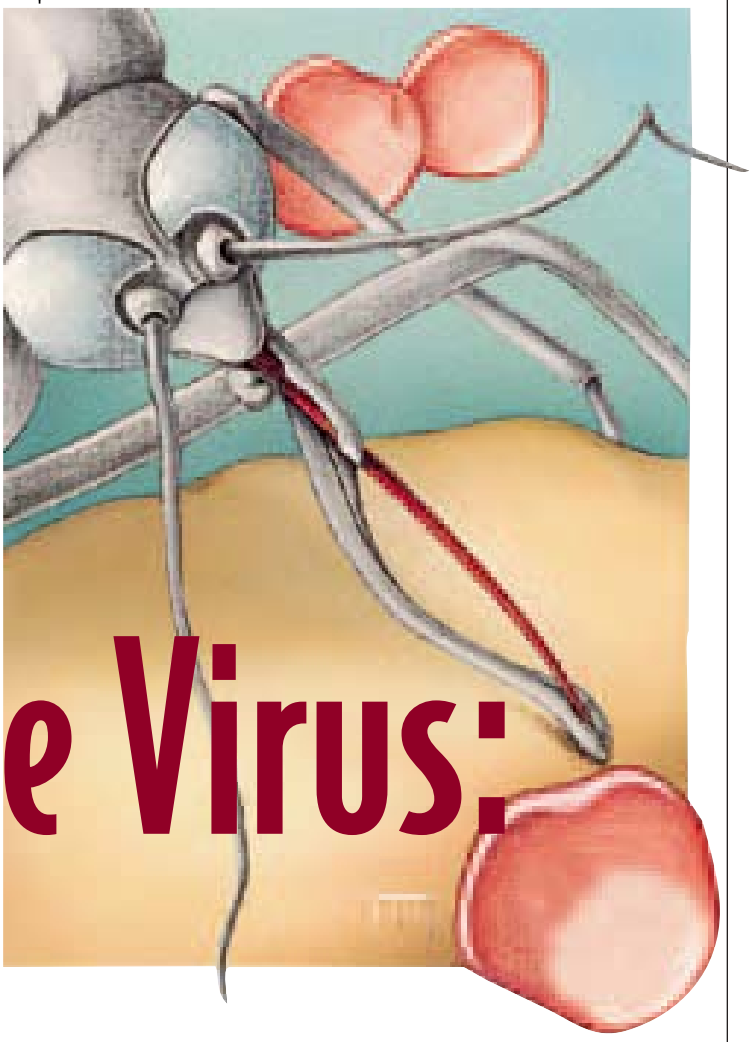

West Nile Virus:
A Global Problem

By Hélène Senay, MD FRCPC

In the summer of 1999, numerous cases of encephalitis emerged in patients residing in the New York City borough of Queens. Subsequent research revealed that the reported encephalitis cases had been caused by West Nile virus (WNV), known on other continents, but never before isolated in North America .

This article summarizes what is known about this virulent newcomer on this side of the Atlantic Ocean. The article will briefly examine the history of the virus, how it came to North America and its clinical signs.

History of the Virus

WNV was first isolated in 1937 in a female patient living in Omogo, in the West Nile District of northwestern Uganda.[1] The woman was suffering from an apparently benign febrile disease. Blood samples, however, revealed a new virus of the Flaviviridae family, *genus flavivirus*. A flavivirus subgroup, Japanese Encephalitis Antigenic Complex, contains closely related micro-organisms. WNV belongs to this subgroup, as do the St. Louis encephalitis (SLE), Japanese encephalitis (JE), Murray Valley encephalitis (MVE) and Kunjin (KUN) viruses. As illustrated in Figure 1, the viruses in this subgroup are found throughout the world.

West Nile Virus

The first true outbreak of WNV-related encephalitis occurred in Israel in the early 1950s.[2] Since then, 16 other countries have reported outbreaks. These countries include Romania in 1996, and Russia and the U.S. in 1999. In Romania and Russia, the cases totaled 500 and 800 respectively.

