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A Systematic Review on Epidemiology, Pathogenesis, Clinical Spectrum, Diagnostic Techniques and Control Strategies of West Nile Fever

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Abstract

Zoonoses that involve multiple etiological agents are an important cause of morbidity and mortality throughout the world. Globally, around one billion are affected by zoonotic diseases every year. West Nile fever, caused by the mosquito-borne West Nile virus (WNV) of the *Flavivirus* genus, is a significant emerging and re-emerging zoonosis with public health and economic ramifications. Primarily infecting birds, WNV also affects humans and other mammals, including horses, with transmission mainly via *Culex* mosquitoes and occasionally through blood transfusion, organ transplantation, and intrauterine transfer. Endemic in tropical and temperate regions, WNV leads to high morbidity and mortality across species. While most human infections are asymptomatic, approximately 20% develop symptoms ranging from mild fever to severe neuro-invasive diseases like meningitis and encephalitis. Horses, like humans, are dead-end hosts, often exhibiting severe neurological symptoms with high fatality rates. Diagnostic techniques include IgM antibody detection via MAC-ELISA and RT-PCR. Effective control measures emphasize mosquito population reduction, public education, and monitoring WNV activity in birds, animals, mosquitoes, and humans.

Keywords

Emerging; Mosquitoes; Public Health; Re-emerging Zoonosis; Transmission; West Nile Virus

1. Introduction

In recent years, numerous emerging and re-emerging zoonoses have drawn significant attention from international and national authorities due to their high morbidity and mortality rates in both humans as well as in animals [1]. Among these zoonotic diseases, West Nile fever stands out as a particularly important viral meta-zoonosis from both public health and economic perspectives [2]. This disease is caused by the West Nile virus (WNV), which belongs to the genus *Flavivirus* and the family *Flaviviridae* [2].

West Nile virus is a zoonotic, mosquito-borne flavivirus, one of approximately 75 virus species within the

Flaviviridae family [3]. These viruses can be categorized into tick-borne and mosquito-borne groups [4]. WNV is part of the Japanese encephalitis virus serocomplex, which includes St. Louis encephalitis virus (SLEV), Murray Valley encephalitis virus (MVEV), and *Alfuy* virus (ALFV) [5]. The virus is prevalent in both tropical and temperate regions and primarily infects birds. However, it also infects humans and other vertebrate mammals, such as horses [2, 6]. WNV has caused significant morbidity and mortality across various animal species, including birds [7], horses [8], sheep [9], reptiles [10], cats [11], and rodents [12].

West Nile virus is transmitted by mosquito vectors of the genus *Culex* through hematophagy [13]. Transmission methods, including ingestion, aerosol, and direct contact, have been observed in experimental settings [14]. In humans, WNV can be transmitted intrauterine and through breastfeeding [15], with recent reports also noting transmission in farmed alligators and crocodiles [16]. To date, only one case of vertical transmission has been documented in humans [17]. Additionally, WNV has been transmitted through blood transfusions and organ transplants in humans [18].

West Nile virus strains are classified into two main lineages: lineage 1 (L1) and lineage 2 (L2). L1 has a broad geographic distribution spanning Europe, Africa, the Middle East, and the Americas and has been associated with outbreaks in the Mediterranean and North America. In contrast, L2 was initially restricted to sub-Saharan Africa and Madagascar until its isolation from a Hungarian goshawk with neurological disease in 2004 [19].

Horses, similar to humans, are considered dead-end hosts epidemiologically, meaning they cannot transmit the virus after infection. Clinical manifestations of WNV in horses include fever, weakness, locomotor dysfunction, ataxia, and blindness. In severe cases, these symptoms can progress to paraplegia within 5 to 10 days, leading to death. Viremia levels in horses are typically low, which limits the possibility of infecting mosquitoes after a blood meal [20].

The symptoms of a severe WNV infection in humans, sometimes referred to as meningitis or West Nile encephalitis, include headache, high fever, stiff neck, weakness in the muscles, stupor, confusion, tremors, convulsions, paralysis, and coma. Roughly one out of every 150 West Nile virus-infected people is predicted to experience a severe illness [21].

Diagnosing West Nile virus infection involves employing various methods, with the most reliable being the detection of IgM antibodies specific to WNV in either serum or cerebrospinal fluid within 8 days of the onset of symptoms. This is achieved through the IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA), a highly sensitive and specific technique crucial for identifying recent WNV infections. Alternatively, rapid diagnosis can also be facilitated by RT-PCR, providing another effective approach in clinical practice [2; 6]. Preventing and controlling WNV infection requires a comprehensive strategy that includes public education, the adoption of personal protective measures, the elimination of mosquito breeding sites at the household level, the implementation of mosquito control measures, and ongoing surveillance of WNV activity in birds, animals, mosquitoes, and humans [2].

Therefore, the objective of this paper is to present a critical review of West Nile fever as an emerging and re-emerging life-threatening viral disease of public health concern.

