

# West Nile fever

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**West Nile fever** is a mosquito-borne infection by the West Nile virus. Approximately 80% of West Nile virus infections in humans have few or no symptoms.<sup>[1]</sup> In the cases where symptoms do occur—termed West Nile fever in cases without neurological disease—the time from infection to the appearance of symptoms is typically between 2 and 15 days. Symptoms may include fever, headaches, feeling tired, muscle pain or aches, nausea, loss of appetite, vomiting, and rash. Less than 1% of the cases are severe and result in neurological disease when the central nervous system is affected. People of advanced age, the very young, or those with immunosuppression, either medically induced, such as those taking immunosuppressive drugs, or due to a pre-existing medical condition such as HIV infection, are most susceptible. The specific neurological diseases that may occur are West Nile encephalitis, which causes inflammation of the brain, West Nile meningitis, which causes inflammation of the meninges, which are the protective membranes that cover the brain and spinal cord, West Nile meningoencephalitis, which causes inflammation of the brain and also the meninges surrounding it, and West Nile poliomyelitis—spinal cord inflammation, which results in a syndrome similar to polio, which may cause acute flaccid paralysis.

West Nile virus is an arbovirus of the *Flavivirus* kind in the family *Flaviviridae*. The main way it is spread is by various species of mosquitoes, with birds being the most commonly infected animal and serving as the prime reservoir host. WNV has been found in various species of ticks, but current research suggests they are not important vectors of the virus. WNV also infects various mammal species, including humans, and has been identified in reptilian species, including alligators and crocodiles, and also in amphibians. Not all animal species that are susceptible to WNV infection, including humans, and not all bird species develop sufficient viral levels to transmit the disease to uninfected mosquitoes, and are thus not considered major factors in WNV transmission.<sup>[2][3]</sup>

Currently, there are no vaccine for WNV. The best method to reduce the rates of WNV infection is mosquito control on the part of municipalities, businesses and individual citizens to reduce breeding populations of mosquitoes in public, commercial and private areas via various means including eliminating standing pools of water where mosquitoes breed, such as in old tires, buckets, sagging gutters, and unused swimming pools. On an individual basis, the use of personal protective measures to avoid being bitten by an infected mosquito, via the use of mosquito repellent, window screens, avoiding areas where mosquitoes are more prone to congregate, such as near marshes, and areas with heavy vegetation, and being more vigilant from dusk to dawn when mosquitoes are most active offers the best defense. In the event of being bitten by an infected mosquito, familiarity of the symptoms of WNV on the part of laypersons, physicians and allied health professions affords the best chance of receiving timely medical treatment, which may aid in reducing associated possible complications and also appropriate palliative care.

WNV is found in temperate and tropical regions of the world. It was first identified in the West Nile subregion in Uganda in 1937. Prior to the mid-1990s, WNV disease occurred only sporadically and was considered a minor risk for humans, until an outbreak in Algeria in 1994, with cases of WNV-caused encephalitis, and the first large outbreak in Romania in 1996, with a high number of cases with neuroinvasive disease. WNV has now spread globally, with the first case in the Western Hemisphere being identified in New York City in 1999,<sup>[4]</sup> over the next five years, the virus spread across the continental United States, north into Canada, and southward into the Caribbean islands and Latin America. WNV also spread to Europe, beyond the Mediterranean Basin, and a new strain of the virus was identified in Italy in 2012.<sup>[5]</sup> WNV spreads on an ongoing basis in Africa, Asia, Australia, the Middle East, Europe, Canada<sup>[6]</sup> and in the United States. In 2012 the US experienced one of its worst epidemics in which 286 people died, with the state of Texas being hard hit by this virus.<sup>[7][8]</sup>

