WEST NILE VIRUS: THE DICHOTOMY OF THE DISEASE,
MILD SYMPTOMS OR DEATH

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DEBRA K. MACDONALD find it satisfactory and recommend that it be accepted.

Chair

[Signatures]
Abstract

West Nile virus made its first appearance in the Western Hemisphere in New York City in 1999. In just three short years it has made a transcontinental movement across the United States. The common North American mosquito, *Culex pipiens*, is the primary vector in the spread of West Nile virus. Birds are the primary carriers and humans and mammals are incidental hosts of West Nile virus. Prevention and public education are the primary focus of prevention of West Nile virus infection. Clinical manifestation of West Nile virus includes mild flu-type symptoms of malaise, anorexia, nausea, vomiting, headaches, and lymphadenopathy. Severe infections of West Nile virus advance to neurological diseases of encephalitis and meningitis. A positive diagnosis of West Nile virus is confirmed with serological testing of cerebral spinal fluid and serum blood samples using IgM and IgG enzyme-linked immunosorbent assay (ELISA), followed by a neutralization test if the ELISA test is positive. Treatment of West Nile virus is mainly supportive, with severe infections usually requiring hospitalization. A vaccine to prevent West Nile virus is under development and clinical trails are scheduled to start in 2003.
West Nile Virus: The Dichotomy of the Disease, Mild Symptoms or Death

Introduction

The warm temperatures of spring bring an increase in adult mosquitoes and the potential for West Nile virus. West Nile virus is an Eastern Hemisphere Flavivirus that first appeared in the Western Hemisphere in New York City in 1999. West Nile virus presents a threat to not only human health, but also equine and bird health. One Hundred Forty-nine cases of human West Nile virus were reported to and confirmed by the Centers for Disease Control and Prevention (CDC) from 1999 through 2001 (CDC, 2002d). Eighteen of those confirmed cases resulted in death. In three short years, West Nile virus has reached across the United States, starting in New York and reaching Washington and California last year. In the year 2002, the CDC received reports of 4,161 cases of West Nile virus and 277 deaths in the United States (CDC, 2003).

Thousands of people can be expected to develop an infection due to West Nile virus during the peak months of June through August. People with immunosuppression, older adults, and the very young are the most susceptible to West Nile virus infection. As the incidence of West Nile virus increases, mosquito control along with public awareness and education need to be a priority in the prevention of the spread of West Nile virus.

Epidemiology

West Nile virus was first isolated 66 years ago in 1937 in the West Nile District of Uganda (CDC, 2002a; Lok, 2002; Petersen & Marfin, 2002). West Nile virus remained a virus of the Eastern Hemisphere with wide distribution in Africa, Asia, the Middle East, and Europe until the summer of 1999, when it was identified in North America. According to Campbell and Dreher (2002) many viruses originate in the Amazon rain
forests and sparsely populated African jungles. Destruction of these forests has caused insects and animals to search for new homes. The migrating insects and animals carry viruses and disease with them that infect the population of their new habitat. Importation of exotic birds and monkeys along with transcontinental travel has also resulted in the spread of viruses and diseases across the world.

Egypt was the site of the first major outbreak of West Nile virus in 1957. The virus caused severe human meningoencephalitis in elderly patients (CDC, 2002a). The virus has been found in numerous cases of equine disease and dead birds throughout the Eastern Hemisphere. According to the CDC (2002a), geographic distribution of West Nile virus has centered in Africa, Europe, the Middle East, west and central Asia, and Oceania (subtype Kunjin). Major outbreaks of West Nile virus encephalitis occurred in humans from 1994 to 2000 in Algeria, Romania, the Czech Republic, the Democratic Republic of the Congo, Russia, and Israel. Epizootics of West Nile virus have also occurred in equine in Morocco 1996, Italy 1998, and France 2000. Major infections in birds were found in 1997-2001 in Israel.

West Nile virus made its first appearance in the Western Hemisphere in New York City in 1999. In July 1999, New York City’s Bronx Zoo had several exotic birds die suddenly. Autopsies of the birds showed severe heart and brain damage. The CDC confirmed on September 23, 1999, that the birds had West Nile virus (Campbell & Dreher, 2002). Simultaneously, six elderly patients were admitted to the hospital in Queens with muscle weakness, fever, and confusion. Later, several more patients were admitted to the hospitals in New York City and in surrounding towns (Asnis, 2002). Brain tissue samples from 3 of the patients were sent to New York Department of Health
and then forwarded to the University of California, Irvine for examination. The threat to
public health caused New York City to begin immediate eradication and vector control
measures against mosquitoes. Encephalitis was the initial diagnosis, however in
September 1999, the CDC and the University of California, Irvine, confirmed West Nile
virus. The strain was very similar to the virus discovered in a dead goose in 1998 in Israel
(Asnis, 2002). No mode of entry into the United States could be found and it was
concluded that the virus had arrived in migratory birds.

