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Research Article

A BRIEF REVIEW ON WEST NILE VIRUS INFECTION

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ABSTRACT

Sensitive indicators of temporal and spatial variation in vector-host contact rates are very critical to understanding the transmission and eventual prevention of arboviruses such as West Nile virus (WNV). Over the last two decades West Nile Virus (WNV) has been responsible for significant disease outbreaks in humans and animals in many parts of the World. West Nile virus (WNV) is a *flavivirus* closely related to Japanese encephalitis and St. Louis encephalitis viruses that is primarily maintained in nature by transmission cycles between mosquitoes and birds. It's extremely rapid global diffusion argues for a better understanding of its geographic extent. The overarching goal of our study was to extend the knowledge about these West Nile virus spread infections and newer therapeutic approaches to eradicate this virus spread infections.

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INTRODUCTION

West Nile Virus (WNV) is a positive sense single-stranded RNA, mosquito-borne virus which belongs to the family *Flaviviridae*. Firstly, identified in the West Nile district of Uganda in 1937 in a woman who presented with a mild febrile illness[1]. The genus *Flavivirus* also includes Japanese encephalitis virus, St Louis encephalitis virus, Murray Valley virus, Usutu virus, and Kunjin virus, among others[2]. WNV is transmitted between birds via mosquito vectors. The enzootic cycle is driven by continuous virus transmission to susceptible bird species through adult mosquito blood-meal feeding which results in virus amplification. Species from the genus *Culex* mosquitoes (family *Culicidae*) are the most important vectors[3], however, it remains unclear how the composition of the mosquito community influences the timing and intensity of avian epizootics and human epidemics[4]. The transmission cycle involve wild birds as the principal hosts and mosquitoes, largely bird-feeding species, as the primary vectors. It exists in rural ecosystems as well as in urban areas where mosquitoes breed in organic-rich water in artificial containers. In particular, low-lying places with poor drainage, urban catch basins, roadside ditches, sewage treatment lagoons, and manmade containers around houses provide good larval development sites for *Culex* spp. mosquitoes to deposit their eggs[5].

Zoonotic pathogens, such as WNV, have been suggested to exist within transmission *networks* where relationships among multiple host and vector species structure transmission rather than traditional transmission *cycles* among single host and vector species. The frequency of vector contacts within these host networks is a critical parameter in understanding the transmission ecology of WNV. Despite the importance of vector-host contact rates on the transmission of WNV, they remain relatively understudied due primarily to the logistical costs of inferring contact rates via blood feeding studies or direct observation of vectors seeking hosts. The use of vector-host contact rates to predict local WNV activity would aid the planning and implementation of WNV prevention and control activities[6].

Emerging infectious diseases, including those that have appeared for the first time, rapidly increased in incidence, or expanded into new geographic areas, are a significant concern in the fields of human and veterinary medicine as well as wildlife conservation. Disease emergence is often connected with the development of human societies and their interactions with the environment, including the proliferation of transportation networks that facilitate pathogen spread, land use and climate change that affect habitats for arthropod vectors, and animal hosts, and population movements that increase human and domesticated animal contact with wildlife and their

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pathogens. The overarching goal of our study was to extend the knowledge about these West Nile virus spread infections and newer therapeutic approaches to eradicate this virus spread infections.

History

WNV has a wide geographical range that includes portions of Europe, Asia, Africa, Australia (Kunjin virus) and in North, Central and South America. Migratory birds are thought to be primarily responsible for virus dispersal, including re-introduction of WNV from endemic areas into regions that experience sporadic outbreaks. The first outbreak of neuro invasive disease caused by WNV (WNND) was reported among the elderly in Israel in 1957. Subsequent outbreaks included adult and pediatric WNND cases[7]. 1937 WNV was first isolated from a feverish 37 year old woman at Omogo in the West Nile District of Uganda during research on yellow fever virus. 1939 A series of sero surveys in central Africa found anti-WNV positive results ranging from 1.4% (Congo) to 46.4% (White Nile region, Sudan). 1942 It was subsequently identified in Egypt. 1950 Sero survey in Egypt found 90% of those over 40 years in age had WNV antibodies. 1953 It was subsequently identified in India, 1953. The ecology was characterized with studies in Egypt and Israel 1957.

The virus became recognized as a cause of severe human meningoencephalitis in elderly patients during an outbreak in Israel. 1960 The disease was first noted in horses in Egypt and France in the early and found to be widespread in southern Europe, southwest Asia and Australia. 1998 The US virus was very closely related to a lineage 1 strain found in Israel. 1999 The first appearance of West Nile virus in the Western hemisphere was 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. 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 horse cases and many birds are infected. The Barbary Macaque, *Macaca sylvanus* was the first non-human primate to contract West Nile Virus. 2001/ 2002 A high level of media coverage through 2001/2002 raised public awareness of West Nile virus. This coverage was most likely the result of successive appearances of the virus in new areas and had the unintended effect of increasing funding for research on this virus and related arthropod-borne viruses. Such research has expanded our understanding of viruses transmitted by mosquitoes[8].