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<b>ICD-10</b>	A92.3 ( <a href="http://apps.who.int/classifications/icd10/browse/2016/en#/A92.3">http://apps.who.int/classifications/icd10/browse/2016/en#/A92.3</a> )
<b>ICD-9-CM</b>	066.4 ( <a href="http://www.icd9data.com/getICD9Code.ashx?icd9=066.4">http://www.icd9data.com/getICD9Code.ashx?icd9=066.4</a> )
<b>DiseasesDB</b>	30025 ( <a href="http://www.diseasesdatabase.com/ddb30025.htm">http://www.diseasesdatabase.com/ddb30025.htm</a> )
<b>MedlinePlus</b>	007186 ( <a href="https://medlineplus.gov/ency/article/007186.htm">https://medlineplus.gov/ency/article/007186.htm</a> )
<b>Patient UK</b>	West Nile fever ( <a href="http://patient.info/doctor/West-Nile-Virus">http://patient.info/doctor/West-Nile-Virus</a> )
<b>MeSH</b>	D014901 ( <a href="https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi?field=uid&amp;term=D014901">https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi?field=uid&amp;term=D014901</a> )

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## Signs and symptoms

The incubation period for WNV—the amount of time from infection to symptom onset—is typically from between 2 and 15 days. Headache can be a prominent symptom of WNV fever, meningitis, encephalitis, meningoencephalitis, and it may or may not be present in poliomyelitis-like syndrome. Thus, headache is not a useful indicator of neuroinvasive disease.

- **West Nile fever (WNF)**, which occurs in 20 percent of cases, is a febrile syndrome that causes flu-like symptoms.<sup>[9]</sup> Most characterizations of WNF generally describe it as a mild, acute syndrome lasting 3 to 6 days after symptom onset. Systematic follow-up studies of patients with WNF have not been done, so this information is largely anecdotal. In addition to a high fever, headache, chills, excessive sweating, weakness, fatigue, swollen lymph nodes, drowsiness, pain in the joints and flu-like symptoms. Gastrointestinal symptoms that may occur include nausea, vomiting, loss of appetite, and diarrhea. Fewer than one-third of patients develop a rash.
- **West Nile neuroinvasive disease (WNND)**, which occurs in less than 1 percent of cases, is when the virus infects the central nervous system resulting in meningitis, encephalitis, meningoencephalitis or a poliomyelitis-like syndrome.<sup>[10]</sup> Many patients with WNND have normal neuroimaging studies, although abnormalities may be present in various cerebral areas including the basal ganglia, thalamus, cerebellum, and brainstem.<sup>[10]</sup>
- **West Nile virus encephalitis (WNE)** is the most common neuroinvasive manifestation of WNND. WNE presents with similar symptoms to other viral encephalitis with fever, headaches, and altered mental status. A prominent finding in WNE is muscular weakness (30 to 50 percent of patients with encephalitis), often with lower motor neuron symptoms, flaccid paralysis, and hyporeflexia with no sensory abnormalities.<sup>[11][12]</sup>
- **West Nile meningitis (WNM)** usually involves fever, headache, and stiff neck. Pleocytosis, an increase of white blood cells in cerebrospinal fluid, is also present. Changes in consciousness are not usually seen and are mild when present.
- **West Nile meningoencephalitis** is inflammation of both the brain (encephalitis) and meninges (meningitis).
- **West Nile poliomyelitis (WNP)**, an acute flaccid paralysis syndrome associated with WNV infection, is less common than WNM or WNE. This syndrome is generally characterized by the acute onset of asymmetric limb weakness or paralysis in the absence of sensory loss. Pain sometimes precedes the paralysis. The paralysis can occur in the absence of fever, headache, or other common symptoms associated with WNV infection. Involvement of respiratory muscles, leading to acute respiratory failure, can sometimes occur.
- **West-Nile reversible paralysis**, Like WNP, the weakness or paralysis is asymmetric.<sup>[13]</sup> Reported cases have been noted to have an initial preservation of deep tendon reflexes, which is not expected for a pure anterior horn involvement.<sup>[13]</sup> Disconnect of upper motor neuron influences on the anterior horn cells possibly by myelitis or glutamate excitotoxicity have been suggested as mechanisms.<sup>[13]</sup> The prognosis for recovery is excellent.
- **Nonneurologic complications** of WNV infection that may rarely occur include fulminant hepatitis, pancreatitis,<sup>[14]</sup> myocarditis, rhabdomyolysis,<sup>[15]</sup> orchitis,<sup>[16]</sup> nephritis, optic neuritis<sup>[17]</sup> and cardiac dysrhythmias and hemorrhagic fever with coagulopathy.<sup>[18]</sup> Chorioretinitis may also be more common than previously thought.<sup>[19]</sup>
- **Cutaneous manifestations** specifically rashes, are not uncommon in WNV-infected patients; however, there is a paucity of detailed descriptions in case reports and there are few clinical images widely available. Punctate erythematous, macular, and papular eruptions, most pronounced on the extremities have been observed in WNV cases and in some cases histopathologic findings have shown a sparse superficial perivascular lymphocytic infiltrate, a manifestation commonly seen in viral exanthems. A literature review provides support that this punctate rash is a common cutaneous presentation of WNV infection.<sup>[20]</sup>

