JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

"Review On West Nile Virus Disease: Its Outbreak And Current Status"

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Abstract:

West Nile virus (WNV) is a single-stranded RNA virus that causes West Nile fever. It is a member of the family *Flaviviridae*, from the genus *Flavivirus*, which also contains the Zika virus, dengue virus, and yellow fever virus. The virus is primarily transmitted by mosquitoes, mostly species of Culex. West Nile virus, a mosquito-borne infection that can cause serious illness, and in some cases, death, was first found in New York State in 1999. While the chances of anyone becoming ill are small, persons over age 50 are at higher risk for serious illness. West Nile virus (WNV) is a Japanese encephalitis antigenic complex of *Flaviviridae* family. It is transmitted by the bite of infected mosquitoes. The virus is maintained in a mosquito–bird–mosquito transmission cycle. Mild signs and symptoms of a West Nile virus infection generally go away on their own. But severe signs and symptoms such as a severe headache, fever, disorientation or sudden weakness need immediate attention. Exposure to mosquitoes where West Nile virus exists increases your risk of getting infected.

There is no specific treatment for West Nile virus infection. Mild illness does not require therapy other than medication to reduce fever and pain. When West Nile infects the brain, intensive supportive therapy is needed. There are no vaccines to prevent or medications to treat WNV in people. Fortunately, most people infected with WNV do not feel sick. About 1 in 5 people who are infected develop a fever and other symptoms. About 1 out of 150 infected people develop a serious, sometimes fatal, illness. The information about prevalence of WNV among animal population in India is scanty. This review updates the most recent investigations in different aspects of WNV life cycle: molecular virology, transmission, host range, epidemiology, pathogenesis, diagnosis, , and highlights some aspects that certainly require further research.

Keywords: West Nile Virus, Mosquitoes, Epidemiology, Diagnosis, Vaccines.

INTRODUCTION:

West Nile virus (WNV) is a flavivirus primarily transmitted by *Culex* mosquitoes. Wild birds are the natural host, while horses and humans are dead-end hosts. [1] WNV strains form at least two main lineages: lineage 1 (L1), which has a wide geographic distribution ranging from Europe, Africa, the Middle East and America and was responsible for previous outbreaks in the Mediterranean and North America, and lineage 2 (L2), which had only been found in sub-Saharan Africa and Madagascar until 2004, when it was isolated in a Hungarian goshawk with Neurological disease.[2-4] WNV is considered to be one of the most

important emerging flaviviral infections in the world, due to the increase in the number of cases with expansion in geographical distribution, and its association with severe neurological disease.[5- 7] Horses, like humans, are epidemiologically considered to be dead-end hosts: they do not have the ability to spread the virus after infection. Disease in horses is manifested by fever, weakness, locomotors dysfunction, ataxia and blindness. In the most severe cases, paraplegia occurs, evolving in 5 to 10 days to death. Viraemia in horses is estimated to be low and does not allow the infection of mosquitoes after a blood meal. [8-9] the symptoms of severe infection (West Nile encephalitis or meningitis) include headache, high fever, neck stiffness, muscle weakness**,** stupor, disorientation, tremors, convulsions, paralysis, and coma. It is estimated that one in 150 persons infected with the West Nile virus will develop a more severe form of the disease. [10]

In Europe, the mosquito species Culex pipiens and Culex modestus are the main vectors of WNV. About 80% of WNV infections in humans are asymptomatic. West Nile fever (WNF) is the most common clinical presentation. The elderly and immune compromised people are at higher risk of developing West Nile neuroinvasive disease (WNND). No specific prophylaxis or treatment exists against the disease in humans [11]

VIROLOGY AND PATHOGENESIS: [12-14]

West Nile virus is 1 of more than 70viruses of the family *Flaviviridae* of the genus *Flavivirus.* Serologically, West Nile virus is a member of the Japaneseence phalitissero complex, which includes Japaneseence phalitis virus and an endemic North American flavivirus, St Louis encephalitis virus. West Nile viruses can be designated into at least 5phylogenetic lineages. Only lineage 1 and 2 West Nile viruses have been associated with significant outbreaks in humans. Mosquito salivary components introduced at the site of infection in vertebrates modulate initial infection of target cells such as keratinocytes19 and skin-resident dendritic cells through several

Mechanisms including focalized suppression of immune effectors cell trafficking to the site of inoculation.20 Infected dendritic cells or keratinocytes migrate to draining lymph nodes from which a serum viremia is generated that then relays infection to visceral organs and potentially to the central nervous system **“Fig.4”**. West Nile virus is capable of replicating and eliciting pathology in the brain (i.e., neurovirulence); however, a critical prerequisite to generating neuroinvasive disease in humans is the virus’ capacity to gain access to the central nervous system (i.e., neuroinvasiveness).

Postulated West Nile virus neuroinvasive mechanisms include (1) direct viral crossing of the blood-brain barrier due to cytokine-mediated increased vascular permeability; (2) passage through the endothelium of the blood-brain barrier; (3) a Trojan horse mechanism in which infected tissue macrophages are trafficked across the blood-brain barrier; and (4) retrograde axonal transport of the virus to the central nervous system via infection of olfactory or peripheral neurons **“Fig.4”** 21 Regardless of how the virus enters the central nervous system, murine models of infection have shown persistent viral replication in various tissues, including the central nervous system, suggesting a potential etiology for long-term neurological sequelae observed in patients with neuroinvasive disease.

