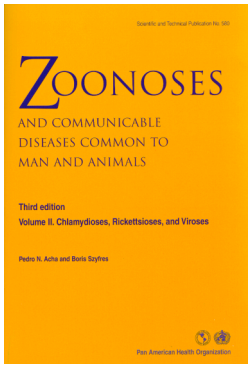




**From Zoonoses and Communicable Diseases Common to Man and Animals, Third Edition. Volume II: Chlamydioses, Rickettsioses, and Viroses.**
**By Pedro N. Acha and Boris Szyfres.**
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This section, reproduced in full from the above book, contains information on Virus Etiology, Geographic Distribution, Occurrence, The Disease in Man, The Disease in Animals, Source of Infection and Mode of Transmission, The Role of Animals in the Epidemiology of the Disease, Diagnosis, Control, and Bibliography.

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## WEST NILE FEVER

## ICD-10 A92.3

**Etiology:** West Nile (WN) virus, a single-stranded RNA virus belonging to the genus *Flavivirus,* family Flaviviridae (formerly Togaviridae)[1]; it forms part of the complex that includes the St. Louis, Murray Valley, Japanese, and Rocio encephalitis viruses. In Madagascar, an antigenic study using monoclonal antibodies from 53 strains of West Nile virus revealed that there were five antigenic groups of the virus in that country: four groups closely related to the strain Eg 101 found in Egypt and unlike the strains found in South Africa and India, and one group closely related to the strain found in India. Antigenic variation is observed in each transmission cycle, a phenomenon attributed to the fact that, in Madagascar, the virus is exchanged among migratory birds (Morvan *et al.,* 1990).
Recent outbreaks of WN fever have been accompanied by an apparent evolution of a new virus variant, which can be divided into two lineages. Only members of lineage 1 WN viruses have been associated with clinical human encephalitis. Lineage 2 WN viruses are maintained in enzootic foci in Africa and have not been associated with clinical human encephalitis. Among lineage 1 WN viruses, those causing the recent human and equine outbreaks throughout Europe and Asia have been closely related to a WN virus first isolated in Romania in 1996 (ROM96) and subsequently in Kenya in 1998. The WN virus responsible for the outbreak in the US is genetically distinguishable from the ROM96-like viruses. The closest relative of NY99 virus was that circulating in Israel from 1997 to 2000 (Isr98). The genotype of the NY99 WN virus in the US has remained stable with few genomic changes (Petersen and Roehrig, 2001 ).

**Geographic Distribution:** The virus has been isolated from humans, other mammals, birds, and arthropods in Africa (Central African Republic, Democratic Republic of Congo, Egypt, Madagascar, Mozambique, Nigeria, South Africa, and Uganda), Asia (India, Israel, Pakistan, the former USSR, and the island of Borneo), and Europe (Cyprus and France). Moreover, serologic evidence suggests that the infection is present throughout practically the entire African continent and also in Albania, Malaysia, the Philippines, Thailand, and Turkey.
The outbreak of WN virus in the Western Hemisphere in the summer of 1999 marked the first introduction of an Old World flavivirus into the New World in recent history (Nash *et al.,* 2001). Surveillance showed the spread of viral activity in the eastern and southern US, extending to 12 states in 2000, from the Canadian border to North Carolina, a distance of some 900 km (Marfin et al., 2001). The close genetic relationship between the WN virus isolates from New York and Israel suggests that the virus

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[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the family Togaviridae to the family Flaviviridae.

was imported into North America from the Middle East. The means of its introduction (via infected bird, mosquito, human, or other vertebrate host) will likely remain unknown.