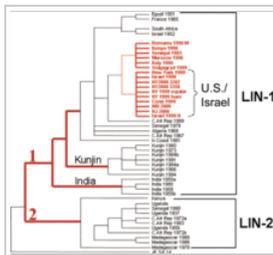
## Virology

WNV is one of the Japanese encephalitis antigenic serocomplex of viruses. Image reconstructions and cryoelectron microscopy reveal a 45–50 nm virion covered with a relatively smooth protein surface. This structure is similar to the dengue fever virus; both belong to the genus *Flavivirus* within the family *Flaviviridae*. The genetic material of WNV is a positive-sense, single strand of RNA, which is between 11,000 and 12,000 nucleotides long; these genes encode seven nonstructural proteins and three structural proteins. The RNA strand is held within a nucleocapsid formed from 12-kDa protein blocks; the capsid is contained within a host-derived membrane altered by two viral glycoproteins.

## Phylogeny

Studies of phylogenetic lineages determined WNV emerged as a distinct virus around 1000 years ago.<sup>[22]</sup> This initial virus developed into two distinct lineages, lineage 1 and its multiple profiles is the source of the epidemic transmission in Africa and throughout the world. Lineage 2 was considered an Africa zoonosis. However, in 2008, lineage 2, previously only seen in horses in sub-Saharan Africa and Madagascar, began to appear in horses in Europe, where the first known outbreak affected 18 animals in Hungary in 2008.<sup>[23]</sup> Lineage 1 West Nile virus was detected in South Africa in 2010 in a mare and her aborted fetus; previously, only lineage 2 West Nile virus had been detected in horses and humans in South Africa.<sup>[24]</sup> A 2007 fatal case in a killer whale in Texas broadened the known host range of West Nile virus to include cetaceans.<sup>[25]</sup>

The United States virus was very closely related to a lineage 1 strain found in Israel in 1998. Since the first North American cases in 1999, the virus has been reported throughout the United States, Canada, Mexico, the Caribbean, and Central America. There have been human cases and equine cases, and many birds are infected. The Barbary macaque, *Macaca sylvanus*, was the first nonhuman primate to contract WNV.<sup>[26]</sup> Both the United States and Israeli strains are marked by high mortality rates in infected avian populations; the presence of dead birds—especially Corvidae—can be an early indicator of the arrival of the virus.