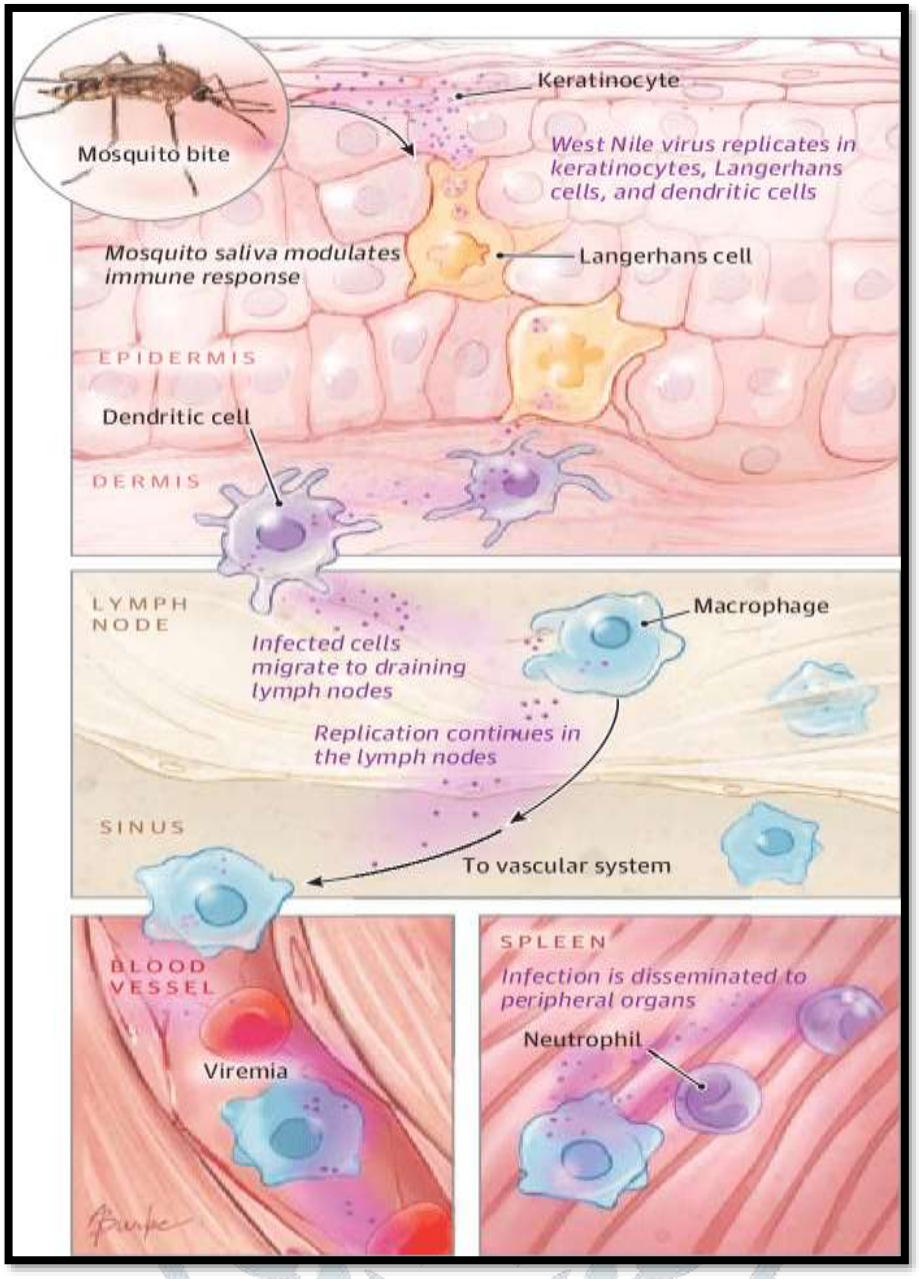


Figure 1. Schematic of Pathogenesis of West Nile Virus Infection

WNV EPIDEMIOLOGY: [15-23]

Life Cycle West Nile Virus

The natural life cycle of WNV involves transmission from mosquitoes (primarily of the genus *Culex*) to wild birds **"Fig.2"**. Birds act as amplifying host of the virus and the WNV has been isolated from nearly 300 species of birds. Mosquitoes become infected when they feed on infected birds that have high levels of viraemia. The virus then infects and replicate in the midgut of the mosquito. After replication in the midgut epithelium, the virus reaches the salivary glands from where it is transmitted to mammalian hosts during feeding Vertical transmission of WNV from female *Culex pipiens* mosquitoes to their progeny has been demonstrated in the laboratory.

Transovarial transmission of WNV has also been experimentally demonstrated in *Cx. vishnui* mosquito WNV can also be transmitted through blood transfusion, organ transplantation, breast–feeding and trans–placental transmission. Ornithophilic mosquito species act as vectors for transmission of infection from viraemic birds to vertebrate hosts. The infected mosquito species vary according to geographical area. *Culex* mosquitoes are accepted as the primary global transmission vector

