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Review article

West Nile virus and its emergence in the United States of America

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Abstract – Zoonotic West Nile virus (WNV) circulates in natural transmission cycles involving certain mosquitoes and birds, horses, humans, and a range of other vertebrates are incidental hosts. Clinical infections in humans can range in severity from uncomplicated WNV fever to fatal meningoencephalitis. Since its introduction to the Western Hemisphere in 1999, WNV had spread across North America, Central and South America and the Caribbean, although the vast majority of severe human cases have occurred in the United States of America (USA) and Canada. By 2002–2003, the WNV outbreaks have involved thousands of patients causing severe neurologic disease (meningoencephalitis and poliomyelitis-like syndrome) and hundreds of associated fatalities in USA. The purpose of this review is to present recent information on the epidemiology and pathogenicity of WNV since its emergence in North America.

West Nile virus / zoonosis / arbovirus / epidemiology / pathogenicity

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1. INTRODUCTION

West Nile virus (WNV) is an emerging mosquito-borne RNA virus of global significance that can infect the central nervous system (CNS) of various host species and cause severe neurological disease [59]. Zoonotic transmission of WNV occurs between avian hosts and ornithophilic mosquito vectors [64, 141]. Horses and humans are regarded as dead-end hosts while sensitive to WNV-induced meningoencephalitis [59, 83]. For the first decades after its isolation in Uganda in 1937 [155], WNV was the frequent cause of epizoonotic in horses during which a high mortality was observed. It was mostly associated with

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asymptomatic, self-limiting childhood infections in humans [131]. The first introduction of WNV in the Western Hemisphere occurred in 1999 in New York City (NYC) of United States of America (USA) [4, 5], presumably by the transport of infected humans, birds or mosquitoes [85]. WNV amplified and extended its distribution across the USA where it has been declared endemic within the 10 years [57, 58]. The spread of WNV continues in the Western Hemisphere [54]. Neurological disease is a WNV complication that was increasingly observed in humans following to the introduction in USA [121, 123]. Up to now, WNV was responsible for over 12 000 cases of meningitis/encephalitis and over 1 100 human fatalities, survivors often suffering long-term neurological sequelae. Mass mortality of resident birds, especially crows, was also observed. The American WNV strains causing the outbreaks in USA might be derivative of a highly neuroinvasive Israeli strain introduced in the Western Hemisphere in 1999 [52]. WNV pathogenesis is complex and involves viral and host factors as well as antiviral immunity in the periphery and the CNS [44]. Control of WNV infection is orchestrated by host cell defenses that are partly mediated by Type-I interferon (IFN) [50]. However, WNV has evolved strategies able to counteract the IFN-mediated antiviral immunity in the infected host [55]. In the present review, we discuss on the emergence of zoonotic WNV in the USA since 1999 and the recent informations on the specific viral and host factors that may have an influence on virus virulence in host species.

2. WNV IS A NEUROTROPIC FLAVIVIRUS

WNV is a member of *Flavivirus* genus (*Flaviviridae* family) [26]. The flaviviruses are positive sense, single-stranded RNA viruses [94]. Classically, they are subdivided into 10 serological complexes. WNV belongs to the Japanese encephalitis virus (JEV) serogroup of flaviviruses. JEV serogroup also contains Murray Valley encephalitis virus (MVEV), St. Louis encephalitis group (SLEV), and Usutu virus (USUV) [102, 138]. The WNV species also contains the Kunjin (KUNV) subtype that is endemic in Australia and Malaysia [56]. The flaviviruses of the JEV serocomplex are the leading cause of arboviral encephalitis in vertebrate hosts including humans.

After virus inoculation in the dermis by the bite of a chronically infected vector, most infections by members of the flavivirus JEV serogroup result in no symptoms or a mild febrile illness [57, 117]. It was shown that mosquito saliva modulates early infection steps and alters the host immune response against arboviruses including WNV [147, 148]. Less than 1% of flavivirus infections cause natural infection of the CNS [34, 57, 115]. Following CNS infection, disease syndromes range from mild meningitis to severe encephalitis with variable morbidity and mortality [34, 117] and possible sequelae [75, 122]. Once inside the CNS, encephalitic flaviviruses infect neurons [33, 78, 151, 164], cause severe immunopathology [2, 90] and apoptosis [43, 89, 129, 132, 169].

