West Nile Virus Infection

West Nile Fever,
West Nile Neuroinvasive Disease,
West Nile Disease,
Near Eastern Equine Encephalitis,
Lordige

Last Updated: May 2023

Importance

West Nile virus (WNV) is a mosquito-borne virus that circulates among birds but can also affect other species, particularly humans and horses. Most infections are subclinical; however, up to 20-25% of people are estimated to develop flu-like signs from the more virulent strains, and neurological signs can be seen in a small minority (< 1%), most often but not always in those who are elderly or immunocompromised. Some of these cases are fatal or result in permanent impairment. Encephalitis also occurs in some infected equids, and occasionally in other mammals or reptiles. Approximately 30-40% of the clinical cases in horses result in either death or euthanasia, in part due to the difficulty of safely treating neurological signs in this species. Vaccines are available for horses and some other animals but not humans.

Many WNV strains are thought to be maintained in Africa; however, migrating birds carry these viruses to other continents each year, and some viruses have become established in these locations. Until 1999, West Nile viruses were seen only in the Eastern Hemisphere, where birds appeared to be relatively unaffected, possibly because they had become resistant to the virus through repeated exposure. However, the entry of one virus into North America in 1999 resulted in significant declines in a number of avian species, though most populations have rebounded since then. Similarly, a new WNV lineage that entered Europe in 2003 was followed by reports of clinical cases and deaths in some birds, particularly raptors. Birds and mammals seem to be less affected in some regions such as South America and Africa, for reasons that are unclear.

Etiology

West Nile virus (formal species name *Orthoflavivirus nilense*) is a member of the Japanese encephalitis virus serogroup in the family Flaviviridae. Under some taxonomic schemes, it might be possible to classify this virus into as many as eight or nine genetic lineages, many of which are poorly understood and/or have been isolated only from birds or mosquitoes. The two most common lineages found in clinical cases are lineage 1, which contains 3 clades (1a, 1b and 1c), and lineage 2. Kunjin virus, a subtype of WNV found in Australia, is the common name for clade 1b. Although individual West Nile viruses can differ in virulence, lineage 1 and 2 viruses seem to cause similar clinical signs. Many of the lineage 1 viruses from recent outbreaks, including the virus that became established in the U.S. in 1999, belong to clade 1a and are considered to be relatively virulent.

Species Affected

Birds

Wild birds are the main reservoir hosts for WNV. Some species of birds are usually infected asymptomatically, while others are more likely to become ill. Geese seem to be the only poultry regularly affected by WNV. Chickens and turkeys develop subclinical infections, but gallinaceous game birds appear to be more susceptible, with outbreaks reported in young farmed chukar partridges (*Alectoris chukar*) and Impeyan pheasants (*Lophophorus impeyanus*). Clinical cases have also been seen in emus and some psittacines. Many cases have been documented in free-living or captive wild birds. Most occurred in North America after the introduction of a lineage 1a virus to naive bird populations. Corvids (e.g., crows, ravens, magpies and jays) were severely affected by this virus. Sporadic clinical cases and outbreaks of varying size were also seen in many other species including other songbirds, woodpeckers, various raptors, some species of grouse, pigeons, penguins, ardeid birds (herons, egrets), flamingos, pelicans, cormorants, gulls, grebes and others.

While there are also sporadic reports of deaths from WNV among wild birds in the Eastern Hemisphere, most species there seem to be relatively unaffected, though significant mortality events occurred in various hawks, falcons and other raptors after the introduction of a lineage 2 virus. Northern goshawks (*Accipiter gentilis*), which feed mainly on other birds, seem to be disproportionately affected by this virus. Why most European bird populations are unaffected by WNV is unclear, as experimental infections of some Eurasian species with European lineage 1 and/or 2 viruses have confirmed their ability to cause illness.

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Mammals and marsupials

Most mammals, including horses, are dead-end hosts that do not transmit WNV to mosquitoes. A few species, such as squirrels (*Sciurus* sp.), eastern chipmunks (*Tamias striatus*), eastern cottontail rabbits (*Sylvilagus floridanus*) and brown lemurs (*Lemur fulvus*), have higher levels of viremia and might be able to act as amplifying or maintenance hosts in some circumstances.