1999 New York Outbreak

In North America, the virus can be traced back to August 1999, when an infectious disease specialist in Queens reported two cases of encephalitis to the New York City Department of Health.[3] The rapid implementation of an encephalitis surveillance system traced six other cases that fit the disease profile. It was astonishing to note that all eight patients lived within the same two-square-mile sector. In light of the proximity of the infected individuals, it was hypothesized that the infection was caused by an arthropod-borne virus. Initial serological analyses detected St. Louis encephalitis virus-specific immunoglobulin M (IgM) antibodies.

Municipal health authorities and the staff of the Bronx Zoo (in a neighboring borough) reported an abnormally high number of deaths in the bird population. St. Louis encephalitis virus does not usually cause such devastation, either in the crow population in the urban context, or in pheasants, cormorants and flamingos in captivity, as was the case with this outbreak.

Deoxyribonucleic acid (DNA) studies were carried out simultaneously on tissue samples from dead birds and the cadavers of humans who had died from encephalitis. It was confirmed that the virus involved was, in fact, not St. Louis virus but WNV. The close similarity between the two viruses explained the false-positive results of the enzyme immunoassays for St. Louis virus.

The global status report compiled in the fall of 1999 indicated seven deaths among a total of 59 patients with encephalitis (*i.e.*, 10% mortality rate).[4] The use of insecticides by ground and aerial spraying at the start of the outbreak, as well as lower temperatures towards the end of September, were two factors that helped stem the outbreak.

Seroprevalence Research

In the fall of 1999, 677 residents of Queens (the first area affected by the outbreak) were tested for WNV antibodies in order to estimate the seroprevalence. The unpublished study, conducted by the Centers for Disease Control and Prevention (CDC) and the New York City Department of Health, demonstrated an overall seroprevalence rate of 2.6%. Approximately 20% of the seropositive subjects reported they had suffered from a minor febrile illness in the few weeks prior to the study. The study indicated that most of the individuals who had been infected by

Summary

West Nile Virus

- Phylogenetic analyses of WNV isolated in humans in New York in 1999 have shown a correspondence of more than 99.8% between the New York virus (WNV-NY, 1999) and the virus involved in cases of encephalitis reported in Israel the previous year.
- Currently, no specific antiviral treatment seems to be effective in lessening the clinical symptoms or reducing the mortality rate, and there is no vaccine available.