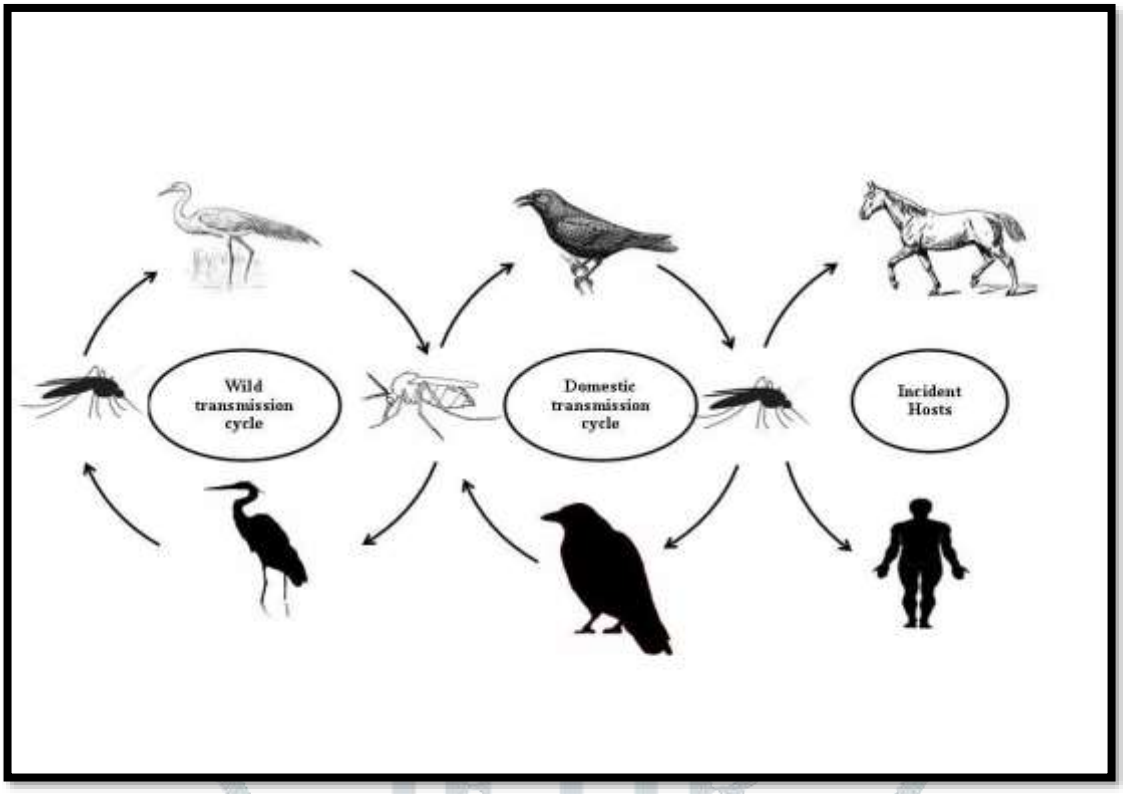


Figure 2. West Nile Virus Transmission Cycle.

TRANSMISSION TO HUMANS: [24-26]

Mosquito bites account for nearly all human infections. West Nile virus can also be transmitted via transfused platelets, red blood cells, and fresh frozen plasma as well as through heart, liver, lung, and kidney transplants. Transmission via organ transplant has occurred from donors without detectable viremia, suggesting viral sequestration in organs shortly after viremia has cleared. One possible transplacental transmission following a second trimester infection resulted in an infant with chorioretinitis, lissencephaly, and cerebral white matter loss. Fortunately, fetal abnormalities due to intrauterine infection are uncommon: none of 72 live infants born to 71 women infected during pregnancy had mal formations linked to West Nile viral infection or had conclusive laboratory evidence of congenital infection.

I. Mosquitoes and Other Arthropods: [27]

WNV is maintained in nature in an enzootic transmission cycle between avian hosts and ornithophilic mosquito vectors. At least 60 species of mosquitoes from 11 different genera have been described as competent vectors in North America, being those of the *Culex* species the most efficient ones (*Cx. pippiens*, *Cx. quinquefasciatus*, *Cx restuans*, *Cx. salinarus*, *Cx. tarsalis*, and *Cx. nigripalpus*), although other species such as *Aedes albopictus*, *Aedes vexans*, *Ochlerotatus japonicas* and *Ochlerotatus triseriatus* may also play a role on viral transmission as bridging vectors that can transmit the virus to mammals In Europe.

The virus has been isolated from more than 40 different species, being again those of the *Culex* species the main vectors several other species have been also described as competent vectors in other geographical areas, *Cx. Univittatus* in Africa, *Cx. annulirostris* in Australia, and *Cx. Vishnui* and *Cx. tritaeniorhynchus* in Asia.

II. Birds: [27]

Birds are the natural reservoir of WNV. Hundreds of avian species representing over 20 birds families from North America have been described as susceptible to WNV infection after its first introduction in 1999. However, the most affected ones have been the Passeriformes, mostly those of the *Corvidae* family, in many of which the virus replicates to high titers before the birds become moribund and die a few days after being infected. Up to 100% mortality has been described in experimentally infected crows and an estimated 45% decrease in crow population has been reported since the introduction of the virus in US; however, recent data indicate that this mortality rate is decreasing. A study carried out with several different avian orders from America reported that blue jay, common grackle, house finch, American crow, and specially house sparrow are among the most important WNV amplifying avian species, while many other did not show any evident sign of WN disease (WND). For instance, no significant mortality has been reported in chickens, beside they showed titers in blood of 105 PFU/mL and virus can be isolated from several organs after experimental infection.

Many avian species shed large quantities of virus in their feces or oral secretions when infected, allowing direct transmission form bird-to-bird and even from bird-to-human. Experimental oral infection of birds has been demonstrated and prey-to-predator infection has been suggested although high bird mortality has been a common feature of WNV activity in US and Israel no such trait has been observed in other regions of the world.

III. Flavivirus Infections in Humans: [28]

In peripheral tissues, early innate immune responses (antiviral cytokine and chemokine secretion, complement activation), and especially the IFN type I response, limit virus infection and dissemination. See also: Immune Evasion by Viruses WNV

infection has mainly been studied in mammals, so there is little information about the early stages of infection in birds. It is supposed that, as for mammals, WNV replicates at the inoculation site and is then distributed to all organs. However, the virus can be detected in the blood as early as 30–45 min (generally 1 day) after a mosquito bite, suggesting that primary viraemia does not necessarily depend on local replication. The viraemia peak and organ distribution vary widely in bird species. WNV can infect all major organ systems **"Fig.3"** and a wide variety of individual cell types. The organs most frequently infected are the spleen, kidneys, skin and eyes, while the liver is the least likely to harbor infectious virus particles. WNV also reaches the CNS via the bloodstream and was shown to infect endothelial cells or invade the CNS through infected immune cells.

Even though little is known about innate avian host defences against WNV infection, it is speculated that immune responses in birds are different from those observed in mammals and could promote viral persistence.