Clinical cases are mostly seen in equids, though there are sporadic reports of illness in other domestic or semi-domestic animals, including alpacas, sheep, goats, cattle, dogs, cats and reindeer (*Rangifer tarandus*), as well as in diverse free-living or captive wildlife such as mountain goats (*Oreamnos americanus*), Indian rhinoceroses (*Rhinoceros unicornis*), a white-tailed deer (*Odocoileus virginianus*), wolf pups, a polar bear (*Ursus maritimus*), a Barbary macaque (*Macaca sylvanus*), squirrels, harbor seals (*Phoca vitulina*) a killer whale (*Orcinus orca*), and a Virginia opossum (*Didelphis virginiana*). Additional species known to be susceptible from experimental infections include some rodents (mice, hamsters, chipmunks) and rhesus monkeys (*Macaca mulatta*). Clinical cases in dogs and cats seem to be rare, though they are readily infected.

Evidence for asymptomatic infections, mostly based on antibodies, has been reported in many other mammals including pigs and other suids, camels, rabbits, skunks, raccoons (*Procyon lotor*), bears, sloths, stone marten (*Martes foina*), a civet, both species of elephant, and various canids, large cats, bats, rodents and insectivores. Susceptibility to infection, without clinical signs attributed to the virus, was confirmed by PCR or virus isolation in a few of these species, such as dromedary camels, and by experimental inoculation in rabbits, pigs, guinea pigs, raccoons and European hedgehogs (*Erinaceus europaeus)*.

Reptiles and amphibians

Clinical cases in reptiles have mainly been seen in farmed alligators and crocodiles, but there is a report of a case in a captive crocodile monitor (*Varanus salvadori*) lizard, and green iguanas (*Iguana iguana*) and eastern garter snakes (*Thamnophis sirtalis*) can be experimentally infected. WNV nucleic acids were also found in oral samples from some free-living eastern garter snakes, though the possibility of contamination from prey or the environment was not ruled out. Turtles were seropositive in one study, but no antibodies were found in these animals during an outbreak in Sardinia. Amphibians including lake frogs (*Rana ridibunda*) and North American bullfrogs (*Rana catesbeiana*) can also be infected.

Some reptiles, such as garter snakes and American alligators (*Alligator mississippiensis*), and amphibians (e.g., *Rana ridibunda* lake frogs) may develop viremia sufficient to infect mosquitoes; however, very few mosquitoes became infected and transmission capable when *Culex* species were fed on infected American alligators in the laboratory.

Zoonotic potential

Humans are susceptible to West Nile virus.

Geographic Distribution

WNV is found on all the major continents in the Eastern and Western Hemispheres, and in some other locations such as Australia and the Caribbean. While viruses are endemic in many regions, they may be regularly re-introduced to others via migratory birds or other means. Relatively little is known about the distribution of WNV in Asia, where the presence of the closely-related Japanese encephalitis virus complicates diagnosis. However, WNV is known to circulate on the Indian subcontinent, and it has been isolated from some other countries, such as China.

The distribution of WNV lineages varies. This virus originated in Africa and a number of lineages are thought to circulate there, though information is limited. Clade 1a viruses can be found in many locations, with different viruses occurring in Europe and the Americas. WNV was introduced to the latter location in 1999, probably from the Middle East. Two different lineage 2 viruses, one more widely distributed, have circulated in parts of Europe and Russia for about 15-20 years. Kunjin virus (clade 1b), is only found in Australia, and clade 1c (or lineage 5) viruses are endemic in India. A few other lineages (e.g., lineages 3 and 4) have also been detected occasionally outside Africa, mainly in Europe.

Transmission

WNV is usually acquired from mosquito bites, though some vertebrate hosts can transmit the virus directly to other animals. Members of the genus *Culex* are the most important vectors worldwide, but other mosquitoes can also be infected. Transovarial transmission has been demonstrated in some mosquito species. There are occasional reports of WNV in other arthropods including soft and hard ticks, infected lice (*Philopterus* spp.) collected from WNV-infected crows, and hippoboscid flies. The significance of these infections is uncertain, but a few species of hard and soft ticks can transmit the virus to animals under laboratory conditions.