**Occurrence:** West Nile fever is both endemic and epidemic. In hyperendemic areas, the infection is acquired at a young age and most of the adult population is immune. In regions where the virus is less active, occasional epidemics occur among persons of all ages (Tesh, 1982). The disease is endemic in the Nile delta in Egypt, where it primarily affects children. In Israel, it occurs in epidemic form and clinical disease is observed in a large number of individuals. In South Africa, the disease is sporadic, with some small epidemic outbreaks occurring regularly during the summer. The most extensive West Nile fever epidemic in South Africa occurred in 1974, concurrently with Sindbis fever, in the Karroo region and the northern part of Cape of Good Hope Province. A serologic survey conducted after the epidemic showed that 55% of the population in the area had been infected by the WN virus and 16% by Sindbis virus (Mclntosh *et al.,* 1976). Serologic studies using the serum agglutination test have shown high reactor rates in human populations. Of 1,168 human serum samples obtained in an endemic region of the Nile delta, 61% had neutralizing antibodies against the disease (Taylor *et al.,* 1956). In the Karachi Region in Pakistan, following the occurrence of several cases of encephalitis, a seroepidemiological study of 237 individuals conducted between July and October 1983 and in 1985 using the hemagglutination inhibition and serum neutralization tests revealed a prevalence rate of 50% to 55%, with variations within that range depending on the year and the serologic test used. Of 156 paired sera obtained in 1985, 13% converted to positive and 8% turned negative. The virus had been isolated from *Culex tritaeniorhynchus*. Conversion from positive to negative might indicate that during the period of study there may have been asymptomatic infections in the area (Sugamata *et al.,* 1988). The virus has been isolated from several species of birds, equines, camels, and a bat. High reactor rates to the neutralization test have been seen in horses (183 of 375 animals examined in Egypt), nonhuman primates, cattle, and dogs.

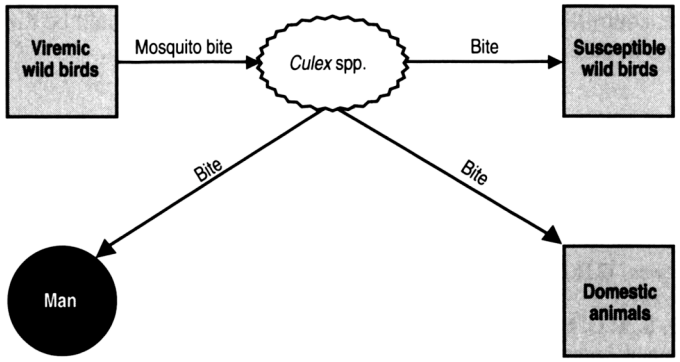
**The Disease in Man:** Infection in humans can be subclinical or produce symptoms ranging in severity from a passing fever to serious encephalitis. The disease tends to be mild in children and more severe in the elderly. The incubation period lasts from three to six days. The onset of the disease is sudden, with fever, cephalalgia, lymphadenopathy, and a maculopapular cutaneous eruption mainly on the trunk; myocarditis, meningitis, and encephalitis occur less frequently. Fatality rates are insignificant. The level of viremia in humans is low, and lasts approximately six days. The disease occurs during the summer, when mosquitoes are abundant.

**The Disease in Animals:** Among domestic animals, clinical manifestations have been observed only in horses, but even in this species most infections are asymptomatic. The characteristic picture is that of meningoencephalitis. A West Nile fever outbreak among equines in Camargue, France, in 1962-1964, produced 10% morbidity with a case fatality rate of 25%.
Little is known about the course of the infection in birds. In crows (*Corvus corone sardonius*) experimentally infected through mosquito bites, the mortality rate was high. Many of these birds have neutralizing antibodies in nature, indicating that a large number of them survive infection. It is probable that the virus can cause disease in other species of birds, as evidenced by the fact that the etiologic agent was isolated from a domestic pigeon captured in Egypt which had clinical symptoms (Taylor *et al.,* 1956).

**Source of Infection and Mode of Transmission (Figure 32):** The WN virus infects a large number of vertebrate hosts, including humans, domestic animals, and several species of fowl. Only birds meet the necessary criteria to serve as a reservoir: they have a high-titer and prolonged viremia that would enable them to serve as a source of infection for the arthropod vector. Moreover, areas within the range of the virus have many birds that reproduce at a sufficient rate to provide enough susceptible young to maintain the infection cycle. The virus has been isolated from pigeons (*Columba livid*), a species of crow (*Corvus corone sardonius*) in Egypt, the long-billed crombec (*Sylvietta rufescens*) in South Africa, and the turtle dove (*Streptopelia turtur*) in Israel. It has also been possible to isolate the virus from wild birds in Borneo, Cyprus, and Nigeria, and its presence has been confirmed by neutralizing antibodies in a number

