

## West Nile virus. Molecular Description, virus pathology and dissemination of the disease to the New World

The flaviviruses (family Flaviviridae, genus Flavivirus) are enveloped, single-stranded RNA viruses that encode a single open reading frame that is translated into a single polyprotein which is post-translationally cleaved into 3 structural (C, pre-M, E) and 7 nonstructural (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) proteins. The current sequence data on the genomes of different flaviviruses has confirmed a high degree of relatedness of these viruses. Sequence homology with DEN is ~50% for JEV and WNV, whereas the homology between the NY99 strain of WNV and Kunjin (KUN) is ~ 89%. Sequence homology varies across the viral genome, and is generally higher in the region encoding nonstructural proteins.

In humans, WNV often produces subclinical infection or an acute viral syndrome, West Nile fever. Only a minority of cases develop encephalitis. In 1954, a study using WNV for the treatment of advanced cancer patients demonstrated that only 11% of subjects developed encephalitis. Virus can be isolated from blood during the first 4 days of illness in West Nile fever and viral RNA can be detected in CSF in some cases of encephalitis. Pathological examination of brains from the 2001 NY outbreak demonstrated microglial nodules; the medulla and thalamus were involved most consistently.

Emerging viruses can be defined as newly discovered viruses or known viruses with an expanding geographic or incidence pattern. Examples of viruses that have emerged in the US in the last decade include Sin Nombre virus, West Nile virus (WNV), dengue viruses and Powassan virus. Sin Nombre, and related viruses, are in the hantavirus group, whereas the other viruses are members of the family Flaviviridae. Man and mosquito are the reservoirs for dengue viruses, which can cause dengue hemorrhagic fever, a plasma leakage syndrome. Man is an incidental host for the other viruses, but all of these viruses induce disease with significant morbidity and mortality (hantavirus pulmonary syndrome, viral encephalitis). Each one of these viruses maintains a life cycle in zoonotic and/or arthropod hosts (rodents for SNV, and birds, some mammals and mosquitoes for WNV, mosquitoes for dengue). In 2001, this virus has spread to 27 states with human encephalitis cases reported in 9 states (2001). Although much has been learned about the epidemiology and clinical manifestations of this disease, large gaps in knowledge exist: why do certain individuals, in particular the elderly, develop encephalitis due to WNV while the majority of infections remain subclinical. The rapidly expanding distribution of this virus across the US necessitates closing these knowledge gaps with research designed to elucidate aspects of the virus-host relationship.

### Ecology and transmission cycle in North America

West Nile virus (WNV) is maintained in a natural cycle, shared between mosquitoes and birds, and also infects people and horses. The infection is endemic in parts of Africa, Europe, the Middle East and Asia, and human outbreaks have occurred in the United States since 1999 also causing disease in vertebrates. The infection has established itself in the western Hemisphere. Recently, WNV began to circulate in Mexico and it is expected to continue spreading into South America. Previous observations on the movement of arboviruses (eastern equine encephalomyelitis, western equine

encephalomyelitis), which are similarly amplified by birds, showed that viruses were actively transported southward into tropical America and northward into the United States by migrating birds. Although it is not currently possible to predict the features of WNV transmission in tropical America, it is feared that the main urban areas of Latin America could experience large outbreaks. Some mosquito species that have been found infected with the virus in the southern United States (e.g., *Culex quinquefasciatus*) are abundant in urban tropical areas. On the other hand, the high prevalence of other flaviviruses in the tropical region, mainly dengue and Yellow Fever, may confer upon the human population either some cross protection against WNV infections or exacerbate the expression of disease due to possible immune enhancement. The lessons are yet to be learned for understanding WNV transmission cycle and its precise mode of dissemination in humans and other vertebrate hosts.