Highly neurovirulent flaviviruses exhibit an upregulation of genes involved in IFN signaling, T-cell recruitment, MHC class I and II antigen presentation, and apoptosis [162, 163]. The mechanism by which encephalitic flaviviruses cross the blood-brain barrier (BBB) and invade the CNS has still not been fully elucidated [34, 74, 107]. It was first assumed that neuroinvasiveness depends on initial virus spread before the establishment of an immune response [107]. Some studies suggest disruption of BBB as mode of entry [37, 81, 121]. Alternatively, endocytosis into the CNS across vascular endothelium was demonstrated [51, 95]. Another suggested mode of CNS entry was the infection of olfactory neurons that are unprotected by the BBB [63, 105, 113]. Cohort and case-control studies have shown that hypertension and vascular disease may predispose to neuroinvasive disease [103, 121, 124]. Although asymptomatic in a majority of cases, WNV infection has been associated with neurotropic human manifestations including meningo-encephalitis and acute flaccid paralysis [43, 59, 123].

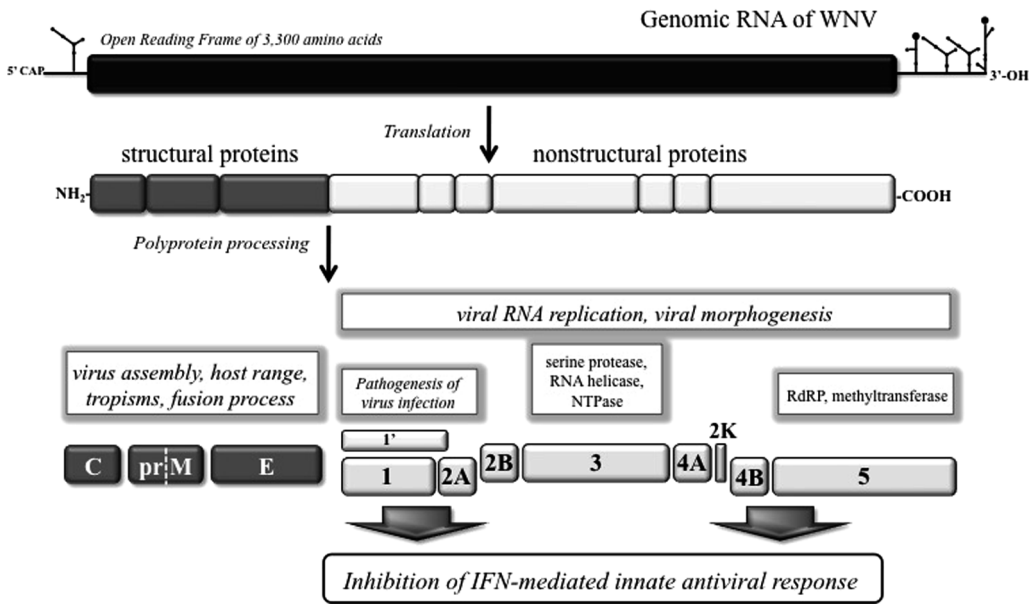

Figure 1. Schematic representation of WNV genomic RNA and the translation of the viral proteins. Functions of individual proteins are shown. See the text for details.