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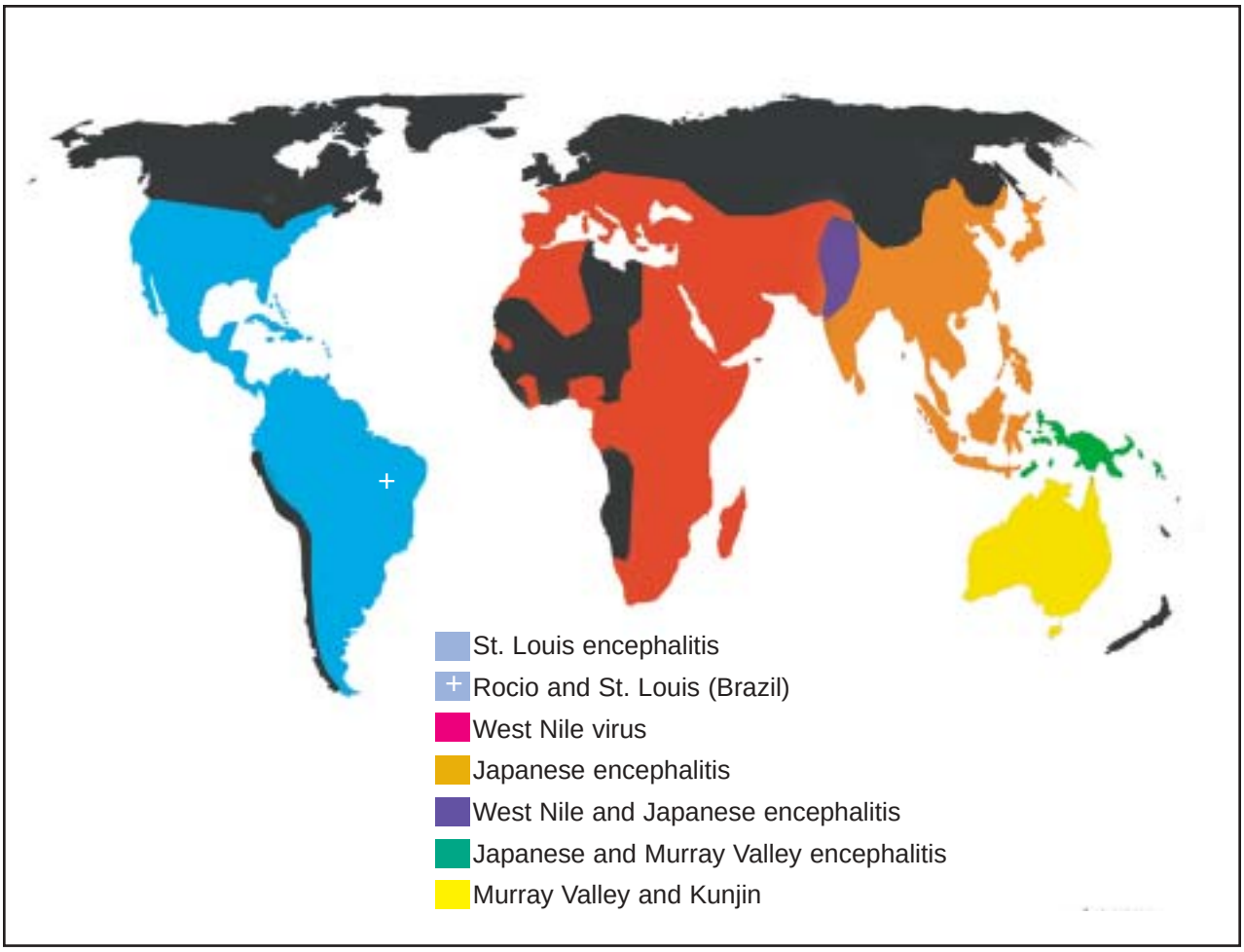

Figure 1 The geographic distribution of the Japanese encephalitis serocomplex of the family Flaviviridae.

WNV remained asymptomatic and that those who developed encephalitis (< 1%) were exceptional cases.

In order to be better prepared for a potential outbreak in the summer of 2000, researchers at the CDC wanted to determine whether WNV could survive a New York winter in mosquito larvae.[5] Of the 67 samples taken at breeding sites during the winter (Queens historical sites, bridges, hangars, airport, *etc.*), polymerase chain reaction (PCR) testing revealed slightly positive results for three sites, including one that also tested positive by cell culture. It was concluded, therefore, that WNV could indeed survive a New York winter, and that all the necessary measures should be taken

Table 1

Incidence of West Nile Virus in the U.S.

Year	1999	2000	2001
No. of human cases	59	21	42
Number of deaths (%)	7 (10)	1 (5)	2 (5)
No. of states with human cases	1	3	7
No. of states where virus is present*	4	12	26

* In the mosquito, bird and animal populations.

to prevent an outbreak in the summer of 2000.

The Summers of 2000 and 2001 in New York and Other Parts of the U.S.

