West Nile Virus

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KEYWORDS

• West Nile virus • Flavivirus • Viral encephalitis

KEY POINTS

- West Nile Virus (WNV) is the most widely distributed flavivirus and causes multiple viral encephalitis outbreaks in humans in different regions worldwide.
- Nearly half of the WNV convalescent patients are reported to have persistent neurologic sequelae or chronic kidney disease.
- Neither treatment nor vaccines are available for human use; current efforts on drug development have been mostly focused on the inhibitors of virus replication.
- Results from field and animal model studies will provide important new insights onto WNV transmission, host immunity, and viral pathogenesis; the findings will also lead to the development of new strategies to prevent and treat WNV-induced encephalitis.

INTRODUCTION

West Nile virus (WNV), a mosquito-borne, single-stranded, positive-sense flavivirus, has been the leading cause of arboviral encephalitis globally. The virus was originally isolated from Uganda in 1937; later caused epidemic outbreaks in Asia, Europe, and Australia; and was introduced into the United States in 1999.[1] The genome of WNV is approximately 11,000 nucleotides in length, which is translated and processed into 10 proteins: 3 structural proteins (envelope [E], membrane, nucleocapsid) and 7 nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5).[2,3]

Although most human infections are asymptomatic, approximately 20% of the infected individuals become symptomatic and develop acute illness, ranging from systemic flu like illness, such as West Nile fever, to neuroinvasive outcomes.[4] In fewer

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than 1% of the symptomatic individuals, virus entry into the central nervous system (CNS) results in neuroinvasive manifestations, such as meningitis, encephalitis, poliomyelitis, and death.[5,6] Both older adults and immunocompromised individuals are at a high risk of developing neuroinvasive disease.[7,8] Ocular manifestations including multifocal choroiditis, retinal hemorrhage, chorioretinal lesions, optic neuritis, and vitritis are also known to be associated with WNV infection.[9–13] Up to 50% of convalescent patients with WNV are reported to have persistent neurologic sequelae or chronic kidney disease, which occurs 6 to 12 months after the acute infection.[14–17] Moreover, follow-up clinical studies reported that some convalescent patients and asymptomatic WNV RNA-positive blood donors, continue to have detectable serum or cerebrospinal fluid (CSF) levels of WNV-specific immunoglobulin (Ig)M and IgA for more than 6 months and up to several years after their initial infection.[18] These facts indicate that WNV antigen may persist in the periphery or in the CNS in humans after acute infection. Indeed, the persistence of WNV antigen and RNA in the CNS of an immunocompromised patient[19] and presence of WNV RNA in urine of convalescent patients with WNV neuroinvasive disease after 1 to 7 years[20] present the evidence of chronic infection. Neither treatment nor vaccines are currently available for human use. In this review, we discuss recent findings from studies in field and animal models of WNV infection and provide new insights onto WNV transmission, host immunity, viral pathogenesis, diagnosis, and vaccine development.

TRANSMISSION CYCLE

WNV is primarily maintained in nature by transmission between ornithophilic *Culex* mosquitoes and a variety of bird species (**Fig. 1**). In the United States, the virus has been detected in 65 different species of mosquitoes.[21] However, only a few of *Culex* species have been reported to drive epidemic transmission to humans and other vertebrates and these primary vector species vary by geographic region.[21] Generally, in the western part of the United States, *Culex tarsalis* mosquitoes are the major WNV

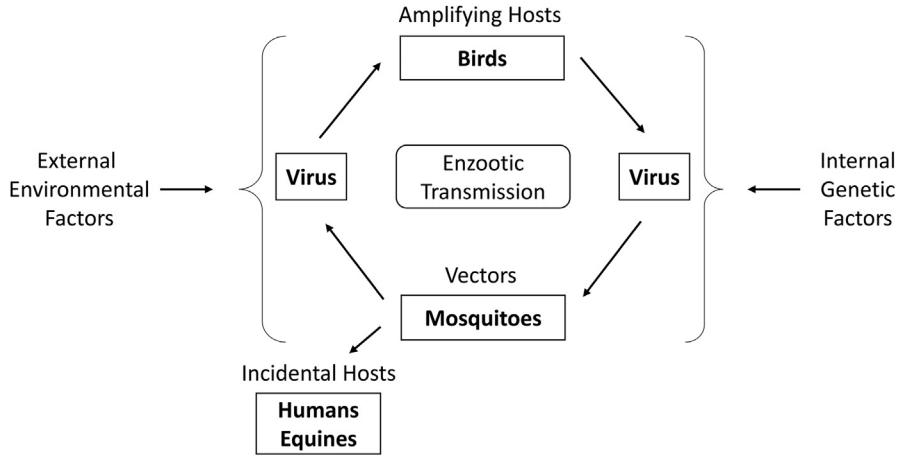

Fig. 1. West Nile virus transmission cycle. The virus is maintained in nature by an enzootic transmission cycle between mosquitoes and avian hosts. Humans and horses are considered incidental or "dead-end" hosts, as they do not generate sufficient viremia to support ongoing transmission. Numerous external environmental factors and internal genetic factors can affect the transmission cycle.