2. Literature Review

2.1 Etiology

West Nile virus is an RNA virus belonging to the *Flaviviridae* family and *Flavivirus* genus [2]. It primarily infects humans through mosquito bites, with the *Culex* species being the predominant vector. Apart from humans, WNV can also infect birds, horses, dogs, and various other mammals [2]. Wild birds are considered ideal hosts that facilitate virus amplification. Humans are incidental dead-end hosts due to the low and fleeting levels of virus in their bloodstream. Serious symptoms develop in about 1% of infected individuals, with increased morbidity observed particularly in those over 50 years old, often manifesting as neurological complications. Additionally, rare modes of transmission include infection via infected donor blood, organs, breast milk, or through transplacental transmission [22].

2.2 Host and Transmission of West Nile Virus

West Nile virus infection has been reported in humans and several species of animals, such as camel, cattle, donkey,

horse, sheep, and birds (crow, duck, fowl, geese, pigeon, turkey, water fowl) [2].

Mosquito bites serve as the primary mode of transmission for WNV [2]. Birds act as reservoir hosts for the virus, which mosquitoes typically acquire when feeding on infected birds. Once a mosquito becomes infected, it can transmit the virus to humans, birds, or other animals during subsequent blood meals, usually occurring 10 to 14 days later. The virus enters the host's bloodstream via the mosquito's saliva during feeding. Apart from mosquito bites, WNV can also spread through breastfeeding, percutaneous inoculation, organ transplants, blood transfusions, and similar routes [23].

Although there isn't any proof of WNV spreading from person to person, it is theoretically feasible for it to spread through shared, contaminated needles. There is no danger of infection from touching or sharing utensils with an infected individual [23]. According to Murray and co-workers [24], humans and horses are regarded as dead-end hosts and are not involved in the virus's transmission cycle.

2.3 Epidemiology

In Uganda, the West Nile virus was discovered for the first time in 1937. When seven fatalities and 62 cases of encephalitis were reported in New York in 1999, it made a dramatic comeback and became the first in the Western Hemisphere. At the moment, Africa, Europe, Asia, North America, Australia, and the Middle East are endemic to the virus [25]. Initially, outbreaks were usually self-limiting, mild illnesses, but by the mid-1990s, the virus was related to severe neurological problems. A comprehensive assessment of the literature conducted in 2013 found that the death rate is approximately 10 percent, with less than 1% of infected people developing meningitis or encephalitis. Roughly 25% of infected individuals develop West Nile fever, while the other 75% either show little symptoms or show no symptoms at all, which probably accounts for a significant underreporting of infections [26].

Between 1999 and 2015 in the United States, nearly 44,000 confirmed and probable cases of West Nile virus have been reported, with over 20,000 cases classified as neuro-invasive diseases. The incidence of neuro-invasive cases varies significantly each year, ranging from 386 to 2,946 cases. Serologic surveys and blood donor screening indicate a neuro-invasive disease rate of approximately 0.5% among infected individuals, with infection rates reaching 10% in outbreak areas. Extrapolating from this data suggests an estimated 3 to 5 million cases of infection nationwide [26].

2.4 Pathogenesis

West Nile virus is thought to spread to lymph nodes and circulation after first replicating at the site of the entrance [27]. Toll-like receptor activation and elevated tumor necrosis factor-α levels are believed to have a role in the virus's capacity to enter the central nervous system and increase blood-brain barrier permeability [28]. WNV predominantly infects neurons, especially in the brain, brainstem, and spinal cord's deep nuclei and gray matter. It has been mentioned by Guarner and others [29] that paralysis may result from collateral injury to neighboring nerve cells. Furthermore, in certain situations, tissue damage may be caused by immune-mediated mechanisms [30]. A lack of oligoadenylate synthetase has been suggested as a hereditary vulnerability for severe disease in mice, yet this genetic susceptibility in humans has not been fully explained. WNV may persist in certain vertebrate hosts, although the majority of nonfatal infections seem to be eliminated by the host immune response [29].

2.5 Clinical Spectrum

In humans, WNV infection usually presents as a subclinical illness; over 80% of infected people have no symptoms at all. Usually, symptoms start to show up during an incubation period of three to fifteen days. When they do appear, symptoms could range from minor ones like fever and sore muscles to more serious ones like meningoencephalitis, which can be deadly [31]. West Nile fever, an acute febrile illness characterized by abrupt fever onset, malaise, appetite loss, headache, muscular aches, exhaustion, eye discomfort, nausea, vomiting, and swollen lymph nodes, is what most symptomatic cases of the disease present with [32].