In November 1999, a common North American Mosquito the *Culex pipiens*
species tested positive for West Nile virus. Three other species of mosquitoes also tested
positive. Twenty species of exotic and native birds (the majority crows) were examined
and tested positive for West Nile virus. Epidemiologists hypothesized that West Nile
virus had been transmitted to humans by mosquitoes that had fed off infected birds, then
fed on humans or other mammals (Campbell & Dreher, 2002).

Since the appearance of West Nile Virus in 1999 in the United States, its
occurrence has escalated. In the year 2000, the virus was identified in 12 states
(Connecticut, Delaware, Maryland, Massachusetts, New Hampshire, New Jersey, New
York, North Carolina, Pennsylvania, Rhode Island, Vermont, Virginia) and the District of
Columbia. In 2001, there were 66 human cases in 10 states and the District of Columbia.
Infected birds were identified in 27 states; and 679 horses in 19 states were identified
with West Nile virus. Mosquitoes in 904 pools (groups of mosquitoes) in 16 states and
the District of Columbia also tested positive for West Nile virus (Asnis, 2002; CDC
2002d). Map 1 shows states reporting confirmed cases of West Nile virus infected
A surveillance network called ArboNET was started by the CDC to track West Nile virus via the Internet. ArboNET tracks cases of West Nile virus in humans, animals, dead birds, captured sentinel birds (chickens), wild birds, and mosquitoes. ArboNET collects information from 54 state and local public health departments and the CDC (CDC, 2002d). For the years 1999-2000, 149 human cases were reported to ArboNET. Chow et al. (2003) summarized the United States data reported to the CDC via ArboNET between January 1 and November 30, 2002. A total of 3,389 human cases of West Nile virus were reported in 37 states (619 counties) and the District of Columbia. The CDC (2002e) released Map 2 that shows the spread of West Nile Virus in the United States between January 1 and December 11, 2002. Illness onset dates ranged from June 10th to November 4th in the southern states and July 10th to October 28th in the northern states. The epidemic peaked during the week ending August 24, 2002. Two weeks before the epidemic peak in August, there was a peak in the number of infected birds leading investigators to believe there is a connection between infected birds and the epidemic in infected humans.

In the year 2002, West Nile virus activity in animals and humans has been reported in 44 states (2,289 counties) and the District of Columbia. West Nile virus enzootic activity was reported in 1,670 of the reporting counties, but no human activity was detected. During 2002, equine cases increased 12 fold with transmission occurring over a longer season and in 9 new states. Horses might be a useful indicator of increased human risk, since the geographic and temporal distribution of equine cases closely paralleled the human epidemic in Midwest and north-central states (CDC, 2002d).
A complete transcontinental movement of West Nile virus has occurred in the 3 years since its arrival in 1999 in New York. The transcontinental movement was completed with the reporting of one human case in Los Angeles County in California and a report of an infected horse in Island County, Washington. Map 3 shows the progress of West Nile virus by state with the first reported case in New York in 1999 and the complete transcontinental movement of West Nile virus in California and Washington in 2002 (CDC, 2003e). The CDC (2002d) also reported the first documented cases of person-to-person transmission of West Nile virus through organ transplants and blood transfusions. Two recent cases of West Nile virus infection have occurred in laboratory workers who had no other known risk factors (CDC, 2003d). Both laboratory workers acquired infection through percutaneous inoculation, while working on West Nile virus infected animals. The first intrauterine transmission of West Nile virus occurred in 2002. An infant was born to a mother who tested positive for West Nile virus during her 29th week of pregnancy. She delivered a live infant of 38 weeks gestation whose cord blood and heel-stick blood samples tested positive for West Nile virus with IgM and neutralizing antibodies. IgM specific antibodies for West Nile virus were found in the infant’s serum and CSF confirming intrauterine infection. Further testing of the infant revealed bilateral chorioretinitis and an MRI of the brain showed severe cerebral abnormalities (Nguyen et al., 2003).