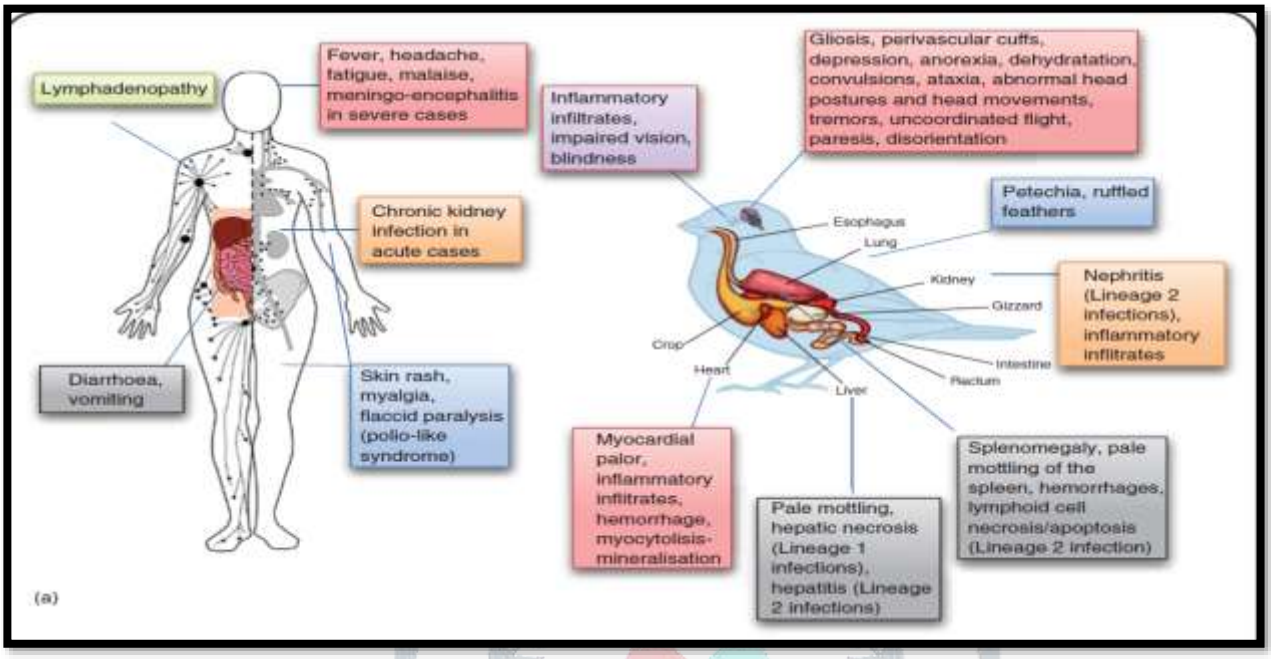


Figure 3.

Flavivirus Infections in Humans.

IV. Non-vector: [27]

WNV transmission to vertebrates usually involves mosquitoes; however sporadic reports of non vector-borne transmission have been documented in humans throughout liver and kidney transplantation, dialysis, needle-stick injury, breast-feeding, by trans placental route, and by blood transfusion, which drove to the consequent screening of blood donors. These transmission routes seem to be mainly anecdotic and have minor effects on disease burden. WNV infected pregnant women included in a retrospective study, most of whom gave birth healthy children with only a few cases of newborns presenting malformations, though no conclusive association to WNV infection could be established in any of them.

In any case, assessment of the fetus or child is recommended when mothers are infected by WNV and clinicians are encouraged to report known or suspected cases of WNV infection during pregnancy.

SIGNS & SYMPTOMS: [29]

I. **No symptoms in most people:** Most people (8 out of 10) infected with West Nile virus do not develop any symptoms.

II. **Febrile illness (fever) in some people:** About 1 in 5 people who are infected develop a fever with other symptoms such as headache, body aches, joint pains, vomiting, diarrhea, or rash. Most people with febrile illness due to West Nile virus recover completely, but fatigue and weakness can last for weeks or months.

III. **Serious symptoms in a few people:** About 1 in 150 people who are infected develop a severe illness affecting the central nervous system such as encephalitis (inflammation of the brain) or meningitis (inflammation of the membranes that surround the brain and spinal cord).

- Symptoms of severe illness include high fever, headache, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, vision loss, numbness and paralysis.
- Severe illness can occur in people of any age; however, people over 60 years of age are at greater risk for severe illness if they are infected (1 in 50 people). People with certain medical conditions, such as cancer, diabetes, hypertension, kidney disease, and people who have received organ transplants, are also at greater risk.
- Recovery from severe illness might take several weeks or months. Some effects to the central nervous system might be permanent.
- About 1 out of 10 people who develop severe illness affecting the central nervous system die.

PATHOGENESIS:

WNV is thought to replicate at the site of inoculation and then spread to lymph nodes and the bloodstream. [30] Viral penetration of the central nervous system appears to follow stimulation of toll-like receptors and increased levels of tumor necrosis factor-α, which increases permeability of the blood-brain barrier. [31] WNV directly infects neurons, particularly in deep nuclei and gray matter of the brain, brainstem, and spinal cord. [32–34] Collateral destruction of by stander nerve cells may contribute to paralysis. [35] Immune-mediated tissue damage may also contribute to pathologic changes in some cases. [36] Genetic susceptibility for severe disease in mice has been postulated to involve a deficiency in production of 2′–5′-

oligoadenylate synthetase, but this genetic susceptibility has not been elucidated in humans. [34] Although most nonfatal WNV infections appear to be cleared by the host immune response, the virus may persist in some vertebrate hosts. [34-37]

Clinical manifestations. [38]

Seroprevalence studies suggest that while the majority of WNV infections are asymptomatic, approximately 20 to 30% of infected individuals develop flu-like clinical manifestations characterized as WNV fever. In a subpopulation of individuals (approximately 1 in 150), a neuroinvasive disease develops. The clinical features of severe WNV infection vary and include severe headache, ocular manifestations, muscle weakness, cognitive impairment, tremors, and a poliomyelitis-like flaccid paralysis. The mortality rate following neuroinvasive infection is approximately 10%, and long-term neurological sequelae are common (>50%), Neuronal damage is most prevalent in the brain stem and anterior-horn neurons of the spinal cord, although in immune suppressed individuals infection can disseminate throughout the central nervous system (CNS).