New York public health authorities were alerted to the first case of encephalitis of 2000 in early August. Information campaigns and the use of insecticides helped reduce the number of reported cases that summer in comparison with 1999, however, the geographical distribution of cases broadened. While all reported human cases in 1999 had been from a single U.S. state, in 2000, cases were reported in three states: New York, New Jersey and Connecticut. In 1999, monitoring for WNV in the mosquito, bird and animal populations had detected the virus in four U.S. states, as compared to 12 states in 2000. As indicated in Table 1, the problem of virus propagation in the U.S. intensified in the summer of 2001.[6] That year, human cases were reported in seven U.S. states: Florida, New York, Connecticut, Maryland, New Jersey, Pennsylvania and Georgia.

Hypotheses on the Arrival of WNV in North America

Phylogenetic analyses of WNV isolated in humans in New York in the summer of 1999 have shown a correspondence of more than 99.8% between the New York virus (WNV-NY, 1999) and the virus involved in cases of encephalitis reported in Israel the previous year.[7] The two strains, which are distinguished by only two nucleotides out of 1,278, in fact probably constitute a single virus. All evidence suggests that WNV-NY 1999 was imported from Israel. The question remains, How did the virus cross the Atlantic?

Normal bird migrations could have been involved in the arrival of WNV in North America. Certain bird species, such as the Eurasian duck, reproduce in Iceland and Siberia and then winter in Europe, the Middle East or Africa. A small proportion then migrate to the Eastern Seaboard of the United States.[8] Few scientists, however, subscribe to this theory, arguing that if WNV had been transported in this manner, it would probably have appeared in North America much sooner.

A second hypothesis holds that WNV crossed the Atlantic by airplane. A traveller to Israel could have contracted the virus there, been viremic upon entering the U.S., and subsequently been bitten by a mosquito shortly after arriving in New York. The newly infected mosquito could then have spread the infection to birds, which are known to be a reservoir of viral infections. This theory is espoused by few, however, as humans are known to be "dead-end hosts" in WNV infection. Even if the traveller were not the source of the infection *per se*, he/she may have transported a carrier mosquito on his person or in his/her luggage, and the mosquito, in turn, could have spread the infection to birds. Alternatively, the virus could have been brought to North America