Some birds, mammals and amphibians can shed WNV in oral secretions and/or feces, and circumstantial and/ or experimental evidence for direct horizontal transmission has been demonstrated in several species including geese, crows, American alligators and saltwater crocodiles (*Crocodylus porosus*). However, not all animals that shed the virus transmit the virus efficiently to their contacts. Carnivorous birds, mammals and reptiles can become infected when they eat infected animals, and the possibility of oral transmission was suggested for insectivores that eat mosquitoes. WNV has also been found in the skin of geese and the blood-feather pulp of crows, possibly contributing to transmission by cannibalism and feather picking. Transplacental transmission was reported in experimentally infected sheep and mice, and in a horse that was fatally infected and aborted in the final stage of the disease.

Humans are usually infected via mosquito bites, but a few cases have been linked to accidental inoculation through breaks in the skin, often in people who handled infected tissues, especially the CNS, from various animals. An outbreak in workers at a turkey farm might have resulted

from fecal-oral transmission from the turkeys, exposure of broken skin or mucous membranes, or inhalation of viruses that had become aerosolized. People are considered dead end hosts for WNV and do not transmit the virus to mosquitoes. Little or no infectious virus also seems to be shed in most secretions and excretions. While WNV RNA is often found in patients' urine, attempts to isolate the virus have been unsuccessful, with rare exceptions such as a patient with encephalitis who had a very high viral load. Rare cases of transplacental transmission, probable transmission in breast milk, and possible sexual transmission (male to female) have, however, been reported. The virus can also be acquired in blood transfusions and organ transplants.

WNV is rapidly inactivated in the environment, with major decreases of its infectivity in avian feces after 24 hours. Some researchers raised the possibility of indirect bird-to-bird transmission in water or crustaceans during an outbreak among grebes at the Great Salt Lake, Utah, and found that infectious virus could be recovered from saltwater spiked with large concentrations of virus and held up to 72 hours at 4°C. Alligators can be experimentally infected by exposure to large amounts of WNV in freshwater; however, infected alligators did not transmit the virus to birds via water, or vice versa. How WNV persists during the winter in temperate climates is uncertain, but possible mechanisms include transovarial transmission in mosquitoes, persistence in dormant mosquitoes, and prolonged persistence of the virus (several weeks to several months) in the tissues of some vertebrate host(s).

Disinfection

West Nile virus can be destroyed by many disinfectants including sodium hypochlorite, hydrogen peroxide, glutaraldehyde, formaldehyde, ethanol, 1% iodine and phenol iodophors. It is also inactivated by UV light and gamma irradiation, as well as exposure to temperatures of 56-60°C (133-140°F) for 30 minutes.

Infections in Animals

Incubation Period

The incubation period is 3-15 days in horses. Some experimentally infected birds can develop clinical signs within a few days.

Clinical Signs

Birds

Many birds are infected asymptomatically with WNV. Clinical cases are often characterized by nonspecific signs of illness (e.g., anorexia, weight loss, lethargy, ruffled feathers), neurological signs, or both. Diarrhea, as well as incoordination, was seen in pheasants in one outbreak, and experimentally infected sage grouse developed a profuse, watery oral and nasal discharge and labored breathing, in addition to other signs. Neurological signs are diverse and may include ataxia, incoordination, paresis or paralysis, disorientation, tremors, nystagmus, torticollis, opisthotonos, impaired vision or blindness, circling and seizures. Sudden death can also be seen, and was the main syndrome in 6-8 week old chukar partridges on game farms, with some birds also developing neurological signs (incoordination) for less than a day before dying. However, there are also reports of a prolonged disease course, for instance in a great horned owl that had intermittent, mild clinical signs for more than five months, or a vulture with neurological signs and progressive deterioration over the course of three weeks. Trauma, as a consequence of the neurological signs, or concurrent bacterial, fungal or viral infections can sometimes complicate the course of the disease.

In early reports, most clinically affected birds died or were euthanized due to their deteriorating condition. However, some birds, including those with neurological signs, can recover with supportive care. Full recovery can sometimes take longer than 6 months in raptors. Sequelae reported in some recovered birds include persistent or recurrent neurological defects, abnormal molting and persistently abnormal feathers.