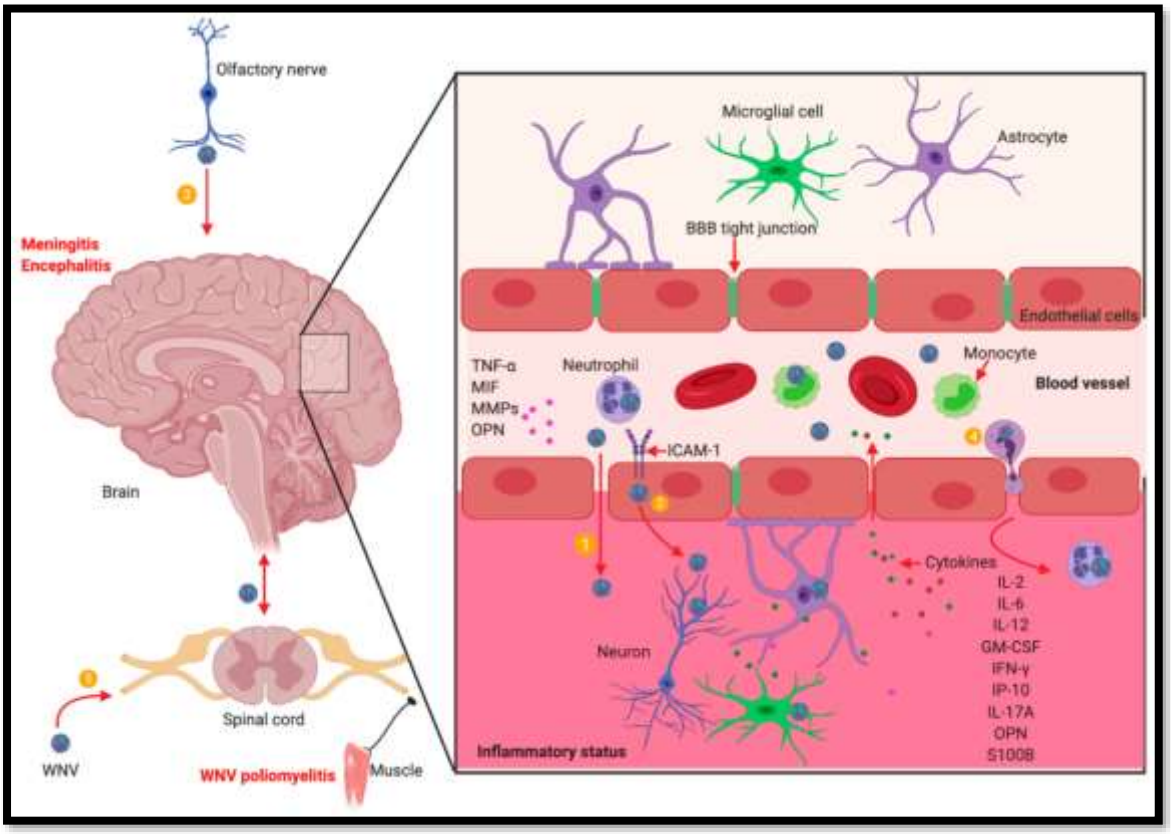


Figure 4: West Nile Virus (WNV) Neuroinvasion and Neuropath Genesis.

WEST NILE VIRUS INFECTION & CAUSES: [39]

West Nile virus is a viral disease spread by mosquitoes. The condition ranges from mild to severe.

Causes:

West Nile virus was first identified in 1937 in Uganda in eastern Africa. It was first discovered in the United States in the summer of 1999 in New York. Since then, the virus has spread throughout the US. Researchers believe West Nile virus is spread when a mosquito bites an infected bird and then bites a person. Mosquitoes carry the highest amounts of the virus in the early fall, which is why more people get the disease in late August to early September. As the weather becomes colder and mosquitoes die off, there are fewer cases of the disease. Although many people are bitten by mosquitoes that carry West Nile virus, most do not know they have been infected.