Pathology

West Nile virus is an arbovirus, an arthropod-borne virus. The virus is maintained in nature through biological transmission between susceptible vertebrate hosts and blood-

Arboviruses are enveloped single-strand of positive-sense RNA viruses (Petersen & Roehrig, 2001). West Nile virus belongs to the family Flaviviridae, one of over 69 viruses in the genus Flavivirus (Petersen & Roehrig, 2001; Tulane University, 1999; University of Saskatchewan, 2001). The virus is not very stable in the environment and it is inactivated easily by heat and common disinfectants (University of Saskatchewan, 2001). Petersen and Roehrig (2001) state that, “recent outbreaks of WN virus have been accompanied by an apparent evolution of a new WN virus variant” (p. 612). Genetically West Nile virus can be divided into two lineages. Viruses of lineage I include viruses from Europe, the Middle East, and North, Central and West Africa, which are associated with human infection. Lineage I includes Japanese encephalitis, St. Louis encephalitis, Kunjin, and the West Nile virus responsible for the epidemic that began in New York in 1999 (identified as NY99) which has spread across the United States. The nearest relative of NY99 is Isr98, a virus circulating in Israel from 1997 to 2000. The United States and Israel are the only countries reporting illness and death both in humans and animals as a result of Isr98/NY99 variant of West Nile virus (Petersen & Roehrig, 2001). Lineage II includes viruses from West, Central, and East Africa, and Madagascar, which have not been associated with human infection (Petersen & Roehrig, 2001; University of Saskatchewan, 2001).

Arboviruses are zoonotic in nature. Their life cycle involves nonhuman primary vertebrate host and a primary arthropod vector. In the United States, the primary vertebrate host are birds and the primary arthropod vector is a mosquito. Although
humans and domestic animals can develop illness they usually are “dead-end” hosts, because they do not produce enough viremia to contribute to the cycle (CDC, 2002b).

The envelope glycoprotein is the viral hemagglutinin agent that facilitates the host-cell binding process during replication. Host-cell binding allows the virus to enter the cell and replicate in the cytoplasm of the host cell. The virus only stops normal mammalian RNA synthesis, and does not affect arthropod cell function (Petersen & Marfin, 2002).

Weiner (2003) found that the destructive protein, West Nile virus capsid (WNV-Cp) that forms the capsid around the genetic material in a cell of West Nile virus causes the inflammation that causes encephalitis and apoptosis in the cell’s mitochondrial pathway. WNV-Cp causes the cell to start a cascade of reactions that affects the transcriptional mechanism of the host cell resulting in cell suicide. The cascade of reactions not only affects the brain, but also causes inflammation in muscle cells. The resulting conditions mimic those observed in natural infections making diagnosis difficult.

Transmission

Mosquitoes are the primary vectors for West Nile virus. They carry virus particles in their salivary glands and infect birds species during blood-meal feedings (CDC, 2002g). Male mosquitoes feed on nectar and plant juice, while female mosquitoes feed on warm-blooded animals like birds, dogs, horses, and humans. The female mosquito needs blood to nourish her eggs, and she seeks out a blood meal just before laying her eggs. Birds are the most satisfactory reservoir for West Nile virus. Birds can sustain an infectious viremia in their system for 1 to 4 days after exposure. If they survive the
infection, they then develop lifetime immunity to the virus. West Nile virus is maintained in an enzootic cycle by large number of mosquitoes feeding on an infected host to ensure that some survive long enough to feed again on a susceptible reservoir host. Figure 1 shows the transmission cycle of West Nile virus. The CDC (2002g) states “people, horses, and most other mammals are not known to develop infectious-level viremias very often, and thus are probably “dead-end” or incidental-hosts” (p. 1).

*Culex pipiens, Culex restuans, and Culex quinequaeefasciatus* are the species of mosquito identified in the eastern United States as maintenance vectors for West Nile virus (CDC, 2002b; Petersen & Marfin, 2002). All three species of mosquitoes are common across the United States. The bird-mosquito-bird cycle begins in spring when temperatures warm. Mild winters followed by hot, dry summers contribute to the spread of West Nile virus. It is believed that West Nile virus lays dormant in mosquitoes over the winter and reappears each summer (Asnis, 2002; Campbell, 2002). As spring temperatures warm the mosquito completes its maturation from egg to adulthood. Female mosquitoes need water to breed and lay their eggs. Any amount of standing water can serve as a breeding place for mosquitoes. Catch basins and city drains are rich in organic matter that the *Culex* mosquitoes thrive in. A female mosquito lays hundreds of eggs at a time on the water; figure 2 shows a *Culex* mosquito laying eggs. As long as climate, predators (dragonflies and frogs), and parasites are conducive, the mosquito eggs will hatch in one week or less. In the summer months, the amount of watering holes for birds is reduced, resulting in more birds in one location that mosquitoes can feast on and transfer West Nile virus to, thus enhancing the bird-mosquito transmission cycle.
A “bridge vector” is a mosquito that bites both humans and birds. The CDC (2002g) reports that mosquitoes become infected with West Nile virus when they feed on a bird that has the virus in their blood. The mosquitoes then go through an incubation period of 10 to 14 days, after which if they bite another bird, person, or animal the virus is transmitted to that bird, person or animal where it replicates and causes illness. However, this cycle is not reversible. Humans and other mammals are incidental hosts; they do not carry enough virus in their blood to infect a mosquito that bites them.