3. MOLECULAR BIOLOGY OF WNV

WNV replication and assembly occur in the reticulum endoplasmic (ER) of infected cells [25]. Genomic RNA encodes a large polyprotein precursor, which is processed by host and cellular proteins to yield individual structural (C, prM/M and E) and nonstructural (NS) proteins NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 [25] (Fig. 1). The NS proteins are assumed to be involved primarily in the replication of viral RNA. Within infected mammalian cells, WNV NS1 is secreted to high levels [101]. Recent studies revealed an involvement of NS1 in modulation of signaling pathways of the innate immune response to WNV [166]. Interestingly, it has been observed that a larger NS1-related protein, designated NS1', might play a critical role in neurovasiveness of the members of JEV serogroup [109]. The NS3 protein is a viral enzyme which exhibits serine protease activity from its N-terminal domain and ATPase and helicase activity from its C-terminal domain. The viral RNA-dependent RNA polymerase, the product of NS5 gene, is responsible for replication of the viral genome within putative complexes comprising both viral and host proteins. NS3 and NS5 have been identified as the major components of the viral RNA replicase complexes (RC). Viral RC were shown to induce rearrangement of intracellular membranes. The functions of small membrane-associated NS2A, 2B, 4A and 4B proteins remain still largely unknown.

4. WNV STRATEGY FOR EVADING HOST INNATE IMMUNITY

WNV has developed strategies for enhancing viral replication in the host by blocking the action of type-I IFN and evading the antiviral activity of IFN-stimulated genes (ISG) [50, 55, 68, 92, 96, 97, 118, 146, 157]. Flaviviral IFN antagonists are involved in the inhibition of type-I IFN signaling. The nonstructural proteins NS1, NS2A, NS4B and NS5 may contribute to the control of IFN-α/β signaling by WNV [97, 118, 119] (Fig. 1). It has been observed that NS2A has the ability to inhibit the activation of

IFN-β transcription [96, 98]. The transcription factors involved in IFN-β mRNA expression whose activity is affected by NS2A are still unknown. A single amino acid substitution in WN NS2A (A30P) has been shown to enhance activation of IFN-α/β expression in vitro and in vivo [98]. Also, the A30P substitution in NS2A attenuates the neuroinvasiveness and neurovirulence of WNV in mouse model. Recent report showed that NS4B is able to block the IFN-signaling cascade at the level of nuclear STAT1 phosphorylation [118, 119]. The N-terminal region of NS4B determines its IFN antagonist activity whereas the central part of NS4B is believed to influence flavivirus virulence [165]. Expression of NS5 has been recently shown to block the IFN-stimulated JAK-STAT signaling [93].

The IFN-inducible 2′, 5′-Oligoadenylate Synthetases (OAS) are part of a regulated RNA decay pathway known as the OAS/RNase L pathway, which has been shown to protect against flavivirus infection [71, 99, 104, 133, 145, 154]. Recently, a genetic case/control study on horses naturally infected with WNV showed a potential role for equine *OAS1* polymorphisms in the host innate resistance to WNV during the epidemics in USA [143]. Genetic variation in human *OAS1* is a host genetic risk factor for initial infection with WNV in North American populations [91]. Similar to human and horse *OAS1*, we and others provided evidence that the murine *Oas1b* plays a critical role in resistance to severe WNV infection in a mouse model of virally-induced encephalitis [71, 99, 104, 133]. Serial passage of WNV in mouse cells expressing *Oas1b* gave rise to a variant that displays resistance to the antiviral effect of *Oas1b* [110]. This is consistent with the assumption that WNV has the ability to counteract the antiviral activity of IFN-inducible OAS [71]. The resistance of WNV to *Oas1b* could be attributed to the S365G substitution in the viral NS3 NTPase/helicase domain and the V9M substitution in the hydrophobic 2K peptide that spans the ER membrane between NS4A and NS4B [110] (Fig. 1). The NS3 and 2K mutations promote WNV resistance to *Oas1b* through enhancement of viral RNA replication. It is of interest to note that a single amino-acid substitution in the NS3 helicase was sufficient to increase the virulence of WNV in American crow in North America [22]. Also, the 2K-V9M substitution has been detected in a WNV isolate collected from birds in North America [40]. So far, a single *OAS* gene has been identified in avian species [158].

These observations are consistent with a model in which the mutations in the nonstructural proteins could act as viral determinants to control IFN signaling or the antiviral effects of ISG such as *OAS* [23, 146]. This opens a new avenue for understanding how viral and host genetic diversity influences WNV pathogenicity in various hosts including humans, horses, and avian species. Whether viral factors that promote WNV subversion to antiviral innate immunity may have consequences for the amplification of WNV in the nature is a critical issue that remains to be investigated.