Mammals

Most horses infected with WNV are asymptomatic, but some develop neurological signs, often accompanied by decreased appetite and depression. Fever is noted in some but not all cases, and can disappear before the onset of CNS signs. Neurological signs may include ataxia, weakness or paralysis of one or more limbs, fasciculations or tremors of the muscles, attitudinal changes (somnolence, apprehension, hyperesthesia or periods of hyperexcitability) and less common signs such as aimless wandering, convulsions, circling or teeth grinding. Cranial nerve deficits can result in weakness or paralysis of the face and tongue, which may lead to difficulty in swallowing. Horses with depression and facial paralysis often hang their heads, resulting in facial edema, which can be severe. Colic and urinary dysfunction, ranging from mild straining to stranguria, have also been reported, and fatal hepatitis accompanied CNS signs in a donkey. Some animals die, but many severely affected horses are euthanized for humane reasons. Most of the surviving horses return to full function, though some have residual neurological defects, decreased exercise tolerance, muscle atrophy or behavioral changes.

Sporadic clinical cases in other mammals were mostly characterized by neurological signs, though a captive Virginia opossum (*Didelphis virginiana*) with a pulmonary adenocarcinoma had only nonspecific signs of illness, with meningoencephalitis from WNV found at necropsy. While CNS signs were the first observed abnormality in many animals, in some cases they were preceded or accompanied by fever, depression, decreased appetite, vomiting and/or diarrhea, oculonasal discharge, labored breathing and other signs. Other non-neurological signs reported in some dogs included conjunctivitis, polydipsia and polyarthritis. Neurological signs can be diverse. In one unusual case in a dog, the first signs were episodes of uncontrolled rolling, which quickly progressed to generalized tremors, ataxia and intermittent fever, while an aged polar bear at a zoo presented

with acute paraparesis. Although WNV is not known to cause reproductive signs in any naturally infected animals, some experimentally infected pregnant sheep aborted, had stillborn lambs, or gave birth to lambs that died soon after birth, though the ewes did not become ill.

Most reported clinical cases have been fatal, but a few animals including an alpaca and a captive seal recovered from mild neurological signs. WNV was also suspected to be the cause of a transient illness in two Indian rhinoceroses characterized by depression, lethargy, decreased appetite and a drooping lip. While rare clinical cases and deaths have been seen in dogs and at least one cat, mild recurrent myopathy was the only sign in experimentally infected dogs, and experimentally infected cats were transiently lethargic with fluctuating fevers. Experimentally infected pigs remained asymptomatic.

Reptiles

Most of the reported clinical cases in reptiles have occurred in farmed alligators and crocodiles, especially juvenile animals. WNV can cause lymphohistiocytic proliferative cutaneous lesions in crocodilians, either with or without other clinical signs. These lesions, known as "pix," appear as transluminant 1-2 mm skin defects that are more prominent after tanning and affect the value of the hide. Systemic illnesses and neurological signs have also been seen. In one outbreak, alligators developed anorexia, lethargy, bloating and neurological signs such as tremors, ataxia, uncoordinated and abnormal swimming, stranding/ inability to submerge, slow reflexes, head tilt, anisocoria and opisthotonos. Affected animals usually died within 24-48 hours. Other signs mentioned in this species include stomatitis and necrotic enteritis. A similar illness with anorexia, weakness, swimming in circles, bloody diarrhea and scoliosis was attributed to WNV in yearling farmed Nile crocodiles (*Crocodylus niloticus*) in Africa. Saltwater crocodile hatchlings experimentally infected with Kunjin virus did not have any clinical signs other than skin lesions (pix).

Other reports of illnesses in reptiles include neurological signs linked to WNV in one naturally infected crocodile monitor, and fatal illnesses in experimentally infected garter snakes. Some of these snakes died suddenly, while others exhibited unusual aggression and immobility of the caudal part of the body. Weakness and cachexia were also seen in some snakes, but could have either been a direct effect of the virus or the result of inappetence.

Post Mortem Lesions

Birds

A wide variety of gross and microscopic lesions, which are often nonspecific, have been reported in birds. Some birds may be thin, emaciated and/or dehydrated, but others are in good body condition. The most common lesions in the internal organs appear to be multiorgan hemorrhages, petechiae and congestion. Splenomegaly, hepatomegaly, myocardial pallor and pale mottling of the liver, spleen or kidney have also been observed, and several reports described cerebral atrophy and malacia in raptors. Gross lesions seem to be minimal or absent in some animals.