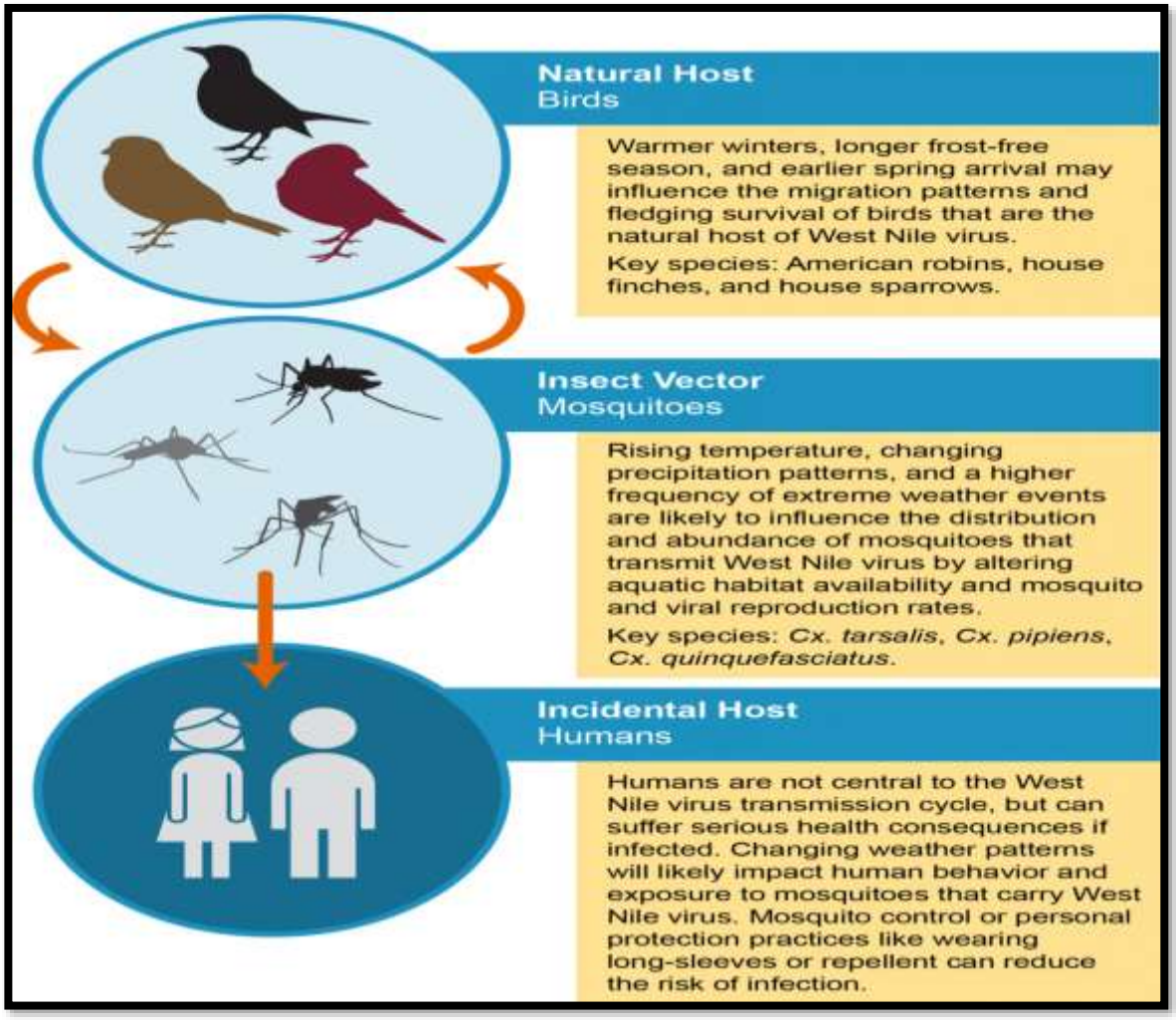


Figure 4: Climate Impacts on West Nile Virus Transmission.

DIAGNOSIS:

Laboratory diagnosis relies on isolation of virus, detection of viral antigens or RNA in blood or tissues, or detection of virus-specific IgM antibody that should be further confirmed by detection of IgG antibody in the same or a subsequent sample.

I. Antibody:

Cross-reactivity between Flavivirus antigens is the greatest drawback for proper serological diagnosis and epidemiological studies and, thus, sera have to be tested against different related viruses and results have to be subsequently confirmed by different assays, namely hem agglutination inhibition, immune fluorescence or plaque reduction neutralization test (PRNT), considered as the gold standard.[40] A 4-fold increase in PRNT titers between 2 sequential serum samples collected 2-3 wk apart usually confirms an acute WNV infection, and WNV neutralizing titers 4-fold higher than titers to other related-flavivirus is usually taken as a probe of the specificity of the infection. Initially, serological testing was based on IgM antibody capture assays (MAC-ELISA) and in indirect IgG ELISAs, followed by retesting of positive samples by PRNT. Later on, ELISAs using monoclonal antibody blocking assays were set up. Presence of IgM in the cerebrospinal fluid is indicative of infection of the CNS, because IgM does not cross the blood-brain barrier; however, data should be taken with caution since IgM may persist for extended period of time. [41]

All these assays have been extensively used for detection of anti-WNV antibodies in human and animal samples. [42] ELISAs, both commercial and in-house, were mainly based in the use of inactivated whole virus as antigen, either produced in mammalian cells or suckling mice; however, its production implies risks for laboratory personnel and needs highly sophisticated biosafety level 3 (BSL-3) containment facilities to grow the virus. For these reasons, several ELISAs have been developed using recombinant viral proteins, mainly the envelope E protein or parts of it, because this protein is highly exposed to the host immune system and bears most of the neutralizing epitopes described. [41]

These recombinant antigens have been expressed in a variety of systems, including bacteria [43] mammalian cells [44, 45], insect cells [45-47], and larvae [47]. Other formats, such as microsphere particles in conjunction with fluorescent labelled antibodies and lateral-flow assays have also been recently assayed [42]

II. Antigen:

Virus isolation in susceptible cell culture is the gold standard for virus detection, but it is usually hampered by the typical short duration and low levels of viremia and by the need of BSL-3 facilities, which has lead to the development of alternative methods. Detection of viral antigens is based on antigen-capture ELISAs, dipstick assays, or immune histochemical methods. [48, 49]

III. Nucleic acid:

Several methods for detection of viral RNA have been applied for WNV surveillance and diagnosis, mainly reverse transcription polymerase chain reaction (RT-PCR) assays, quantitative real-time RT-PCR and nucleic acid sequenced-based

amplification. [50] All these assays have been extensively used in mosquito pools, and animal and human samples (blood and/or CFS), although the latter are usually collected after the onset of clinical signs, when virus is unlikely to be present on them.