5. ENZOOTIC TRANSMISSION OF WNV

The principle mode of maintenance and amplification of WNV in nature occurs between avian hosts and ornithophilic mosquito vectors while human and horses are regarded as dead-end hosts unable to uphold transmission cycles (Fig. 2). *Culex* ssp. is the key vector in this transmission cycle [66, 161], however, the virus has also been isolated from *Aedes* ssp., *Anopheles* ssp. and many other mosquito species in Europe and Africa [61, 62, 64, 168] as well as in North America [13, 14, 53, 83, 127]. Ticks and other blood-sucking arthropods were also found capable of WNV replication and transmission under experimental conditions [64, 65, 130], although the role of these potential vectors in a natural setting has not been determined. Avian hosts that maintain a sufficient viremia to subsequently infect mosquitoes are mostly passerine species, particularly corvids [1, 13, 14, 62, 70, 79, 83, 159, 168].

6. EPIDEMIOLOGY OF ZOONOTIC WNV

WNV was first isolated from a febrile woman in the West Nile district of Uganda in 1937 [155]. WNV infection was mostly associated with

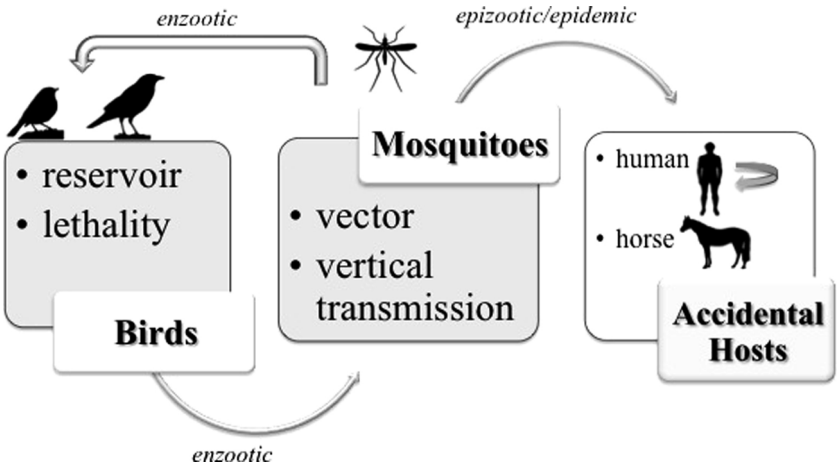

Figure 2. WNV transmission cycle.

asymptomatic, self-limiting childhood infection, with adults showing a high percentage of immunity [159]. The earliest epidemics were associated with low mortality, however severe neurological disease was reported in Israel [15], France [131], and South Africa [70, 106]. Historically, WNV was the frequent cause of epizootics in horses, during which a high mortality was observed [69, 120].

At present, WNV is endemic to Europe [61, 82], the Middle East, Africa [49, 113], Asia [74], Australia [74], and now North America. The first introduction of WNV into the Western Hemisphere occurred in 1999 in NYC [5, 24, 28, 128], probably by transport of infected humans, birds or mosquitoes [54, 140, 141].

Two predominant genetic lineages of WNV have been identified by phylogenetic analysis [16]. Lineage 1 contains an antigenically diverse group of isolates from Europe, the Middle East, India, Africa, Australia and the Western Hemisphere [19]. Lineage 2 contains isolates from Southern Africa and Madagascar. Lineage 2 strains were considered less virulent than lineage 1 strains [9] but recently also southern African strains have been associated with cases of severe encephalitis. WNV lineage 1 strains were mostly associated with severe and neuroinvasive disease, but recent studies show that viruses with high and low neuroinvasive phenotype exist in each of the lineages [9, 10, 21, 164]. Evidence for further genetic lineages was recently reported. It was reported that a single amino-acid substitution in the WNV NS3 helicase was sufficient to increase virulence in avian hosts [22, 44]. Change in pathology and neuroinvasiveness observed in some WNV strains was suggested to have originated from a change in the N-glycosylation pattern of the envelope protein resulting in altered virion stability [10, 12, 32, 108, 150].