Dogs and cats do not seem to be affected the same way that West Nile virus affects birds and humans. However, horses are susceptible to the virus in much the same way that humans are. The CDC (2002g) reports that 40% of infected horses will die from the virus. Horses need to be protected from mosquito bites to prevent their infection. In many areas where infections of West Nile virus have been seen, birds and horses have been diagnosed with the virus before human infections surface.

Prevention

Petersen and Marfin (2002) suggest that there are two general directions that can be taken in the prevention of West Nile virus. The first is for public and municipal authorities to take action in reducing the number of vector mosquitoes. The second is for each person to take responsibility in preventing mosquitoes from biting by using mosquito repellents; avoiding locations where mosquitoes are biting; and using barrier methods against mosquitoes such as clothing, window screens, or insect repellent.

The United States Environmental Protection Agency (US EPA, 2002) and the Center for Disease Control (CDC) issued a joint statement regarding mosquito control in the United States. Their recommendation to obtain the greatest impact on decreasing the
mosquito population is to focus on killing mosquitoes before they become adults. Mosquitoes go through three aquatic phases before becoming adults; egg, larvae, and pupa. By controlling habitat and killing mosquito eggs, larvae, and pupa before they mature to adults, there will be a reduction in the need for widespread pesticide control in populated areas.

The first step in this process is to reduce breeding sites. Mosquitoes can lay eggs in any amount of standing water, on lake and pond water, and on moist soil. Campbell and Dreher (2002), Washington State Department of Health (2001a & b), and the CDC (2002c) urge each person to take action by starting with the small things: change water in birdbaths, fountains, wading pools, and animal watering troughs each week; recycle cans, bottles and buckets that can collect water; clean gutters and drains so they are not clogged; fix leaky faucets and sprinklers; empty any containers with standing water, e.g. an old tire can hold over 100,000 mosquito larvae. State and local governments are responsible for mosquito control activities in their communities. The United States Department of Environmental Protection Agency (US EPA, 2002) and CDC encourage government agencies to adhere to integrated pest management (IPM) as the next step in controlling mosquito habitat. IPM uses systematic surveillance to monitor mosquito habitat and then destroy the habitat or eliminate the mosquitoes. Mosquitoes in the larvae stage are concentrated, immobile, and accessible making them easier to kill. Most adult mosquitoes have a limited flight range; however some can fly from flood plains or coastal marshes to residential areas (US EPA, 2002; Petersen & Marfin, 2002). Under these circumstances government officials should consider using insecticides under proper environmental conditions. Up-to-date information concerning which pesticide to use
during for each life cycle of the mosquitoes (egg, larvae, pupa, or adult), and how to use the pesticides correctly can be obtained from the US EPA on their internet web site http://www.epa.gov or from the National Pesticide Information Center at http://npic.orst.edu

The second focus of prevention is the avoidance of mosquito bites. Avoiding mosquito-infested areas and teaching patients precautions can reduce their risk of contracting West Nile virus. Mosquitoes are attracted to carbon dioxide, heat, and moisture. They can detect breath, skin temperature, and sweat, and can find an animal or human from 20 feet away. Wearing long sleeved shirts and long pants will help to reduce detection by mosquitoes. Applying an insect repellent with 35% DEET (10% DEET for children two through twelve years old) to exposed skin and clothing will help deter mosquitoes. However, DEET is not recommended for pregnant women or children under two months old (Campbell & Dreher, 2002; CDC, 2002c; Lok, 2002; Weil, 2001). One of the most effective ways of avoiding mosquitoes is to advise persons stay indoors during dawn and dusk hours, when mosquitoes are the most active. Table 1 contains recommendations to teach patients to increase their awareness and reduce their risk of contracting West Nile virus.