Phylogenetic tree of West Nile viruses based on sequencing of the envelope gene during complete genome sequencing of the virus<sup>[21]</sup>

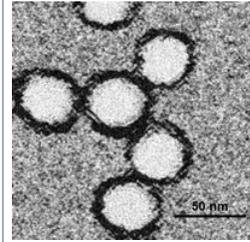
## Transmission

West Nile virus (WNV) is transmitted through female mosquitoes, which are the prime vectors of the virus. Only females feed on blood, and different species take a blood meal from different types of vertebrate hosts. The important mosquito vectors vary according to geographical area; in the United States, *Culex pipiens* (Eastern United States, and urban and residential areas of the United States north of 36–39°N), *Culex tarsalis* (Midwest and West), and *Culex quinquefasciatus* (Southeast) are the main vector species.<sup>[27]</sup>

The mosquito species that are most frequently infected with WNV feed primarily on birds.<sup>[28]</sup> Mosquitoes show further selectivity, exhibiting preference for different species of birds. In the United States, WNV mosquito vectors feed on members of the Corvidae and thrush family more often than would be expected from their abundance.<sup>[29]</sup> Among the preferred species within these families are the American crow, a corvid, and the American robin (*Turdus migratorius*), a thrush.<sup>[29]</sup>

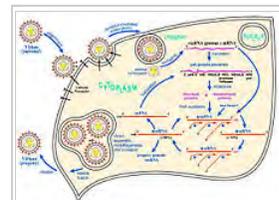
Some species of birds develop sufficient viral levels ( $> \sim 10^{4.2}$  log PFU/ml;<sup>[30]</sup>) after being infected to transmit the infection to biting mosquitoes that in turn go on to infect other birds. In birds that die from WNV, death usually occurs after 4 to 6 days.<sup>[31]</sup> In mammals, and several species of birds the virus does not multiply as readily (i.e., does not develop high viremia during infection), and mosquitoes biting infected these hosts are not believed to ingest sufficient virus to become infected, making them so-called dead-end hosts.<sup>[30]</sup> As a result of the differential infectiousness of hosts, the feeding patterns of mosquitoes play an important role in WNV transmission,<sup>[28][29]</sup> and they are partly genetically controlled, even within a species.

### West Nile virus



### Virus classification

Group: Group IV ((+) ssRNA)  
 Order: *Unassigned*  
 Family: *Flaviviridae*  
 Genus: *Flavivirus*  
 Species: ***West Nile virus***



West Nile virus life cycle. After binding and uptake, the virion envelope fuses with cellular membranes, followed by uncoating of the nucleocapsid and release of the RNA genome into the cytoplasm. The viral genome serves as messenger RNA (mRNA) for translation of all viral proteins and as template during RNA replication. Copies are subsequently packaged within new virus particles that are transported in vesicles to the cell membrane.



The proboscis of a female mosquito—here a southern house mosquito (*Culex quinquefasciatus*)—pierces the epidermis and dermis to allow it to feed on human blood from a capillary: this one is almost fully tumescent. The mosquito injects saliva, which contains an anesthetic, and an anticoagulant into the puncture wound, and in infected mosquitoes, West Nile virus.

Direct human-to-human transmission initially was believed to be caused only by occupational exposure, such as in a laboratory setting,<sup>[32]</sup> or conjunctive exposure to infected blood.<sup>[33]</sup> The US outbreak identified additional transmission methods through blood transfusion,<sup>[34]</sup> organ transplant,<sup>[35]</sup> intrauterine exposure,<sup>[36]</sup> and breast feeding.<sup>[37]</sup> Since 2003, blood banks in the United States routinely screen for the virus among their donors.<sup>[38]</sup> As a precautionary measure, the UK's National Blood Service initially ran a test for this disease in donors who donate within 28 days of a visit to the United States, Canada, or the northeastern provinces of Italy, and the Scottish National Blood Transfusion Service<sup>[39]</sup> asks prospective donors to wait 28 days after returning from North America or the northeastern provinces of Italy before donating.

Recently, the potential for mosquito saliva to affect the course of WNV disease was demonstrated.<sup>[40][41][42]</sup> Mosquitoes inoculate their saliva into the skin while obtaining blood. Mosquito saliva is a pharmacological cocktail of secreted molecules, principally proteins, that can affect vascular constriction, blood coagulation, platelet aggregation, inflammation, and immunity. It clearly alters the immune response in a manner that may be advantageous to a virus.