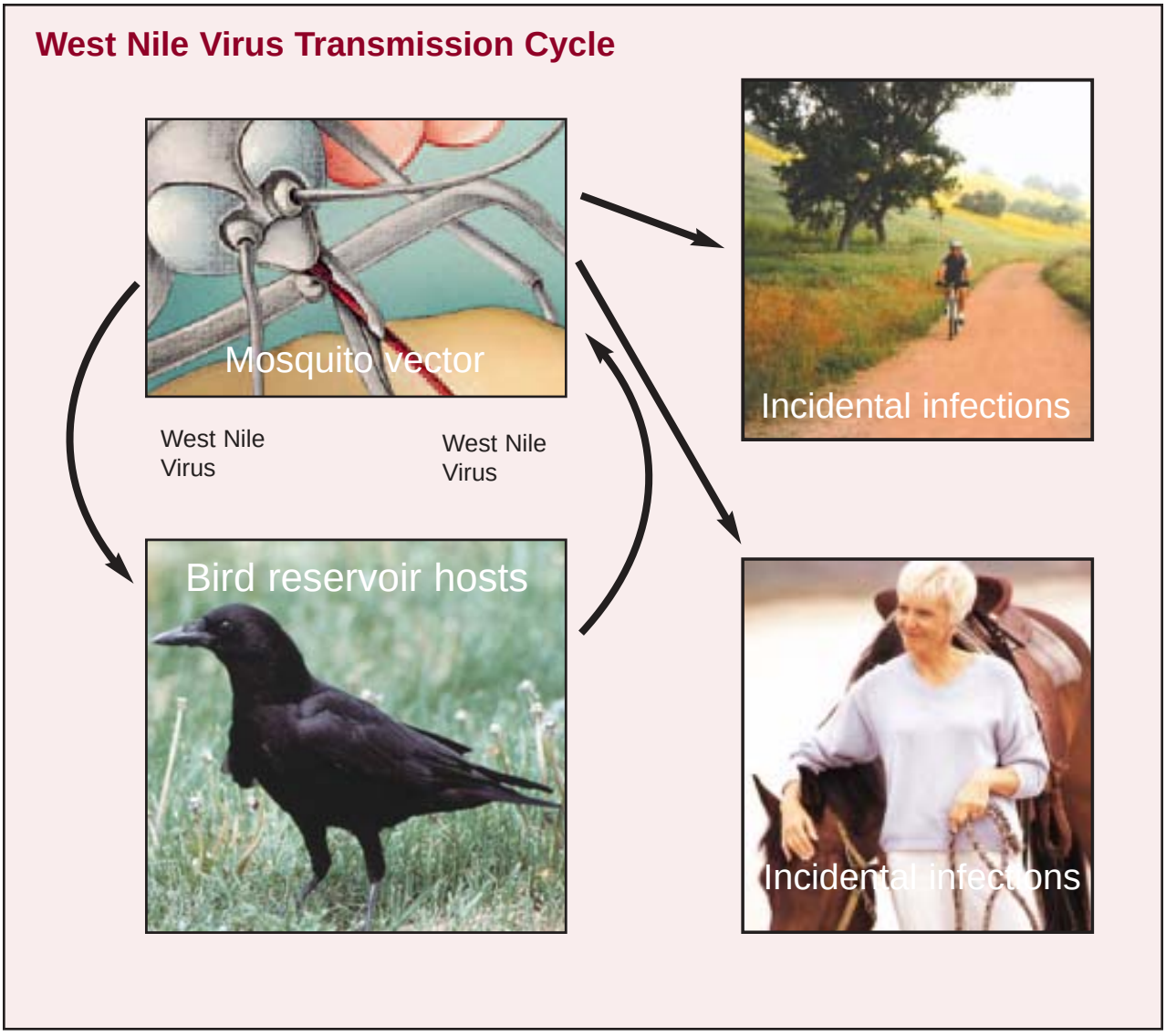

Figure 2 West Nile virus transmission cycle
Adapted from Web site of the Centers for Disease Control and Prevention:*www.cdc.gov/ncidod/dvbid/westnile*.

through the importation of birds. In 1999, some 3,000 birds intended for consumption or resale in the U.S. arrived at John F. Kennedy International Airport. Moreover, nearly 13,000 were transported *via* JFK for other final destinations. It would only have taken a single WNV-infected bird to be bitten by a local mosquito for the infection to take hold in North America.

While there is still debate over how the virus was brought to North America, experts are more apt to agree on when the virus arrived — most likely shortly before the 1999 outbreak. The high death rate, especially among the crow population in New York City (nearly 5,000 deaths) during the human out-

Table 2

Preventive Measures To Reduce Risk Of Infection

1. Remain indoors at dawn and dusk.
2. Wear light-coloured clothing (trousers and long-sleeved shirts).
3. Use mosquito repellent (permethrin or DEET 35%) on clothing and exposed skin.
4. Eliminate mosquito breeding habitats in your environment.

break in 1999 is characteristic of the recent arrival of a new pathogen in a population never before exposed to the virus (Figure 2).

Epidemiology

In temperate climates, infections generally occur in late summer and early fall — the period in which the vectors of WNV are active. Although about 40 species of mosquitoes are known to have been infected by WNV, three are primarily involved in transmitting the infection to humans: Culex pipiens, Aedes vexans and Anopheles. Less than 5% of mosquitoes that belong to the species of known carriers of WNV are actually infected with it.

In hot climates, infection can occur at any time of the year. Birds are the reservoir of WNV, and more than 70 bird species are infected by it. In the U.S., crows are the primary species affected. Once they are infected through a mosquito bite, they are viremic for four days. The virus is located in the salivary glands of the insect, which feeds on the blood of other organisms. At the mosquito's next blood meal, the virus enters the bloodstream of the host, which could be an animal or human rather than a bird. Animals most affected are horses. Wild animals such as skunks, squirrels and raccoons are less frequently affected and domestic pets are rarely infected.