Clinical Manifestations

When, after the mosquito bite does West Nile virus manifest itself? West Nile virus signs and symptoms can range from unnoticeable to a severity that requires hospitalization. West Nile virus has an incubation period of 3 to 14 days with symptoms of sudden onset that last 3 to 6 days. The virus often goes undetected, because people
often think they have the flu and do not seek medical treatment for the symptoms (CDC, 2002f; Petersen & Marfin, 2002).

Mild forms of West Nile virus imitate flu symptoms: malaise, anorexia, nausea, vomiting, conjunctivitis, headache, myalgias, lymphadenopathy, and a non-pruritic roseolar or maculopapular rash (see Figure 3) on chest, back and arms (Asnis, 2002; Campbell & Dreher, 2002; CDC, 2002f; Lok, 2002; Petersen & Marfin, 2002). Practitioners must remember that West Nile virus is new to the United States, and as such, the CDC (2002f) has warned that the full clinical spectrum of the virus has probably not been determined.

Severe forms of West Nile virus are uncommon. Patients with the highest risk of severe West Nile virus are the very young, adults over 50 years of age, and those that are immunosuppressed (Campbell & Dreher, 2002; Petersen & Marfin, 2002). During the 1999 New York West Nile virus epidemic, people aged 50 to 59 years old had ten times greater risk of contracting West Nile virus than people in the age group of 0 to 19 (Petersen & Marfin, 2002). Less than one percent of West Nile virus cases advanced to encephalitis or meningitis, and the CDC reported that approximately one in 150 infections would result in severe neurological disease with encephalitis more commonly reported then meningitis (Asnis, 2002). Ninety percent of patients that were hospitalized with West Nile virus showed signs of high fever, muscle weakness, gastrointestinal upset, headache, and change in mental status (Petersen & Marfin, 2002). Campbell & Dreher (2002) also included in their list of symptoms for severe infection from West Nile virus neck stiffness, stupor, disorientation, coma, tremors, and convulsions. The CDC (2002f) described myocarditis, pancreatitis, and fulminant hepatitis as part of severe West Nile
virus, but these symptoms have not been observed in recent outbreaks. Table 2 lists signs and symptoms for both mild and severe cases of West Nile virus.

A high index of clinical suspicion is used to diagnosis West Nile virus along with specific laboratory testing. Clinicians should question patients regarding recent travel, especially to tropical and subtropical areas or areas where West Nile virus is suspected because of the presence of mosquitoes. Clinicians should be suspicious for West Nile virus in areas where birds have been found dead and/or horse are sick and dying. The CDC (2002f) makes special note that West Nile virus should be considered in all persons with unexplained encephalitis and meningitis regardless of the time of year, the age of the patient, or their location residence.

Diagnosis

Pathologic changes can occur in serum blood counts, but the most definite diagnosis of West Nile virus is made from serum and cerebral spinal fluid using IgM antibody testing. Serum blood testing can show normal to slightly elevated levels of leukocytes, with lymphocytopenia and anemia occurring. In patients with encephalitis, hyponatremia is often present (Asnis, 2002; CDC, 2002f; Petersen & Marfin, 2002).

Examination of cerebral spinal fluid (CSF) will show pleocytosis (increased lymphocytes) with leukocyte counts ranging from 0 to 1782 cells /mm3 (CDC, 2002f; Petersen & Marfin, 2002). Elevated protein levels with normal glucose levels are found in the CSF (Asnis, 2002; CDC, 2002f).

Serological testing of CSF and serum blood samples using IgM and IgG enzyme-linked immunosorbent assay (ELISA) is the front-line method of diagnosing West Nile virus. There are no commercial kits available for human serology testing of West Nile
virus, but testing can be obtained through local and state health departments. The CDC guidelines for human and animal testing state that the ELISA test for West Nile virus is a screening test only because of cross-reactions between flaviviruses such as dengue, yellow fever, and West Nile. Therefore, if a positive ELISA test is obtained, it should be followed by a plaque reduction neutralization test for definite diagnosis of West Nile virus (Petersen & Marfin, 2002). Table 3 contains information that is required for specimens that are submitted for serological testing for West Nile virus.

The CDC (2002f) reported that computed tomographic (CT) scans of the brain did not show evidence of West Nile virus, but during magnetic resonance imaging (MRI) changes could be seen in the leptomeninges and periventricular areas. MRIs can detect changes in a patient’s brain, if they are done on a serial basis over a week or more. Case studies showed that when MRIs were done on days 5, 8, 11, 18, and 32 there were dramatic changes in the brain (Peck, 2002). If you have a disease that is puzzling, then you may need to do several MRIs over a period of a few days until you are able to obtain an answer, because damage may not be detectable for 7 to 10 days (Peck, 2002).