Histopathologic lesions have been detected in many organs, but in most birds, they are most common in the CNS, heart (myocarditis), spleen, liver, kidney and eye. The lesions vary, but a combination of encephalitis, endophthalmitis and myocarditis is reported to be characteristic of West Nile disease in some raptors, though all three lesions are not invariably present.

Mammals

Gross lesions are uncommon in horses, and are usually limited to small multifocal areas of discoloration and hemorrhage in the spinal cord, brainstem and/or midbrain. Congestion and hemorrhages of the meninges have also been described. Gross lesions in other tissues are uncommon, though myocarditis has been reported. Histopathologic lesions described in the CNS include lymphocytic or histiocytic poliomeningoencephalitis with perivascular cuffing of mononuclear cells, neuronal degeneration, neuronophagia and focal gliosis. The lesions in other mammals seem to resemble those in horses.

Reptiles

Gross lesions reported in alligators include red to yellow mottling of the liver, which was slightly enlarged, as well as tan to red mottling in the spleen and myocardium, and moderately sized fat bodies and small amounts of clear yellow fluid in the coelomic cavity. Congestion of the lungs, hydropericardium, and hemorrhagic intestines and trachea were attributed to WNV in farmed Nile crocodiles.

Diagnostic Tests

Infectious virus, nucleic acids and antigens may be found in the brain and spinal cord of animals with neurological signs, and sometimes in other affected tissues and/or the blood, depending on the species. Viremia is low and short-lived in horses, and virological confirmation of cases with CNS signs is usually limited to tissue samples collected from the brain and spinal cord at necropsy. WNV is detected more readily in the blood and major organs (e.g., heart, liver) of many birds. It may also be found in oral and/or cloacal swabs in some avian species. Likewise, virus replication seems to be widespread in sick alligators, with virus recovered from blood as well as various tissues. In one outbreak, viral titers were higher in the liver than the CNS.

RT-PCR tests are useful for both antemortem and postmortem diagnosis in birds, but nucleic acids are usually not detectable in live horses with CNS signs. PCR tests vary in their specificity, and some commercial tests may not detect lineage 2 viruses. Virus isolation can also be used for diagnosis, especially when the disease is suspected in a species not previously known to be susceptible; however, its availability can be limited. WNV is often recovered in Vero or RK-13 cells, but other cell lines, including mosquito cells, and embryonated chicken eggs can also be used. The identity of the virus can be confirmed with tests such as immunofluorescence or RT-PCR.

Immunohistochemistry and antigen-capture ELISAs are useful for detecting viral antigens in birds and alligators. Rapid tests include an antigen capture dipstick assay, which can be used to test oral or cloacal swabs from live birds and tissue homogenates from dead birds. Equine CNS does not contain large amounts of virus, and while immunohistochemistry on postmortem tissues can detect some (though not all) infected horses, ELISAs are not sensitive enough to be useful in this species. Cross-reactions with other flaviviruses, particularly those in the Japanese encephalitis serogroup (e.g., Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley encephalitis virus), can be an issue with antigen tests.

WNV infections can also be diagnosed by serology, which is particularly useful in live horses. At least a four-fold increase in WNV-specific antibodies in serum, the detection of specific IgM in cerebrospinal fluid (CSF), or the detection of IgM in serum confirmed by IgG in the same or a later sample are diagnostic. The available tests include ELISAs, hemagglutination inhibition (HI), and virus neutralization assays such as the plaque reduction neutralization (PRN) assay or a microwell format. Either ELISAs or PRN may be employed in horses, and the PRN test can confirm positive or equivocal ELISA results. ELISAs have also been validated for some species of birds. The interpretation of tests other than virus neutralization can be complicated by cross-reactivity to other flaviviruses. Vaccination history must also be considered in horses, some birds and alligators.

Treatment

Animals are treated supportively, with the goal of reducing inflammation in the CNS, preventing self-inflicted injuries and adverse effects from recumbency, and providing nutrition and fluids.

