefore, all veterinarians should be familiar with the ecologic and neurotropic features of WNV infection. Knowledge of the seasonal pattern of WNV infection and the availability of local and state surveillance data can assist practicing veterinarians with determining the likelihood of WNV disease in their patients. Laboratory testing is available and necessary for confirmation of WNV infection. The use of environmental modification, mosquito repellents, and vaccination in horses are preventive measures that can be taken against WNV. Any person handling a sick or dead animal that is potentially infected with WNV should take appropriate precautions to prevent contact with infectious material. In addition, pets should not be allowed contact with dead or sick animals that are potentially infected with WNV.

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