<sup>[43][44][45][46]</sup> Studies have shown it can specifically modulate the immune response during early virus infection,<sup>[47]</sup> and mosquito feeding can exacerbate WNV infection, leading to higher viremia and more severe forms of disease.<sup>[40][41][42]</sup>

### Vertical transmission

Vertical transmission, the transmission of a viral or bacterial disease from the female of the species to her offspring, has been observed in various West Nile virus studies, amongst different species of mosquitoes in both the laboratory and in nature.<sup>[48]</sup> Mosquito progeny infected vertically in autumn, may potentially serve as a mechanism for WNV to overwinter and initiate enzootic horizontal transmission the following spring, although it likely plays little role in transmission in the summer and fall.<sup>[49]</sup>

### Risk factors

Risk factors independently associated with developing a clinical infection with WNV include a suppressed immune system and a patient history of organ transplantation.<sup>[50]</sup> For neuroinvasive disease the additional risk factors include older age (>50+), male sex, hypertension, and diabetes mellitus.<sup>[51][52]</sup>

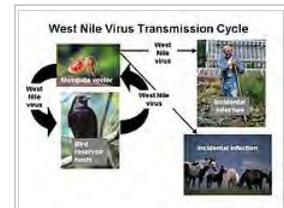
A genetic factor also appears to increase susceptibility to West Nile disease. A mutation of the gene *CCR5* gives some protection against HIV but leads to more serious complications of WNV infection. Carriers of two mutated copies of *CCR5* made up 4.0 to 4.5% of a sample of West Nile disease sufferers, while the incidence of the gene in the general population is only 1.0%.<sup>[53][54]</sup>

## Diagnosis

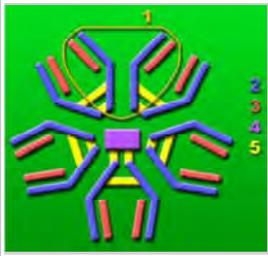
Preliminary diagnosis is often based on the patient's clinical symptoms, places and dates of travel (if patient is from a nonendemic country or area), activities, and epidemiologic history of the location where infection occurred. A recent history of mosquito bites and an acute febrile illness associated with neurologic signs and symptoms should cause clinical suspicion of WNV.

Diagnosis of West Nile virus infections is generally accomplished by serologic testing of blood serum or cerebrospinal fluid (CSF), which is obtained via a lumbar puncture. Initial screening could be done using the ELISA technique detecting immunoglobulins in the sera of the tested individuals.

Typical findings of WNV infection include lymphocytic pleocytosis, elevated protein level, reference glucose and lactic acid levels, and no erythrocytes.



West Nile virus maintains itself in nature by cycling between mosquitoes in the genus *Culex* and certain species of birds. A mosquito (the vector) bites an uninfected bird (the host), the virus amplifies within the bird, an uninfected mosquito bites the bird and is in turn infected. Other species such as humans and horses are incidental infections, because the virus does not amplify well within these species and they are considered dead-end hosts.



An immunoglobulin M antibody molecule:  
Definitive diagnosis of WNV is obtained through detection of virus-specific IgM and neutralizing antibodies.

Definitive diagnosis of WNV is obtained through detection of virus-specific antibody IgM and neutralizing antibodies. Cases of West Nile virus meningitis and encephalitis that have been serologically confirmed produce similar degrees of CSF pleocytosis and are often associated with substantial CSF neutrophilia.<sup>[55]</sup> Specimens collected within eight days following onset of illness may not test positive for West Nile IgM, and testing should be repeated. A positive test for West Nile IgG in the absence of a positive West Nile IgM is indicative of a previous flavavirus infection and is not by itself evidence of an acute West Nile virus infection.<sup>[56]</sup>

If cases of suspected West Nile virus infection, sera should be collected on both the acute and convalescent phases of the illness. Convalescent specimens should be collected 2–3 weeks after acute specimens.