Control

Disease reporting

Veterinarians who encounter or suspect a WNV infection should follow their national and/or local guidelines for disease reporting. Cases are reportable in some U.S. states although the virus is endemic. Dead bird surveillance programs were common in the U.S. after the introduction of WNV, but they have since been phased out or reduced in many areas. State and/or wildlife agencies should be contacted for information about the current programs.

Prevention

Vaccines are the primary means of prevention in horses. They have also been licensed for geese in Israel, may be used off-label in some other species of birds (e.g., endangered California condors), and may be available for alligators in some countries. Knowledge about the efficacy of West Nile vaccines in most species of birds is still limited.

Topical repellents may reduce the risk of WNV during the mosquito season, and housing susceptible species indoors or in screened barns, cages or pens can also decrease mosquito bites. Fans may be helpful, as mosquitoes are not strong flyers. Other mosquito reduction measures, such as emptying containers of standing water, the use of mosquito traps, or mosquito abatement programs with larvicides and/or adulticides may help reduce mosquito populations locally. Isolation of infected animals is necessary if a species can transmit the virus horizontally, and carnivores should not be fed meat that might be contaminated with WNV. Horsemeat was implicated in one outbreak in alligators.

Morbidity and Mortality

In endemic regions, WNV is maintained in an enzootic cycle between culicine mosquitoes and birds, possibly with some other vertebrates playing a minor role. Under some conditions, the virus also causes outbreaks in susceptible incidental hosts, such as equids and humans. Birds are mainly affected from summer to late fall in temperate regions, and cases in horses usually peak in late summer and fall. Cases can also be seen occasionally when mosquitoes are absent, as the result of horizontal transmission, for instance in crows, or in animals that become infected via carnivory, such as bald eagles that fed on infected grebes in late fall/ early winter.

Reported morbidity and mortality rates in birds range from 0% to 90-100%, depending on the species, with particularly high mortality in corvids, some other songbirds, and certain other species, such as greater sage grouse (*Centrocercus urophasianus*). In naturally infected birds, these rates are also influenced by other factors, such immunity, including maternal antibodies transferred in the egg, and the general health of the host. Age is a factor in some species, with deaths mainly reported in nestlings and chicks, though other birds such as crows can be affected at any age. Outbreaks in domestic geese have mainly affected goslings, with older birds usually infected subclinically. Morbidity and mortality rates of approximately 40% were reported in 3-8 week-old goslings during outbreaks in Israel, and 25% mortality was seen in 6-week-old goslings during an outbreak in Canada. Morbidity and mortality rates were 100% in farmed Impeyan pheasants, and the mortality rate was 25% in an outbreak among 6-8 week-old chukar partridges. Many clinical cases in captive wild birds at zoos and other facilities have also been fatal.

With minor exceptions (e.g., imported birds in zoos), birds in the Western Hemisphere were first exposed to WNV in 1999. Some species of free-living wild birds experienced significant regional or, less frequently, continent-wide drops in their numbers. With time, most species have apparently recovered; however, there are exceptions such as the crow population, which seems to be fluctuating at a level last seen in the 1970s and 1980s, and yellow-billed magpies (Pica nutalli), which still appeared to be declining as of 2019. There are also reports of ongoing sporadic deaths or outbreaks in the chicks of some species, often without major effects on the population. Birds in South and Central America, Mexico and the Caribbean seemed to be significantly less affected than birds in North America after virus introduction, despite also being naive to WNV.

Major outbreaks generally do not seem to occur among wild birds in the Eastern Hemisphere, though there are sporadic reports of deaths in various species. However, a number of fatal cases were reported in many wild or captive raptors, particularly northern goshawks, after the introduction of a lineage 2 virus to Europe around 2003. Experimental infections suggest that European birds are not inherently resistant to WNV: significant mortality was seen in some species native to the Eastern Hemisphere, and one report described similar numbers of deaths in house sparrows (*Passer domesticus*) inoculated with lineage 1 isolates from Europe, Africa and North America, though Kunjin virus (Australia) seemed to be less virulent, and the North American isolate killed birds more rapidly.

Mammals and reptiles

From 10% to 43% of infected horses have been estimated to develop neurological signs, though this may underestimate the incidence of asymptomatic infections. Limited evidence suggests that older horses may be more susceptible to illness. Up to 30-45% of the horses with neurological signs either die or are euthanized for humane or economic reasons. Most of the surviving animals have returned to full function, with residual neurological defects in approximately 10-20%.