Health care providers should consider West Nile virus in their differential diagnosis when a patient presents with classic signs and symptoms of encephalitis, meningitis, or Guillain-Barre’ Syndrome. West Nile virus should be suspected in viral encephalitis when characterized by a fever greater than 100°F, altered mental status, cranial nerve palsies, paralysis, or convulsions, and abnormal CSF profile with viral etiology (Utah Department of Health, 2001). A case of aseptic meningitis that does not have a confirmed cause should also be suspect for West Nile virus infection. If Guillain-Barre’ syndrome is atypical with features of fever, altered mental status, and/or a
pleocytosis the patient should be tested for West Nile virus (Utah State Department of Health, 2001).

Treatment

An infection from West Nile virus can range from an unnoticeable illness to one severe enough to cause major complications and even death. Many people contract West Nile virus and show only mild symptoms of nausea, vomiting, malaise, myalgia, and headache; symptoms similar to the flu-these people do not even generally seek medical treatment. Other people may seek out medical treatment for mild symptoms and be diagnosed with West Nile virus. The treatment for a mild infection is supportive care (Petersen & Marlin, 2002).

However, West Nile virus can develop into a severe infection that can cause meningitis or encephalitis and require hospitalization. Patients who are hospitalized receive supportive treatment with intravenous fluids, airway management, ventilation support, and prevention of secondary infections like pneumonia or urinary tract infection (Campbell & Dreher, 2002; CDC, 2002f; Lok, 2002; Petersen & Marlin, 2002). In the year 2000, nineteen patients were hospitalized in New York and New Jersey with severe West Nile virus infections. Weiss et al. (2001) reported that nine patients had encephalitis, eight had meningitis, and two had meningoencephalitis. The mean age of the nine patients with encephalitis was 71 years (SD=11.7). The eight patients with meningitis had a mean age of 51 (SD 14.5). The mean time period for symptom onset to hospitalization for all patients was 7.7 day. Ten patients recovered from their West Nile virus infection, but not to their functional level before the illness. They required physical,
speech, or occupational therapy and/or assistance in ambulation. Seven patients fully recovered and two died.

Some providers use steroids, anti-seizure medications, anti-herpes medications, and osmotic agents in the management of West Nile virus encephalitis (Campbell & Dreher, 2002; CDC, 2002f; Petersen & Marfin, 2002). However, no controlled studies have been conducted to examine their effectiveness of the use of these medications. Dr. James Rahal, a researcher at Cornell University, stated in an interview conducted by DeNoon (2002) that he and his colleagues have started a clinical trial to test the drug alpha interferon on people who have serious West Nile virus. They plan on enrolling 40 patients from all over the United States. Acceptable study participants will receive two weeks of treatment, half of them will receive placebo and the other half alpha interferon. The researchers speculate that by treating the patients early in the course of the West Nile virus infection that they will prevent brain damage from occurring (DeNoon, 2002). Only by doing this type of study will researchers get the answers to the effectiveness of alpha interferon for the treatment of West Nile virus encephalitis.

The National Institutes of Health (NIH) announced in August 2000, that they would award a $3 million contract to a firm to research and develop a vaccine for the prevention of West Nile virus. OraVax, a division of Acambis, was awarded the contract and began work on the vaccine. Acambis reported that a vaccine has been developed using proprietary ChimeriVax technology. They derived a live vaccine by genetically changing the envelope genes of a yellow fever vaccine with corresponding genes from West Nile virus. ChimeriVax technology will give the vaccine the ability to induce protection within a short interval after a single dose, long-lasting immunity without
additional boosters, and a high safety profile (Acambis, 2002). In September 2002, Acambis reported that they had positive results from pre-clinical trails conducted on healthy adults using West Nile vaccine. The vaccine was reported to be safe and induce high levels of neutralizing antibodies against West Nile virus. The West Nile vaccine also demonstrated the ability to protect against wild-type West Nile virus (viruses not controlled in the laboratory). Production of the vaccine has begun and clinical trials are expected to begin in the year 2003 (Acambis, 2002).

Conclusion

St. Louis encephalitis, La Crosse encephalitis, eastern equine encephalitis, dengue fever, and now West Nile virus are serious diseases borne by mosquitoes in the United States. West Nile virus encephalitis is a nationally notifiable arboviral encephalitis. Information on reporting, specimen collection, and clinical and laboratory case definitions for West Nile virus are available from the CDC at www.cdc.gov/ncidod/dvbid/westnile/resources/wnv-guideline-apr-2001.pdf. Physicians, Nurse Practitioners, other medical personnel, and veterinaries should report all cases of viral encephalitis, aseptic meningitis, and West Nile virus to ArobNET, a CDC multi-state surveillance program that identifies animal and human infections.