It is common in serologic testing for cross-reactions to occur among flaviviruses such as dengue virus (DENV) and tick-borne encephalitis virus; this necessitates caution when evaluating serologic results of flaviviral infections.<sup>[57]</sup>

Four FDA-cleared WNV IgM ELISA kits are commercially available from different manufacturers in the U.S., each of these kits is indicated for use on serum to aid in the presumptive laboratory diagnosis of WNV infection in patients with clinical symptoms of meningitis or encephalitis. Positive WNV test results obtained via use of these kits should be confirmed by additional testing at a state health department laboratory or CDC.

In fatal cases, nucleic acid amplification, histopathology with immunohistochemistry, and virus culture of autopsy tissues can also be useful. Only a few state laboratories or other specialized laboratories, including those at CDC, are capable of doing this specialized testing.

## Differential diagnosis

A number of various diseases may present with symptoms similar to those caused by a clinical West Nile virus infection. Those causing neuroinvasive disease symptoms include the enterovirus infection and bacterial meningitis. Accounting for differential diagnoses is a crucial step in the definitive diagnosis of WNV infection. Consideration of a differential diagnosis is required when a patient presents with unexplained febrile illness, extreme headache, encephalitis or meningitis. Diagnostic and serologic laboratory testing using polymerase chain reaction (PCR) testing and viral culture of CSF to identify the specific pathogen causing the symptoms, is the only currently available means of differentiating between causes of encephalitis and meningitis.

## Prevention

Personal protective measures can be taken to greatly reduce the risk of being bitten by an infected mosquito:

- Using insect repellent on exposed skin to repel mosquitoes. EPA-registered repellents include products containing DEET (N,N-diethylmetatoluamide) and picaridin (KBR 3023). DEET concentrations of 30% to 50% are effective for several hours. Picaridin, available at 7% and 15% concentrations, needs more frequent application. DEET formulations as high as 30% are recommended for children over two months of age.<sup>[58]</sup> Protect infants less than two months of age by using a carrier draped with mosquito netting with an elastic edge for a tight fit.
- When using sunscreen, apply sunscreen first and then repellent. Repellent should be washed off at the end of the day before going to bed.
- Wear long-sleeve shirts, which should be tucked in, long pants, socks, and hats to cover exposed skin. Insect repellents should be applied over top of protective clothing for greater protection. Do not apply insect repellents underneath clothing.
- The application of permethrin-containing (*e.g.*, Permanone) or other insect repellents to clothing, shoes, tents, mosquito nets, and other gear for greater protection. Permethrin is not labeled for use directly on skin. Most repellent is generally removed from clothing and gear by a single washing, but permethrin-treated clothing is effective for up to five washings.
- Be aware that most mosquitoes that transmit disease are most active during twilight periods (dawn and dusk or in the evening). A notable exception is the Asian tiger mosquito, which is a daytime feeder and is more apt to be found in, or on the periphery of, shaded areas with heavy vegetation. They are now widespread in the United States, and in Florida they have been found in all 67 counties.<sup>[59]</sup>
- Staying in air-conditioned or well-screened housing, and/or sleeping under an insecticide-treated bed net. Bed nets should be tucked under mattresses and can be sprayed with a repellent if not already treated with an insecticide.



Low-cost, ceiling hung mosquito netting for a bed

## Monitoring and control

West Nile virus can be sampled from the environment by the pooling of trapped mosquitoes via ovitraps, carbon dioxide-baited light traps, and gravid traps, testing blood samples drawn from wild birds, dogs, and sentinel monkeys, as well as testing brains of dead birds found by various animal control agencies and the public.