As mentioned previously, most infections remain asymptomatic or result in only mild febrile symptoms. Less than 1% of infected patients develop encephalitis, meningitis or meningo-encephalitis. Most of those patients develop muscular weakness to varying degrees. Infected people sometimes present with pancreatitis, hepatitis or myocarditis. The incubation period ranges from three to 15 days. The average age of those who develop encephalitis is around 70. The mortality rate, which mainly involves people 75 years of age or older, varies between 3% and 15%.[4]

The infection cannot be transmitted through person-to-person contact, nor can it be transmitted from infected birds or animals to humans. Infected people need not take any specific isolation measures.

The Situation In Canada

In the summer of 2000, public health authorities established sentinel chicken surveillance from Saskatchewan to Atlantic Canada.[9] In Quebec, four sentinel chicken coops were set up (in the Mauricie, Estrie, Montérégie and Eastern Quebec regions). Throughout the summer and early fall, the chickens were tested weekly for WNV. Mosquito populations also were monitored, as were unusual deaths among bird and animal populations. Moreover, physicians were asked to report all cases of suspected viral encephalitis to their public health units. The generally accepted definition of encephalitis is described as "An acute febrile illness with clinical signs that are compatible with a diagnosis of viral encephalitis: Altered mental state and/or muscular weakness and/or acute flaccid paralysis and cerebrospinal fluid indicative of viral infection (mild to moderate

pleiocytosis [predominantly lymphocytic] and/or elevated protein level) and no evident etiological agent."[10]

In the summer of 2001, no cases of WNV were found in the mosquito, bird or animal populations tested in Canada.

Although no cases of human infection have been reported to date in Canada, in 2001, the virus was isolated in dead birds in Southern Ontario.[11] The virus, therefore, has made its way into Canada. In all probability, WNV will survive the winter, as it did in New York, and could resurface in the summer of 2002.

Diagnosis, Treatment and Prevention

Two serum samples taken 14 days apart could indicate a rise in antibodies in an infected host. The method used to detect the presence of WNV antibodies is the hemagglutination-inhibition test. Positive results must be confirmed by an enzyme immunoassay (EIA). A diagnosis also can be made on the basis of a cerebrospinal fluid sample or through a reverse transcriptase polymerase chain reaction (RT-PCR) assay.[12]

Currently, no specific antiviral treatment seems to be effective in lessening the clinical symptoms or reducing the mortality rate, and there is no vaccine available. Preventive measures that reduce the risk of infection are summarized in Table 2.

Future Perspective

The U.S. experience of the past three years has shown that the geographical distribution of WNV has broadened. The number of U.S. states in which infected mosquitoes, birds and/or animals have been found increased from four in 1999 to 26 in 2001. Propagation of the virus to neighbouring states can be anticipated in the summer of 2002. The migration patterns of birds on the U.S. Eastern Seaboard also suggests that infection could spread into Mexico, the

Caribbean and South America.[8]

In Canada, in the summer of 2002, we can expect the geographical distribution of WNV to extend to more than one province, as seen in 2001. We may also witness the first human case of WNV-related encephalitis in Canada in the late summer or early fall of 2002.

WNV can be considered firmly anchored in North America. It is here to stay. Appropriate mosquito-control measures must be implemented to minimize the impact of the virus on bird, animal and human populations. Furthermore, public education on the existence of the virus, its mode of transmission and how to protect oneself against it are needed. In thinking about WNV transmission and prevention, one inevitably draws a parallel with plasmodium, the agent that causes malaria. The World Health Organization's experience with malaria has shown that controlling arthropod-borne diseases is often more difficult than may be thought initially. Time will tell whether the spread of WNV in North America can be controlled more effectively than the spread of malaria in endemic countries.

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