Public awareness and education of West Nile virus, mosquitoes, and its dangers can help to prevent epidemics from occurring. A strong relationship between health departments, community medical practitioners, veterinarians, and entomologists must be promoted to meet the challenges of West Nile virus across the United States.

Health experts and scientists at the National Institute of Allergy and Infectious Diseases (NIAID) and public health officials have intensified research of West Nile virus.
NIAID supports research that will enable practitioners to better understand the host, pathogenesis, and environmental factors that influence West Nile virus. This research will help the United States to develop strategies to prevent, treat, and control West Nile virus. There is also research being conducted in Mexico by the International Centers for Infectious Disease Research (ICIDR) that studies the migration of birds from their presumed point of entrance in the Western Hemisphere to points in Central and South America. West Nile virus may emergence in this new area where there is an abundant mosquito population and conditions for a potentially severe epidemic exist (NIAID, 2002).

Additional research is being funded by the National Institutes of Health to establish a system to screen chemical compounds for possible antiviral activity against West Nile virus. An antiviral drug will be tested in animals before human trials are begun. Twelve out of three hundred drugs screened were identified as being potential candidates for testing in animal trials. Research is also under way by biotechnology companies who are attempting to develop diagnostic assay tests that can rapidly detect West Nile virus in humans, animals, and vector mosquitoes. NIAID has also established two Emerging Viral Diseases Research Centers in New York and Texas to focus research on West Nile virus (NIAID, 2002).

Summary

West Nile virus, an arbovirus, first appeared in New York City in 1999. In three years the virus has made a transcontinental movement across the United States to the west coast leaving sick and dead humans, animals, and birds behind. It is biologically transmitted between susceptible vertebrate hosts and blood-feeding arthropod,
mosquitoes (ASTDHPPE, 2003). As temperatures warm in the spring and more mosquitoes hatch to adulthood, there will be an increase in the cases of West Nile virus reported to ArboNET, the CDCs internet surveillance network, by public and state health departments.

Prevention of West Nile virus infection concerns both the public and private sectors. Public and municipal authorities need to take action to reduce the number of vector mosquitoes as weather warms, and private persons should take responsibility in prevention of mosquito bites. Everyone should be responsible in reducing mosquito-breeding sites by reducing areas of standing water and moist soil.

West Nile virus clinically manifests itself with symptoms ranging from unnoticeable to a severity that requires hospitalization. Incubation period of West Nile virus is 3 to 14 days, and then there is a sudden onset of symptoms. Many people get flu like symptoms of malaise, anorexia, nausea, vomiting, and headache and the virus goes undiagnosed because they do not seek medical treatment. Very young children, adults over 50 years old, and persons with immune compromise run the highest risk of a severe West Nile virus infection that can turn into meningitis or encephalitis. A high level of clinical suspicion is used to diagnosis West Nile virus, along with specific laboratory testing. If West Nile virus is active, mosquitoes are present, and sick/dead birds and horses are found the practitioner should suspect West Nile virus in their patients who present with suspicious symptoms.

Diagnosis of West Nile virus is with CSF using IgM and IgG ELISA testing, and if positive, followed by neutralization testing for a definitive diagnosis. MRI scans of the brain, done on a serial basis will show changes over a week or more in the leptomeninges
and periventricular areas of the brain. Patients with suspected meningitis, encephalitis, or symptoms similar to Guillain-Barre' syndrome should be tested for West Nile virus.

Treatment for West Nile virus is supportive for mild cases, but severe cases may require hospitalization with IV therapy, airway management, ventilation, and prevention of secondary infections of pneumonia or urinary tract infection. Research is underway to approve a vaccine for West Nile virus; production of the vaccine is underway and clinical trials are expected to start in 2003. Public awareness and education of West Nile virus can help prevent epidemics from occurring. A strong relationship between the public and private sectors must be fostered to promote the safety of all individuals, animals, and birds across the United States and the world.
References


University of Pittsburg School of Medicine, Department of Pathology, 1996. Maculopapular rash. Retrieved February 3, 2003 from http://path.upmc.edu/cases/case70/images/gross4.jpg