Testing of the mosquito samples requires the use of reverse-transcriptase PCR (RT-PCR) to directly amplify and show the presence of virus in the submitted samples. When using the blood sera of wild birds and sentinel chickens, samples must be tested for the presence of WNV antibodies by use of immunohistochemistry (IHC)<sup>[60]</sup> or enzyme-linked immunosorbent assay (ELISA).<sup>[61]</sup>

Dead birds, after necropsy, or their oral swab samples collected on specific RNA-preserving filter paper card,<sup>[62][63]</sup> can have their virus presence tested by either RT-PCR or IHC, where virus shows up as brown-stained tissue because of a substrate-enzyme reaction.

West Nile control is achieved through mosquito control, by elimination of mosquito breeding sites such as abandoned pools, applying larvicide to active breeding areas, and targeting the adult population via lethal ovitraps and aerial spraying of pesticides.

Environmentalists have condemned attempts to control the transmitting mosquitoes by spraying pesticide, saying the detrimental health effects of spraying outweigh the relatively few lives that may be saved, and more environmentally friendly ways of controlling mosquitoes are available. They also question the effectiveness of insecticide spraying, as they believe mosquitoes that are resting or flying above the level of spraying will not be killed; the most common vector in the northeastern United States, *Culex pipiens*, is a canopy feeder.



A carbon dioxide-baited CDC light trap at NPS monitoring site: The highest individual light trap total for 2010 was from a trap located in a salt marsh in the Fire Island National Seashore: around 25,142 mosquitoes were collected during a 16-hour period on August 31.<sup>[64]</sup>

Eggs of permanent water mosquitoes can hatch, and the larvae survive, in only a few ounces of water. Less than half the amount that may collect in a discarded coffee cup. Floodwater species lay their eggs on wet soil or other moist surfaces. Hatch time is variable for both types; under favorable circumstances, i.e. warm weather, the eggs of some species may hatch in as few as 1–3 days after being laid.<sup>[65]</sup>

Used tires often hold stagnant water and are a breeding ground for many species of mosquitoes. Some species such as the Asian tiger mosquito prefer manmade containers, such as tires, in which to lay their eggs. The rapid spread of this aggressive daytime feeding species beyond their native range has been attributed to the used tire trade.<sup>[59][66]</sup>

## Treatment

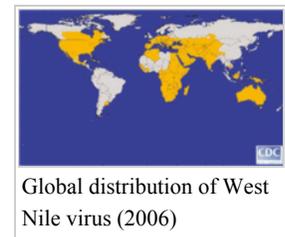
No specific treatment is available for WNV infection. In severe cases treatment consists of supportive care that often involves hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections.

## Prognosis

While the general prognosis is favorable, current studies indicate that West Nile Fever can often be more severe than previously recognized, with studies of various recent outbreaks indicating that it may take as long as 60–90 days to recover.<sup>[12][67]</sup> People with milder WNF are just as likely as those with more severe manifestations of neuroinvasive disease to experience multiple long term (>1+ years) somatic complaints such as tremor, and dysfunction in motor skills and executive functions. People with milder illness are just as likely as people with more severe illness to experience adverse outcomes.<sup>[68]</sup> Recovery is marked by a long convalescence with fatigue. One study found that neuroinvasive WNV infection was associated with an increased risk for subsequent kidney disease.<sup>[69][70]</sup>

## Epidemiology

WNV was first isolated from a feverish 37-year-old woman at Omogo in the West Nile District of Uganda in 1937 during research on yellow fever virus.<sup>[71]</sup> A series of serosurveys in 1939 in central Africa found anti-WNV positive results ranging from 1.4% (Congo) to 46.4% (White Nile region, Sudan). It was subsequently identified in Egypt (1942) and India (1953), a 1950 serosurvey in Egypt found 90% of those over 40 years in age had WNV antibodies. The ecology was characterized in 1953 with studies in Egypt<sup>[72]</sup> and Israel.<sup>[73]</sup> The virus became recognized as a cause of severe human meningoencephalitis in elderly patients during an outbreak in Israel in 1957. The disease was first noted in horses in Egypt and France in the early 1960s and found to be widespread in southern Europe, southwest Asia and Australia.