Since the mid-1990s, three epidemiologic trends have emerged regarding WNV: (1) increased frequency of outbreaks in humans and horses, (2) increase in reported cases of neuroinvasive disease in humans, and (3) high case fatality rates in birds coinciding with human outbreaks, mainly in the USA and Israel [134]. Beginning in 1996, the Eastern Hemisphere has experienced several WNV-encephalitis outbreaks with human fatalities in Algeria [86], Romania [27, 86, 160], Tunisia [120], Israel [17, 38, 153] and Russia [100, 136]. These more recent outbreaks have been attributed to evolution of a new, more pathogenic WNV variant belonging to lineage 1.

7. EMERGENCE OF WNV IN THE USA

In late August of 1999, an unusual cluster of encephalitis cases was reported to NYC's

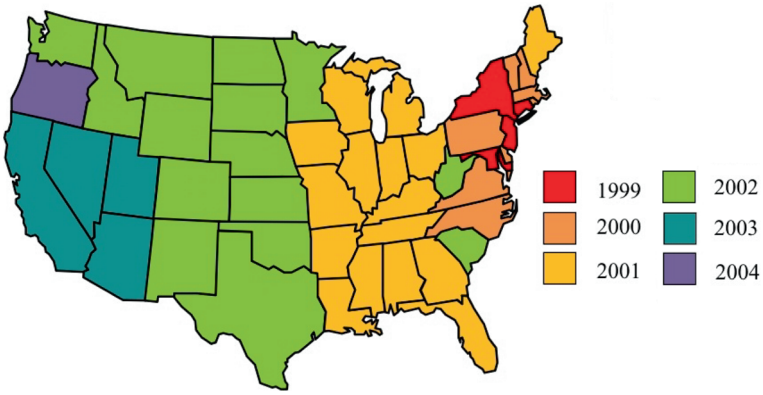

Figure 3. The enzootic spread of WNV across the lower continental USA since its first introduction in Western Hemisphere in 1999. (A color version of this figure is available at www.vetres.org.)

Department of Health [4, 128]. Initially, laboratory findings suggested infection with SLEV which is serologically related to other flaviviruses in the JEV serogroup [28]. Laboratory sequencing of virus isolated from brain tissue of birds identified WNV lineage 1 [67]. Retesting of clinically ill human cases and testing of horses presenting with CNS disease in Long Island, NY revealed WNV as the cause of disease. A total of 62 human cases of WNV were identified during this outbreak, including seven deaths. By extrapolation from a household-based study it was estimated that the NYC WNV outbreak in 1999 caused around 8 200 asymptomatic infections, causing disease in approximately 1 700 individuals [115]. This was the first evidence of WNV activity in the Western Hemisphere.

Phylogenetic analysis suggests that American strains might be derivatives of an Israeli strain introduced into the Western Hemisphere [6, 36, 52, 67, 85]. Again, it is unknown as to how this virus was introduced into the USA. *Culex pipiens* mosquitoes collected during the NYC outbreak were susceptible and able to transmit WNV [161]. Overwintering mosquitoes showed low levels of WNV RNA by real-time PCR [29]. WNV spread into several Canadian states that border to the USA, causing infections in both humans and birds [46, 167]. Surveillance of WNV-infected horses and birds detected spread of WNV through Mexico [18], the Caribbean [8, 39, 47, 80, 87, 139] into South America [20, 45, 80, 114].

During the first years of circulation in North America, WNV persistence over the winter months was attributed to continued transmission during winter [142], overwintering of the virus in mosquitoes [29, 126, 140], and vertical WNV transmission from infected females to their offspring [7, 111, 142]. WNV infection of migratory birds was suggested to contribute to the fast dissemination of WNV in North and South America [16, 54, 170]. WNV is also rarely isolated from mammals [1, 62, 137] and reptiles [77, 112] but, like humans, these species are regarded as dead-end hosts unable to uphold transmission cycles (Fig. 2). Contrasting to this, non-viremic transmission during co-feeding between mosquitoes on dead-end hosts was described [60]. Non-vector routes of WNV transmission include oral infection [79, 84, 112], intrauterine infection [31, 59], breast-feeding [30, 59], blood transfusion [35, 59].