Epidemiology

Abiotic and biotic conditions are both important determinants of WNF epidemiology. The establishment and transmission of WNV is determined by a number of factors: the presence of susceptible avian hosts, infected (viremic) birds, and local (amplifying) birds; abundant competent mosquito vectors that feed on birds and bridge vectors that feed both on birds and humans/horses; and finally interactions of the pathogen and the vector with the biotic and abiotic environment. The epidemiology of the disease is also a function of a vector and vertebrate host population densities that facilitate WNV amplification among competent insect vectors and vertebrate hosts. The intensity of the transmission of WNV is related to the dynamics and interactions between the pathogen, vector, and vertebrate hosts[9].

Weather conditions and climatic factors were found to be direct abiotic factors that influence vector competence for WNV. Moreover, the presence of favorable ecological habitats for vectors and hosts, with permissive weather conditions and their appropriate seasonal timing are crucial constituents for a successful transmission cycle. Increase temperature plays an important role in viral replication rates and transmission of WNV, affecting the length of extrinsic incubation, seasonal phenology of mosquito host populations and geographical variation in human case incidence. Role of precipitation in WNV transmission is more indirect, impacting abiotic conditions and biotic factors, the scientific literature presents inconsistent results. Although the patterns of disease incidence can be influenced by the amount of precipitation, the response may change over large geographic regions, depending on differences in the ecology of mosquito vectors. Research into the linkage between relative humidity and WNV is limited. Significant positive correlations were found between relative humidity in the Tel-Aviv metropolis (Israel) and hospital admission dates of WNF patients[10].

Ecology

West Nile virus is mainly maintained in a bird-mosquito-bird transmission cycle. Till now, West Nile virus has been detected in 65 different mosquito species and 326 bird species in the United States, only a few *Culex* mosquito species drive transmission of the virus in nature and subsequent spread to humans: *Culex pipiens* (northern housemosquito) in the northern half of the United States, the closely related species *Cx quinquefasciatus* (southern house mosquito) in the southern states, and *Cx tarsalis* in many areas of the plains and western states that overlap with the distribution of *Cx pipiens* and *Cx quinquefasciatus*. Numerous passerine birds (perching birds of the order Passeriformes) develop sufficient serum viremia to effi-competent amplifier hosts[11]. A relatively small subset of the bird community may significantly influence transmission dynamics and certain passerine species such as the American robin (*Turdus migratorius*) are important amplifiers despite their low abundance relative to other West Nile virus-susceptible birds. Humans are unlikely to infect with these mosquitoes because they only develop a low-level serum viremia and thus are considered dead-end hosts[11].

Etiology

West Nile virus is a single stranded RNA virus of the family *Flaviviridae*, genus *Flavivirus* shown in figure 1. It is a member of the Japanese encephalitis virus sero complex, which contains several medically important viruses, Japanese encephalitis, St. Louis encephalitis, Murray Valley encephalitis and Kunjin virus (a subtype of Australian West Nile virus).

The West Nile virus is a type of virus known as a flavivirus. Researchers believe West Nile virus is spread when a mosquito bites an infected bird and then bites a person. Mosquito's carry the highest amounts of virus in the early fall, which is why the rate of the disease increases in late August to early September. The risk of disease decreases as the weather becomes colder and mosquito's die off. Although many people are bitten by mosquito's that carry West Nile virus, most do not know they've been exposed. Few people develop severe disease or

even notice any symptoms at all. Mild, flu-like illness is often called West Nile fever. More severe forms of disease, which can be life threatening, may be called West Nile encephalitis or West Nile meningitis, depending on what part of the body is affected. Risk factors for developing a more severe form of West Nile virus include: Conditions that weaken the immune system, such as HIV, organ transplants and recent chemotherapy older age, Pregnancy. West Nile virus may also be spread through blood transfusions and organ transplants. It is possible for an infected mother to spread the virus to her child through breast milk[12].

Vector-Virus Relationship

Vector Preference

The ability of different mosquito species to acquire and transmit WNV is highly variable. *Culex* mosquitoes are accepted as the primary global transmission vector; *C. tarsalis* is a main mosquito vector of WNV in the western United States and can feed on a variety of avian and mammalian species[13]. 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 direct viral crossing of the blood-brain barrier due to cytokine-mediated increased vascular permeability; passage through the endothelium of the blood-brain barrier; a Trojan horse mechanism in which infected tissue macrophages are trafficked across the blood-brain barrier; and retrograde axonal transport of the virus to the central nervous system via infection of olfactory or peripheral neurons 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[14].