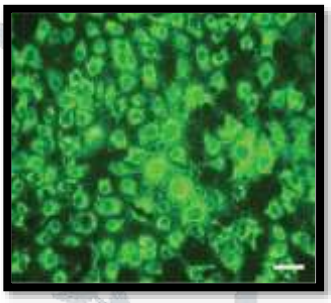
Sr.No	VNT	HIT	IFA	ELISA
Principle	Neutralisation of virus attachment to the cells or of post-binding steps	Inhibition of virus-induced erythrocyte aggregation	Antibody binding to virus-infected cells coated on microscope slides, revealed by fluorophore-conjugated antibodies	Antibody binding on plates coated with a viral antigen and revealed by enzyme-conjugated antibodies
Antibody target	Neutralising epitopes in the E protein	E protein	Whole virus	Whole virus, viral cell lysate or recombinant proteins (prM-E, NS1, E-DIII, etc.)
Diagram of Method's				
Interpretation	Protection from viral lysis in the presence of neutralising antibodies	Haemagglutination inhibition in the presence of antibodies in the serum	Fluorescence of virus-infected cells in the presence of antibodies in the serum	Colorimetric reaction intensity correlating with the amount of antibodies
Field applications	Confirmation of past infections	Screening tool	Investigation of clinical cases	Investigation of clinical cases, screening tool and trade certification

Table 1 Main serological tests used for WNV diagnosis [28]

VNT, virus neutralisation test; HIT, haemagg lutination-inhibition test; FA, immune fluorescence assay; ELISA, enzyme-linked immunosorbent assay.

TREATMENT AND PREVENTION:

Treatment of West Nile virus infection remains supportive. Several investigated therapeutic approaches include immune γ-globulin, West Nile virus–specific neutralizing monoclonalantibodies, corticosteroids, ribavirin, interferon α-2b, and antisense oligomers.[51,52] No study has documented efficacy, in part due to difficulty in recruiting sufficient numbers of patients. Case reports or uncontrolled clinical series suggesting efficacy should be interpreted with extreme caution due to West Nile virus's highly variable clinical course. No vaccine is licensed forhumans.Despite4licensed equine vaccines and promising preliminary results from several phase 1 and 2 human vaccine candidates, phase 3 efficacy trials have not been attempted due the unknown market potential of a West Nile virus vaccine and logistical difficulties in conducting phase 3 clinical trials for this sporadic and widely dispersed disease.[51] Preliminary analysis suggested that universal West Nile virus vaccine coverage would not be cost-effective[53]; however, the cost-effectiveness of vaccination of specific target groups such as elderly individuals has not yet been established. Because humans are dead-end hosts, a human vaccination program would not influence viral amplification in nature. West Nile virus prevention relies in part on methods to reduce the numbers of West Nile virus–infected mosquitoes. Community based mosquito control programs using integrated pest management Principles proactively identify the sources of vector mosquitoes and use several methods such as elimination of breeding sites, larviciding, and targeted adult mosquito control to prevent adult

Mosquito populations from achieving levels that increase human infection risk. When increasing human case incidence or surveillance of vector mosquito populations indicates an impending human epidemic, the immediate goal is to reduce rapidly the number of infected adult mosquitoes by widespread ultra-low volume application of organophosphate or synthetic parathyroid

insecticides. Organophosphates irreversibly block the enzyme acetyl cholinesterase; pyrethroids open sodium channels of neuronal membranes, paralyzing the mosquito, andare usually combined with piperonyl but oxide preventing the mosquito's microsomal oxidase enzymes from metabolizing pyrethroids. Although the efficacy of these control measures is difficult to measure, strategically timed early-season control of adult mosquitoes in the Coachella Valley of California using ultra-low volume insecticide applications decreased subsequent West Nile virus transmission. [54] In addition, aerial ultra-low volume insecticide application decreased infected mosquito abundance and reduced human- case incidence during a West Nile virus outbreak in the Sacramento area. [55]

Human health risks associated with ultra-low volume organo phosphate or synthetic pyrethroid use appear negligible, largely because the timing of application and low volume of pesticide used result in minimal human exposure.[56,57] Insect repellent use has been associated with reduced West Nile virus risk.[58] Unfortunately, few people report regular repellent use even during well-publicized outbreaks. Commercially available insect repellents containing DEET, IR3535, oil of lemone ucalyptus, and picaridin are registered by the US Environmental Protection Agency on the basis of their excellent safety profiles and proven efficacy in reducing or preventing mosquito biting. Many other commercially available unregistered products, such as those containing citronella oil, cedar oil, geranium oil, peppermint oil, and soybean oil, have unproven efficacy.

COMBINATION THERAPIES:

It is possible that a combination of specific therapies may be more effective than single agents and this approach is being used for other viral diseases. For example, ribavirin and interferon-a Provide a clinically synergistic effect in the treatment of chronic hepatitis C infection.[59-61] Combination therapy with intra ventricular interferon-a/b and ribavirin has also been used for the treatment of SSPE.[62,63] No reports have yet been published using combination therapy in WNV infection. Unfortunately, we do not yet have any therapies that are known to be effective for the treatment of WNV neurological disease. Hopefully, the results of studies in both animal models and in human clinical trials will soon become available.

WEST NILE VIRUS VACCINES: [28]

Only veterinary vaccines are currently used in Europe for vaccinating horses. An inactivated vaccine (EQUIP® WNV, formerly Duvaxyn® WNV, Zoetis) and a canarypox recombinant vaccine (PROTEQ WEST NILE®, Merial/Sanofi Aventis) have been commercialized in Europe since 2009 and 2011, respectively. They have proven to be very effective in protecting horses from meaning encephalitis in North America where four vaccines are available (two inactivated, one DNA and one canarypox recombinant vaccine). Also demonstrated their efficacy in protecting horses against heterologous strains Human vaccines are under development. One of them, the Chimerivax-West Nile virus vaccine (Acambis, Sanofi-Pasteur) based on the attenuated Yellow Fever Virus (YFV) vaccine strain (17D) incorporating the WNV prM and E genes, is currently undergoing clinical trials A recombinant live attenuated measles virus (MV)

Vaccine expressing the soluble ectodomain of WNV E elicited protective immunity in mice and non-human primates as early as 2 weeks after immunization. Several therapies are under investigation, including immune γ-globulins, WNV-specific neutralizing monoclonal antibodies, corticosteroids, ribavirin, interferon α-2β and antisense oligomers.