In the following years monitoring of bird die-offs and intense mosquito control measures were established to minimize human infections [140]. Nevertheless, WNV amplified and extended its distribution across the lower 48 continental states and has been declared endemic within 10 years of its introduction (see Fig. 3) [3, 13, 59, 135]. For two years, a homogenous viral population (genotype NY99) prevailed in New York State before

Table I. Summary of WNV human cases reported annually to CDC, 2002–2009.

	1999	2000	2001	2002	2003*	2004	2005	2006	2007	2008	2009
Human cases	62	21	66	4 156	9 862	2 539	3 000	4 269	3 630	1 338	720
Deaths	7	2	10	284	264	100	119	177	124	44	32

* National surveillance practices changed to include reporting of West Nile fever cases.

introduction of a new genotype (WN02) in 2002 containing two non-coding changes in the E (C2466U) and NS5 (C9352U) gene and one coding change in the E gene (U1441C, V159A) [11, 41]. WN02 soon became the dominant genotype in the USA, displacing its predecessor by 2004 [156]. This displacement was a result of both earlier and more efficient transmission in *Culex* ssp. mosquitoes [48, 116] and increased adaptation to replication at higher temperatures by WN02 [73].

Human and equine clinical cases, avian mortality cases, positive sentinel chicken flocks, and positive mosquito pools are reported to CDC by each individual state through the Arbonet surveillance system. Initially, only WNV encephalitis and meningitis (also referred to as neuroinvasive disease) cases were reportable. Starting with the 2003 transmission season, CDC requested that uncomplicated fever cases also be reported, resulting in a dramatic increase the reported numbers. Since 1999, our knowledge of WNV infection has evolved and changed. Likewise, CDC definitions of the various clinical entities associated with infection have changed, as have the laboratory criteria for diagnosing infection.

8. WNV INFECTION IN HUMANS

Since its introduction into the USA in 1999, WNV has been responsible for over 12 000 cases of meningitis/encephalitis and over 1 100 fatalities[1]. Survivors often suffer long-term neurological disorders. Neurological disease is a WNV complication that is increasingly observed following to the introduction of WNV into North America [128, 144]. Infection of spinal anterior horn motor neurons can cause acute flaccid paralysis during WNV infection [88, 149]. Upon WNV infection, neurons were observed to exhibit a direct antiviral response by secretion of the proinflammatory cytokine CXCL10 [76]. TNF-α was associated with accumulation of $CD8^+$ T cells and activated macrophages in the CNS that contribute to increased clearance of WNV infection [152].

Very recently, WN viral RNA was identified in the urine of 20% of convalescing WNV patients up to seven years post-infection, leading to the discovery of persistent infection of the kidneys with associated renal pathology [124]. The authors speculate that persistent infection of the CNS is also possible and warrants investigation. Considering the vast number of human cases across the USA and in other parts of the world, further research is needed to understand the pathologic lesions and outcomes underlying persistent infection.

9. CONCLUDING REMARKS

Complex ecological factors determine the geographic spread of WNV. Since 1999, a dramatic westward and southward spread of WNV activity has occurred in the USA, likely due its emergence into areas with immunologically naïve reservoir populations, leading to vast numbers of viremic birds, as well as adaptation to New World *Culex* species mosquitoes, including *Cx. quinquefasciatus* and *Cx. tarsalis*. The number of USA counties reporting WNV activity increased dramatically (Fig. 3). Ten years after it was discovered in NYC, more than 25 000 cases of WNV had been reported in humans, including over 1 000 deaths (Tab. I). This virus is likely to establish an endemic cycle

[1] See the web site http://www.cdc.gov/ncidod/dvbid/westnile/

of transmission across the USA, Canada, and Central and South America, leading to a continued rise in cost associated with acute and long-term treatment of human cases and vaccination of horses, as well as the cost of continued surveillance, prevention and control measures.

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