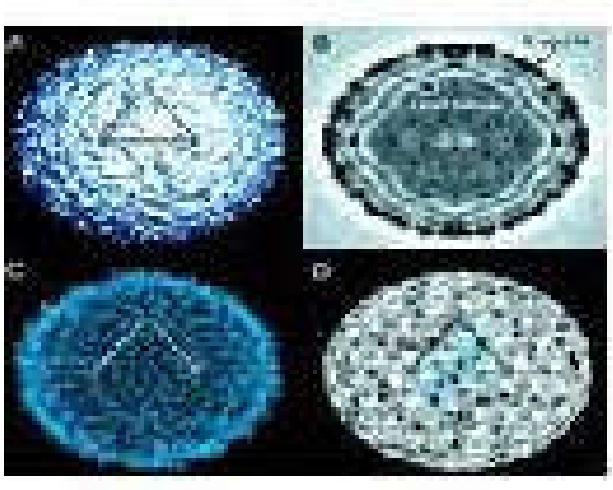

Figure 1 west nile virus - genomic structure

WNV is maintained in nature in a cycle between mosquitoes and animal hosts (Fig. 2 shows a schematic of mosquito-mammal transmission), with the predominant and preferred reservoir being birds. Birds of some species become ill, show symptoms of disease, and may die, while others become infected and serve as carriers without showing signs of disease. Although house sparrows and crows are highly susceptible to WNV, they make up a small fraction of analyzed mosquito blood meals and may be of minor importance in transmission. The American robin is instead thought to be the main host species responsible for the maintenance and transmission of WNV in the United States due to the feeding preference for robins by the dominant viral vectors [15]. Bird-bird transmission has been demonstrated in the laboratory, with several species proving to be capable of contact transmission. Humans are considered "dead-end" hosts for WNV, as the low level of viremia in mammals is usually not sufficient to be transmitted to mosquitoes, thereby ending the transmission cycle[16]. The ability of mammals to act as hosts could change, though, should *Aedes* mosquitoes, which feed primarily on humans, become primary transmission vectors for WNV.

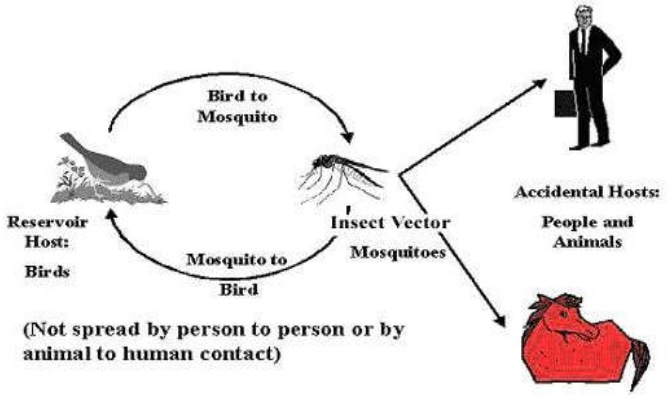

Figure 2 Transmission cycle

Pathophysiology

WNV is a member of the Japanese encephalitis complex of viruses that category also includes the Japanese encephalitis virus and St. Louis encephalitis virus, which accounts for cross-reactivity in serologic testing[17]. This virus group belongs to the Flaviviridae, a family of single-stranded positive RNA viruses transmitted by arthropods, mostly Culex mosquitoes in the case of WNV. After a phase of initial replication and seeding of the reticulo endothelial system, a secondary viremia occurs with seeding of the central nervous system (CNS). Viremia is usually a transient phenomenon that precedes onset of symptoms and disappears with development of specific immunoglobulin (Ig) G and IgM antibodies. The presence of intact B cells plays a critical early role in the development of IgM antibodies and thus the defense against disseminated infection, a fact that explains prolonged periods of viremia (up to 1 month) and more severe CNS disease and delays in the seroconversion of WNV infected immunosuppressed patients.
Clinical symptoms develop in less than 1% of cases. This appears to be due to the strength of the host immune system but could partly be due to the difference in severity of neurovirulence among different WNV strains. Risk factors for increased mortality include host characteristics such as older age (less than 75 years), diabetes mellitus and level of immuno suppression, as well as measures of disease severity such as decreased level of consciousness, neuro imaging abnormalities and the development of limb weakness. WNV shares with the