The first appearance of WNV in the Western Hemisphere was in 1999<sup>[4]</sup> with encephalitis reported in humans, dogs, cats, and horses, and the subsequent spread in the United States may be an important milestone in the evolving history of this virus. The American outbreak began in College Point, Queens in New York City and was later spread to the neighboring states of New Jersey and Connecticut. The virus is believed to have entered in an infected bird or mosquito, although there is no clear evidence.<sup>[74]</sup> West Nile virus is now endemic in Africa, Europe, the Middle East, west and central Asia, Oceania (subtype Kunjin), and most recently, North America and is spreading into Central and South America.

Recent outbreaks of West Nile virus encephalitis in humans have occurred in Algeria (1994), Romania (1996 to 1997), the Czech Republic (1997), Congo (1998), Russia (1999), the United States (1999 to 2009), Canada (1999–2007), Israel (2000) and Greece (2010).

Epizootics of disease in horses occurred in Morocco (1996), Italy (1998), the United States (1999 to 2001), and France (2000), Mexico (2003) and Sardinia (2011).

Outdoor workers (including biological fieldworkers, construction workers, farmers, landscapers, and painters), healthcare personnel, and laboratory personnel who perform necropsies on animals are at risk of contracting WNV.<sup>[75]</sup>

## Research

A vaccine for horses (ATCvet code: QI05AA10 (WHO ([http://www.whocc.no/atcvet/atcvet\\_index/?code=QI05AA10](http://www.whocc.no/atcvet/atcvet_index/?code=QI05AA10)))) based on killed viruses exists; some zoos have given this vaccine to their birds, although its effectiveness is unknown. Dogs and cats show few if any signs of infection. There have been no known cases of direct canine-human or feline-human transmission; although these pets can become infected, it is unlikely they are, in turn, capable of infecting native mosquitoes and thus continuing the disease cycle.<sup>[76]</sup> AMD3100, which had been proposed as an antiretroviral drug for HIV, has shown promise against West Nile encephalitis. Morpholino antisense oligos conjugated to cell penetrating peptides have been shown to partially protect mice from

WNV disease.<sup>[77]</sup> There have also been attempts to treat infections using ribavirin, intravenous immunoglobulin, or alpha interferon.<sup>[78]</sup> GenoMed, a U.S. biotech company, has found that blocking angiotensin II can treat the "cytokine storm" of West Nile virus encephalitis as well as other viruses.<sup>[79]</sup>

A vaccine called Chimerivax-WNV is being actively researched and has undergone phase II Clinical trials in 2011.<sup>[80][81]</sup>

## References

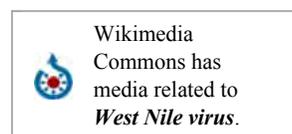
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- Virus Pathogen Database and Analysis Resource (ViPR): Flaviviridae (<http://www.viprbrc.org/brc/home.do?decorator=flavi>)
- Species Profile- West Nile Virus (*Flavivirus*) (<http://www.invasivespeciesinfo.gov/microbes/westnile.shtml>), National Invasive Species Information Center, United States National Agricultural Library. Lists general information and resources for West Nile Virus.
- 3D macromolecular structures of the West Nile Virus archived in the EM Data Bank(EMDB) (<http://www.pdbe.org/emsearch/west%20nile%20virus>)
- West Nile Virus ([http://rad.usuhs.edu/medpix/parent.php3?mode=TFcase\\_thumbnails&case\\_prog=/medpix/cow\\_image.html&pt\\_id=14187&topic\\_id=4124&imageid=58164&quiz=no#](http://rad.usuhs.edu/medpix/parent.php3?mode=TFcase_thumbnails&case_prog=/medpix/cow_image.html&pt_id=14187&topic_id=4124&imageid=58164&quiz=no#))  
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