Both lineage 1 and lineage 2 viruses can cause serious cases and outbreaks in equids, but Kunjin virus in Australia usually results in only a few cases wth severe neurological signs. However, one variant of Kunjin virus caused more than 1000 cases of neurological disease, with a 10-15% case fatality rate, in Australian horses in 2011. Subsequent investigations found that this virus was not unusually virulent compared to historical strains and the outbreak probably resulted from specific circumstances, including the severe flooding that preceded the outbreak.

Antibodies to WNV can also be found in other mammals and marsupials in endemic regions, and seropositivity is relatively common in some species, such as dogs, cats and some wildlife. Clinical cases appear to be sporadic and uncommon in most species. In livestock, they were limited to one to a few animals in a herd even during the initial WNV outbreaks in North America. However, more susceptible hosts might exist, particularly among wildlife. Sick and dead squirrels have been seen in some regions during periods of high WNV activity, and the morbidity rate in experimentally infected fox squirrels was 10%. Most clinically affected mammals have died, although there are reports of recovery in animals with relatively mild neurological signs.

Among reptiles, clinical cases have been reported mainly in farmed alligators and crocodiles. Approximately 250 alligators died in an outbreak at one U.S. alligator farm housing more than 10,000 animals, and more than 1,000 died the following year at the same facility. Young crocodilians appear to be more severely affected than adults.

Infections in Humans

Incubation Period

The incubation period in humans is approximately 2-14 days.

Clinical Signs

Most infections in people are subclinical, but some develop West Nile fever or West Nile neuroinvasive disease. West Nile fever is usually a flu-like illness. Common symptoms include fever, malaise, weakness, headache and body aches, with anorexia, lymphadenopathy, nausea, diarrhea, vomiting, sore throat and conjunctivitis also seen in some patients. An erythematous, nonpruritic, macular, papular or morbilliform skin rash occasionally develops on the neck, trunk, arms or legs. Most uncomplicated infections are mild and resolve within a few days to a week, but persistent fatigue (post-viral syndrome) can occasionally be seen for a month or more in severe cases. Deaths are rare, are often the result of cardiac or respiratory complications, and occur mainly in elderly patients, especially those who have underlying health conditions such as heart disease or cancer.

West Nile neuroinvasive disease generally appears as encephalitis, meningitis and/or acute flaccid paralysis. Meningitis, the mildest form, is characterized by signs such as fever, headache, a stiff neck and photophobia. Symptoms of West Nile encephalitis vary, but they can include changes in consciousness, disorientation, ataxia, tremors, involuntary movements, seizures, signs that resemble Parkinson's disease (rigidity, postural instability and bradykinesia), various cranial nerve abnormalities (e.g., facial weakness, dizziness, vertigo, nystagmus) and other signs. Complete recovery is common in patients with meningitis alone, but encephalitis is sometimes fatal, and some patients who recover have persistent neurological dysfunction.

Acute flaccid paralysis, sometimes called West Nile poliomyelitis, appears suddenly, in many cases with no preceding signs of illness. It progresses rapidly, usually reaching a plateau within hours. The paralysis is typically asymmetrical and can affect one or more limbs, often the legs, which darken. There can also be muscle aches in the lower back, abnormalities in bladder and bowel function, or respiratory distress, which may require mechanical ventilation. Sensory functions are usually normal or minimally affected. Late in the illness, the muscles may atrophy. Recovery is highly variable: some patients recover completely within weeks, while others remain paralyzed.

Uncommon syndromes reported in West Nile outbreaks include myocarditis, pancreatitis, orchitis and fulminant hepatitis, as well as a life-threatening hemorrhagic syndrome, which occurred in a few West Nile cases in Africa and at least one patient in the U.S. Ocular complications including chorioretinitis, uveitis, vitritis and/or optic neuritis are common. Acute kidney disease has been seen in some patients with encephalitis, and possible associations between West Nile neurological disease and chronic kidney disease were suggested by some authors.