other Japanese encephalitis complex viruses a tendency to cause encephalitis and, less often, aseptic meningitis and paralytic poliomyelitis. Those Flavivirus, including WNV, infect neurons throughout the CNS, but more severely in certain sites appropriate for the different clinical syndromes[18]. More severe infections of the basal ganglia and thalamus, as suggested by neuroimaging were found in patients with prominent Parkinsonism and movement disorders. Prominent inflammation of the brainstem was pathologically confirmed in patients with bulbar and ophthalmoplegic symptoms. Acute flaccid paralysis observed in WNV was correlated in multiple studies with perivascular lymphocytic infiltration and neuronophagia of the anterior horn cell region, similar to poliomyelitis. Although the presence of specific viral receptors on motor neurons explains the anterior horn cell neurotropism with polioviruses, the pathogenesis of the preferential rostral and anterior horn cell infection with WNV remains poorly understood[19].

Diagnosis

Tests to diagnose West Nile virus include

- Complete blood count (CBC)
- Head CT scan
- Head MRI scan
- Lumbar puncture and cerebrospinal fluid (CSF) testing.

The most accurate way to diagnose this infection is with a serology test, which checks a blood or CSF sample for antibodies against the virus. Rarely, a sample of blood or CSF may be sent to a lab to be cultured for the presence of West Nile virus. The virus can also be identified in body fluids using a technique called polymerase chain reaction (PCR).

The incubation period for WNV infection is thought to range from about 2 - 14 days. The presence of anti-WNV IgM, particularly from cerebrospinal fluid (CSF), is used for diagnosis. Cross-reactivity with related flaviviruses (Japanese encephalitis virus, St. Louis encephalitis virus, YFV, and DENV), if suspected, can be accessed through plaque neutralization assays[20].

Signs and Symptoms

Most human infections with WNV (~80%) are asymptomatic, and symptomatic infections may vary from flu-like malaise to serious neuroinvasive diseases, for which there is no specific treatment. Fewer than 1% of human infections progress to severe disease, for which the most frequently reported risk factors include advanced age, immune suppression, and chronic medical conditions including, but are not limited to, hypertension, diabetes, and chronic renal failure[21].

Treatment and Prevention

There is no specific treatment available for WNV infection and those with mild symptoms do not need any special care. Severe cases are provided with supportive care; in WNND cases, hospitalization is required, while critically ill patients may need special management in an intensive care unit. Encephalitis cases, in particular, should be constantly monitored for elevated intracranial pressure or seizures, while special attention should be given in cases that may need respiratory support. Current therapeutic options against WNV are mainly supportive; there are no FDA-approved vaccines or treatments available[22]. Investigations to identify individual susceptibility markers, recombinant antibodies, peptides, RNA interference, and small molecules with the ability to directly or indirectly neutralize WNV have been reported; however, an effective drug is still lacking.

A formalin-inactivated whole-virus veterinary vaccine originally developed by Fort Dodge Animal Health, Fort Dodge, IA, USA was licensed. This vaccine was shown to be safe and efficacious in horses and was granted full license by the USDA[23]. A Vaccine by fusing the DIII domain of the highly neuroinvasive WNV LSU-AR01 to equine CD40L is found out .These data showed that the vaccine induced strong neutralizing antibody responses in horses as measured by plaque reduction neutralization test (PRNT) after a single vaccination. A booster shot enhanced the antibody response. The vaccine was safe with no injection site reactions. More recently, a capsid deleted Kunjin virus DNA vaccine was developed with the capsid being provided in *trans*. These single-cycle viruses replicate once to generate VLPs, which were highly immunogenic in mice and horses[24]. An equine WNV vaccine based on the ChimeriVax technology was licensed by the USDA in 2006 and marketed by Intervet under the brand name Prevenile. This vaccine encoded the WNV NY 99 pre-membrane and envelope genes on a YFV backbone, but was recalled in 2010 due to acute side effects including fatality among vaccinated horses.

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.

Insect repellent use has been associated with reduced West Nile virus risk. There have also been attempts to treat infections using ribavirin, intravenous immunoglobulin, or alpha interferon. Geno Med, 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[25].

CONCLUSION

A number of vaccine strategies have been explored and showed promise to combat WNV. It is also evident that vaccines against lineage I WNV are able to protect against lineage II viruses and the converse is also true. In this regard, Kunjin virus-based vaccines were able to protect against lineage I viruses. A number of successful, licensed veterinary vaccines against WNV are readily available and several promising human WNV vaccine candidates have undergone successful early phase clinical trials. WNV remains a special pathogen that has gathered much attention due to its spreading pattern around the globe. It has been established in many countries worldwide causing epidemics in humans, birds and equines every year. Several countries of the Mediterranean Basin were the first to be affected after the first virus isolation in 1937, but the most impressively rapid spreading of the virus was observed in the USA starting from New York State in 1999.

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