I. Vaccines: [64]

NIAID supports research on a variety of vaccine approaches that could potentially lead to a safe and effective preventive vaccine for West Nile virus (WNV). These approaches include vaccines containing cocktails of individual WNV proteins and chimeric vaccines, which combine genes from more than one virus into a single vaccine. A third approach involves DNA vaccines, in which DNA that codes for a particular virus protein is combined with bacterial DNA, and the combined product is injected directly into the skin of the person or animal being vaccinated. Currently, there is no licensed WNV vaccine for people. In 2005,

The U.S. Department of Agriculture licensed a DNA vaccine to prevent WNV in horses, and since then, at least four other types of WNV vaccines have been approved for use in horses. Because federal regulations for veterinary products are less stringent than those intended for human use, products developed for animals can proceed at a faster pace.

II. WNV vaccine research conducted and supported by NIAID includes:

- Early-stage research by scientists at Oregon Health and Science University who used hydrogen peroxide treatment as a way to develop inactivated vaccines. This method is being investigated to develop vaccines for a number of illnesses, including West Nile fever and neuroinvasive disease, yellow fever, and dengue.
- A vaccine grown in insect cells that has been shown to produce protective antiviral antibodies in mice infected with WNV and has been shown to prevent WNV disease in horses. This research was conducted by the biotech company L2 Diagnostics, LLD, of New Haven, Connecticut. It remains to be seen if the product will be advanced for use in humans.
- A candidate vaccine made with portions of two WNV proteins is being developed by Hawaii Biotech, Inc., in Aiea, Hawaii. Early research on this product was funded by NIAID. The company has completed a Phase I trial of the vaccine, which successfully demonstrated safety and immunogenicity.
- NIAID-supported researchers at Duke University are working on a WNV vaccine made of immune proteins (called mast cell-activating peptides, or MCAPs) that would be formulated for delivery as a dry nasal powder. The use of MCAPs to create vaccines that can be administered through the nose might be applicable to other diseases as well.
- NIAID provided initial support to the biotech firm Acambis to develop a live attenuated recombinant vaccine for WNV called ChimeriVax. The chimeric vaccine is derived from the well-established yellow fever 17D vaccine, in which two genes from the yellow fever vaccine virus, including the gene for the viral envelope protein, are replaced with comparable genes from WNV. Several successful Phase I and Phase II trials were conducted in various populations of healthy volunteers. ChimeriVax was acquired by Sanofi Pasteur in 2008.
- NIAID scientists are developing a molecularly engineered, live attenuated chimeric West Nile/dengue vaccine. In this candidate vaccine, genes coding for two proteins from dengue-type 4 viruses (a related flavivirus) were replaced with

the corresponding WNV genes. The candidate vaccines have been further weakened by deleting additional portions of dengue viral genetic material. Several vaccine candidates have been tested in Phase I clinical trials; further trials are planned with varying doses of vaccine and in older healthy individuals.

In collaboration with the San Diego biotech firm Vical and the Centers for Disease Control and Prevention (CDC), scientists from the NIAID Vaccine Research Center developed a DNA-based investigational WNV virus vaccine. This vaccine candidate was tested in Phase I and II clinical trials, and it has been licensed by CDC to Vical.

RISK FACTORS WNV: [65-67]

Any person who is bitten by a mosquito in an area where the bird population carries West Nile virus is susceptible to infection. Since these areas now cover a large portion of the globe, almost any mosquito bite could potentially transmit the virus, to any person. The more mosquito bites you receive, the higher your risk. Most people who are infected with the West Nile virus suffer only a self-limited illness or no symptoms at all. However, a small proportion of infected individuals (less than one percent) will develop the serious, life-threatening neurological form of the infection. While this severe result can affect anyone infected with West Nile virus, some appear to have a higher risk of developing meningitis or encephalitis. Factors that increase this risk include:

- Advanced age
- Cancer
- Recent chemotherapy
- Diabetes
- Alcohol abuse
- Kidney disease

In these scenarios, it's important to work with your doctor if you notice anything out of the ordinary, even if it seems like a typical cold.

FUTURE PERSPECTIVES:

The resurgence of West Nile virus in 2012 after several years of decreasing incidence in the United States suggests that West Nile virus will continue to produce unpredictable local and regional outbreaks. These outbreaks are associated with considerable long- and short-term morbidity from West Nile virus neuroinvasive disease and West Nile fever, respectively. Thus, sustainable, community-based surveillance and vector management programs are critical, particularly in metropolitan areas with a history of West Nile virus and large human populations at risk WNV infection is emerging as an important infection of human and animals across the globe. In India, WNV infection has been reported from humans, pigs, bats and birds. A few studies indicate the seroprevalence of WNV among horses in India.

Mosquitoes of mainly *Culex* species and sometime *Anopheles subpictus* are the main vectors of WNV in India. Some data has emerged during last 5 decades on epidemiology of WNV in India. However, there is a need for systematic study to know the status of WNV infection in human and different animals, particularly horses in India. Role of mosquitoes and various birds in spread of WNV in newer geographical regions of India also needs further investigations. Research has gained pace regarding the public health significance of the WNV infection. However, there is greater amount of serological cross–reactivity of WNV with related flavivirues circulating in a region.

For instance, in India WNV and Japanese encephalitis virus (JEV) both are endemic and co–circulate in human and animal population. Therefore, there is need for development of sensitive and rapid sero–diagnostics, which can clearly discriminate WNV from JEV in India.

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