of countries.
Ornithophilic mosquitoes of the genus *Culex* serve as the vector. They become infected when the female feeds on the blood of a viremic bird, and they pass the infection along when they bite a susceptible avian or mammalian host. The virus has been isolated from several species of *Culex*. It is clear that in Egypt, Israel, and South Africa, *Cx. univittatus* plays a key role in transmitting the infection and maintaining the virus in circulation in nature, but the main vector has not yet been definitively identified in other areas. In India and Pakistan, the *Cx. vishnui* complex appears to be important. In Camargue, France, this role is attributed to *Cx. molestus*. A few isolations have been obtained from *Aedes anopheles* and from argasid and ixodid ticks.

**Figure 32. West Nile fever. Transmission cycle.**




It is not yet fully understood how the virus overwinters. One hypothesis holds that the mechanism consists of delayed transmission by mosquitoes that remain active during the cold months. There have been reports of female *Cx. univittatus* found feeding on occasional warm days in winter, and the virus has also been isolated from sentinel pigeons during that time of year. Vertical transmission has been demonstrated in the laboratory in *Aedes albopictus, A e. aegypti,* and *Cx. tritaeniorhyncus* (Baqar *et al.,* 1993) and in argasid ticks (Abassy *et al.,* 1993); experimentally infected *Argus arboreus* ticks have transmitted the virus both horizontally and vertically (Abassy *et al.,* 1993). However, it remains to be confirmed whether transmission occurs naturally in mosquitoes and ticks.
A striking feature of the initial human epidemic in New York City in 1999 was the high number of avian deaths, particularly in American crows (*Corvus brachyrhynchus*) and other corvids. Subsequent work demonstrated fatality rates of almost 100% among American crows experimentally infected with the NY99 WN virus strain (Eidson *et al.,* 2001). A study in 1955 showed high fatality rates among Egyptian hooded crows (*Corvus comne*) and house sparrows (*Passer domesticus*) experimentally infected with the prototype Egypt 101 WN virus strain.
In the United States in both 1999 and 2000, infections in humans peaked in August and in horses in September, suggesting either different mosquito species transmitting the virus to humans and horses, or temporal differences in exposure to the same species. In 2000, 14 mosquito species in five states had evidence of WN virus infection (by culture or nucleic acid amplification). *Cx. pipiens* and *Cx. restuans*, the common ornithophilic maintenance vectors of St. Louis encephalitis virus in the northeastern US, were by far the most frequently identified species with WN virus. One important observation in the New York City area was the high virus infection rates and abundance of *Cx. salinarius* mosquitoes on Staten Island in 2000, which temporally coincided with the human outbreak. This species indiscriminately feeds on both birds and mammals and readily bites humans.

**Role of Animals in the Epidemiology of the Disease:** West Nile fever is a zoonosis transmitted from birds to humans and other animals by mosquitoes of the genus *Culex*. Humans, equines, sheep, and cattle are only accidental hosts of the virus, and they are not involved in the agent's basic cycle. Viremia in equines, sheep, and cattle is low-level, or may even be absent in cattle, and it is incapable of infecting the vector. On the other hand, wild birds have high-titer viremia and can serve as a reservoir. It has been

demonstrated experimentally that several species of mosquitoes and argasid ticks are capable of serving as both reservoirs and vectors.

**Diagnosis:** Laboratory confirmation consists of either isolation of the virus by inoculating blood from acute-phase patients in mice or serologic conversion, primarily by means of the serum neutralization test. In addition, a polymerase chain reaction assay has been developed for rapid detection of the virus (Porter *et al.,* 1993).

**Control:** A mixed vaccine to prevent human infection with the WN virus and other group B arboviruses is in the experimental stage.
At present, control of the vector is difficult, since the mosquito species that transmit the infection to humans are not yet fully known in the different countries.Although Culex mosquitoes are ornithophilic, they are not always anthropophilic. In some countries where the virus is present, there is probably a vector that serves as a link between the wild cycle and the infection in humans. Should that be found to be the case, controlling the population of that "liaison" vector would be the most logical action to take.

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