In animals, WNV infections generally lead to a disease that resembles human infections. The clinical manifestations vary depending on the species affected, with birds (especially exotic species) and horses being most susceptible to the virus and its associated disease. Certain bird orders, such as *Passeriformes*, *Charadriiformes*, and *Falconiformes*, are particularly prone to developing clinical disease compared to others like *Galliformes*, which can be infected but typically remain asymptomatic. In *Galliformes* species, clinical signs of WNV infection may include

nonspecific symptoms such as depression, lethargy, ruffled feathers, loss of appetite, rapid weight loss, and neurological signs like ataxia, paralysis, tremors, pedaling movements, circling behavior, abnormal head posture, torticollis, nystagmus, seizures, opisthotonos, and occasionally death [33].

Horses are the mammals most affected by WNV after humans, showing a disease of similar severity [34]. The incubation period for WNV infection in horses is typically 3–15 days, paralleling that observed in humans. Similar to humans, the majority of infected horses remain asymptomatic, but a small percentage may progress to encephalitis and potentially fatal outcomes [35]. Clinical signs in horses can include depression, loss of appetite, colic, limb weakness, recumbency, and muscle twitching [34]. A neurological syndrome may develop, characterized by ataxia, stupor, changes in behavior, limb paralysis, lateral recumbency, profuse sweating, pedaling movements, seizures, cranial nerve deficits, opisthotonos, and other abnormalities such as hemi neglect [34].

2.6 Diagnostic Techniques

The clinical signs are not characteristics to make a tentative diagnosis, and therefore, laboratory help is imperative to establish an accurate diagnosis of West Nile fever. Diagnosing WNV infection typically involves a combination of clinical examination, laboratory tests, and post-mortem analysis. In humans, clinical examination focuses on observing symptoms such as acute fever, anorexia, nausea, vomiting, eye pain, headache, muscle pain, rash, swollen lymph nodes, and joint pain [36]. When WNV infection is suspected, both neurological and ophthalmological examinations are recommended to assess potential manifestations [37].

Laboratory-based diagnostic methods for WNV include virus isolation, RT-PCR, serology, and pathological examination [2]. Serologically, diagnosis relies on detecting IgM and IgG antibodies against WNV, which typically appear 3-7 days after exposure. However, IgM antibodies can persist for up to two years, particularly in horses, which limits their diagnostic utility [38]. Pathological diagnosis plays a crucial role in both clinical and experimental investigations of WNV infections. It involves identifying macroscopic and microscopic lesions and detecting viral antigens in tissue samples using immunohistochemical (IHC) techniques [39].

2.7 Control Strategies

2.7.1 Vaccination and Vaccine Development

Efforts to develop a vaccine against WNV for humans have been made, but as of now, there is no approved commercially available vaccine [40]. However, there is a commercially available recombinant, live attenuated vaccine for veterinary use. This vaccine, known as Recombitek and developed by Merial, utilizes a recombinant live canarypox virus expressing WNV prM and E genes from the WNVNY99 strain. It is administered to horses with two initial doses given intramuscularly five weeks apart. Following this regimen, vaccinated horses are protected against the disease for up to one year with 100% efficacy [40]. Neutralizing antibodies can be detected in vaccinated horses as early as 26 days after a single dose [41]. Moreover, this vaccine has also demonstrated successful use in dogs and cats [42].

2.7.2 Environmental Sanitation for Vector Control

Presently, no chemotherapeutic agent is available for the treatment of disease. Therefore, measures, such as the provision of proper drainage facilities, filling in the breeding sites of mosquitoes, reclamation of swamp areas for agricultural use, spraying of insecticides like benzene hexachloride, lindane, malathion, application of repellent cream on exposed parts of the body, and wearing of protective clothes during outdoor activities will certainly mitigate the incidence of this mosquito-borne viral zoonosis [2].

3. Conclusion and Recommendations

West Nile fever is a life-threatening metazoonosis of public health significance. West Nile virus, a member of the *Flavivirus* genus in the *Flaviviridae* family, primarily cycles between birds and mosquitoes, with humans and horses also susceptible to infection. Human cases range from asymptomatic to severe neurological disease, underscoring the virus's public health significance. Similarly, infected horses often exhibit severe neurological symptoms, highlighting their role in surveillance efforts. Diagnostic methods include immuological assays for IgM and IgG antibodies, RT-PCR for viral RNA, and pathological examination to confirm tissue infection. Rapid and accurate diagnosis is crucial for effective public health responses. Control strategies encompass public education, mosquito bite

prevention, vector control measures, and surveillance systems monitoring virus activity. While there's no approved human vaccine, veterinary vaccines have proven effective in protecting animals, particularly horses, against WNV.

Based on the insights from this review, several recommendations can be made to enhance the understanding and management of West Nile virus:

- It is imperative to maintain monitoring to track WNV activity, spot new trends, and assess the efficacy of control efforts over time.
- To reduce human exposure to mosquito bites, it is crucial to promote the use of insect repellents, wear protective clothing, and reduce mosquito breeding areas.
- Understanding and reducing the spread of WNV requires implementing a One Health approach that incorporates environmental, animal, and human health concerns.

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Contribution of Authors

All the authors contributed equally. They read the final version and approved it for publication.

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