<table>
<thead>
<tr>
<th>TABLE 1: Recommend patient education for protection from mosquito bites.</th>
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<tr>
<td>• Empty anything that holds standing water: old tires, buckets, plastic covers, and toys.</td>
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<tr>
<td>• Change water in birdbaths, fountains, wading pools, and animal troughs weekly.</td>
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<td>• Recycle unused containers: bottles, cans, and buckets that could collect water.</td>
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<td>• Clean roof gutters and drains in spring and fall.</td>
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<td>• Fix leaky faucets and sprinklers to prevent standing water.</td>
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<td>• Repair or replace window and door screens to prevent bugs from entering buildings.</td>
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<td>• Stay indoors at dawn and dusk when mosquitoes are most active.</td>
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<td>• Wear long sleeve shirts, long pants, and a hat when going outside, especially in wetlands and wooded areas.</td>
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<tr>
<td>• Use mosquito repellent on exposed skins. For adults it should contain 35% DEET; children 2 to 12 years old should use 10% DEET. <strong>Pregnant women should not use insect repellent.</strong></td>
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Campbell & Dreher, 2002; CDC, 2002c; Lok, 2002; Washington State Department of Health, 2001a & b.
### TABLE 2: Signs and Symptoms of West Nile virus infection

<table>
<thead>
<tr>
<th>Mild Infection:</th>
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</thead>
<tbody>
<tr>
<td>• Malaise</td>
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<tr>
<td>• Anorexia</td>
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<tr>
<td>• Nausea</td>
<td></td>
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<tr>
<td>• Vomiting</td>
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<tr>
<td>• Eye Pain/Conjunctivitis</td>
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<tr>
<td>• Headache</td>
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<tr>
<td>• Myalgia</td>
<td></td>
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<tr>
<td>• Rash</td>
<td></td>
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<tr>
<td>• Lymphadenopathy</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe Infection:</th>
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<tbody>
<tr>
<td>• High fever</td>
<td></td>
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<tr>
<td>• Muscle weakness and flaccid paralysis</td>
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<tr>
<td>• Gastrointestinal symptoms</td>
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<tr>
<td>• Headache</td>
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<tr>
<td>• Neck stiffness</td>
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<tr>
<td>• Change in mental status including stupor, disorientation, and coma</td>
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<tr>
<td>• Tremors</td>
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<tr>
<td>• Convulsions</td>
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<tr>
<td>• Rash: maculopapular or morbilliform rash on neck, trunk, arms, and/or legs</td>
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<tr>
<td>• Neurological presentations include</td>
<td></td>
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<tr>
<td>➢ Ataxia and Extrapyramidal signs</td>
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<tr>
<td>➢ Cranial nerve abnormalities</td>
<td></td>
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<tr>
<td>➢ Myelitis</td>
<td></td>
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<tr>
<td>➢ Optic Neuritis</td>
<td></td>
</tr>
<tr>
<td>➢ Polyradiculitis</td>
<td></td>
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<tr>
<td>➢ Seizures</td>
<td></td>
</tr>
</tbody>
</table>

Asnis, 2002; Campbell & Dreher, 2002; CDC, 2002f; Petersen & Marfin, 2002.
TABLE 3: Data to Accompany Specimens submitted for serology testing for West Nile virus.

- Symptom onset date when known
- Date of sample collection
- Unusual immunological status of patient (e.g., immunosuppression)
- Current Address and travel history in Flavivirus-endemic areas
- History of prior vaccination against Flavivirus disease (e.g., yellow fever, Japanese encephalitis, or Central European encephalitis)
- Brief clinical summary including suspected diagnosis (e.g., encephalitis, aseptic meningitis)

Map 1: States reporting confirmed West Nile virus infection in birds, mosquitoes, animals, or humans, 1999-2001.

West Nile Virus in the United States, 1999-2001

Note: The data presented reflect public reports by state and local health departments.

CDC, 2002d.
Map 2: States reporting laboratory-positive West Nile virus infection in birds, mosquitos, animals, or humans between January 1 - December 11, 2002.

West Nile Virus in the United States, 2002

Verified avian, animal, and mosquito infections during 2002, as of December 11, 2002

Indicates human case(s) verified as of December 11, 2002

CDC, 2002d.

West Nile Virus in the United States, 1999 - 2002

CDC, 2002d.
Figure 1: Transmission cycle of West Nile Virus

MAINTENANCE VECTOR MOSQUITOES

BIRDS

MAINTENANCE VECTOR MOSQUITOES

HUMANS, HORSES

BRIDGE VECTOR MOSQUITOES

BIRDS

Petersen & Marfin, 2002.
FIGURE 2: Culex Mosquito laying her eggs.

CDC, 2002b.
FIGURE 3: MACULOPAPULAR RASH

University of Pittsburg School of Medicine, Department of Pathology, 1996.