Diagnostic Tests

West Nile virus infections in humans are often diagnosed by serological tests similar to those used in animals. Diagnostic criteria include a rising titer or the presence of IgM in serum or CSF. As in animals, cross-reactions with closely related flaviviruses can complicate diagnosis. Virological confirmation is usually possible in the blood of patients with West Nile fever during the first few days of illness, and nucleic acids may also be found in urine or other body fluids. The virus usually disappears from the blood before the onset of neurological signs, but viral RNA may be found in the CSF. Immunohistochemistry to detect viral antigens is mainly a postmortem test, and virus isolation is rarely done.

Treatment

Treatment of neuroinvasive disease and severe West Nile fever is mainly supportive and symptomatic, though more specific therapies (e.g., intravenous immunoglobulins) have been investigated. Intensive care and mechanical ventilation may be required in some cases.

Control

There are currently no vaccines for humans, and prevention, particularly in those who are more susceptible to serious illness, is based on avoiding mosquito bites. This may include measures such as limiting outdoor activities when mosquitoes are active, using mosquito repellents, wearing protective clothing such as long pants and long-sleeved shirts or mesh outer garments, and employing bed nets where mosquitoes may enter houses. Measures to reduce mosquito populations locally are similar to those in animals. People who handle WNV-containing tissues or certain live animals that may shed the virus should protect their mucous membranes and skin from contact with infectious material. Blood products may be screened for WNV to prevent transfusion-associated cases. Surveillance in sentinel animals and mosquitoes can help predict human exposure.

Morbidity and Mortality

Most human WNV infections are thought to be asymptomatic; however, an estimated 20-25% of those infected by some recent, relatively virulent viruses develop West Nile fever and < 1% have West Nile neuroinvasive disease. West Nile fever is typically self-limited and mild in healthy people. Deaths are uncommon in this condition, and approximately 80% occur in those over 70-75 years of age, often from the exacerbation of an underlying health condition. Neuroinvasive disease can be life-threatening, though the case fatality rate is much higher in encephalitis or acute flaccid paralysis than meningitis, which has a case fatality rate around 1%. Neuroinvasive disease is also strongly age-dependent. Cases are much more likely to be seen in the elderly and/or immunocompromised, and these cases are more likely to be fatal than those in younger, healthier people. While rare neurological cases have been seen in children, especially those who have other serious health issues, children mostly tend to develop meningitis and recover completely.

Serious clinical cases caused by WNV, with occasional outbreaks, have been reported in North America since the introduction of a lineage 1a virus in 1999. The incidence peaked soon after virus introduction, then declined, but has fluctuated since then. Outbreaks have also been seen recently in Europe, though neuroinvasive disease was uncommon before the introduction of a lineage 2 virus. Outbreaks are often focal, with shifts in their locations from year to year. They are thought to be affected by weather patterns as well as various interactions of the virus with mosquitoes and vertebrate hosts, and are difficult or impossible to predict. Cases in temperate regions typically peak in late summer and fall, like cases in horses.

WNV seems to cause relatively little mortality in Africa or South America, though some serious cases and a few large outbreaks have been reported. One outbreak, which occurred in 1974, took place in a semi-arid part of Africa where seroprevalence is normally low, and affected tens of thousands of people. One possible explanation for the limited number of cases in the Southern Hemisphere is that cases are underdiagnosed, especially in areas where infections with other flaviviruses complicate diagnosis and/or diagnostic testing is limited. However, it is also plausible that related flaviviruses provide some cross-protective immunity, or that people in areas with abundant mosquito populations tend to become infected as children and are immune by the time they become more susceptible to neuroinvasive disease. Kunjin virus in Australia mainly seems to cause relatively mild, nonfatal neurological disease in people. Severe human cases were not seen during the equine outbreaks in 2011.

Internet Resources

Public Health Agency of Canada. Pathogen Safety Data Sheets

The Merck Manual

United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS). Equine West Nile Virus.

The Merck Veterinary Manual

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

WOAH Terrestrial Animal Health Code

Acknowledgements

This factsheet was written by Anna Rovid Spickler, DVM, PhD, Veterinary Specialist from the Center for Food Security and Public Health. The U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) provided funding for this factsheet through

a series of cooperative agreements related to the development of resources for initial accreditation training.

The following format can be used to cite this factsheet. Spickler, Anna Rovid. 2023.*West Nile Virus Infection*. Retrieved from http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php.

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