# West Nile Virus Encephalitis in the United States

*Richard T. Johnson, MD, and David N. Irani, MD*

**Address**
Department of Neurology, The Johns Hopkins Hospital, 600 North Wolfe Street, Pathology 627, Baltimore, MD 21287, USA.
E-mail: rtj@jhmi.edu

**Current Neurology and Neuroscience Reports** 2002, **2**:496–500
Current Science Inc. ISSN 1528–4042


West Nile virus appeared in New York City in 1999 and has subsequently spread over the eastern United States. The mode of transport across the Atlantic Ocean is unknown. During the past decade, encephalitis has been a more prominent feature of West Nile virus infection in Europe, the Middle East, and the United States, suggesting the emergence of more neurovirulent strains. The rapid spread of the virus and more serious disease caused by the virus have spurred vaccine development.

## Introduction

West Nile virus is a flavivirus. The prototype of this family of arthropod-borne viruses (arboviruses) is yellow fever virus, hence the name flavi (Latin for yellow). West Nile virus has been regarded as the African and Middle Eastern member of an antigenically related complex of flaviviruses, including Japanese encephalitis virus (Asia), St. Louis encephalitis virus (North America), and Murray Valley encephalitis virus (Australia).

During the summer of 1999, West Nile virus abruptly appeared in birds and humans in the United States. New York City was the focus of patients with encephalitis, but infections of mosquitoes and birds were also found in neighboring New Jersey and Connecticut. To the surprise of some observers, the virus survived the winter. In the summer of 2000, infections spread along the North Atlantic seaboard to 12 states. By the end of the mosquito season in 2001 the virus had been found in 27 states, extending south to Florida, west across the Mississippi River to Iowa, Missouri, and Arkansas, and north into Canada.

The emergence of West Nile virus in the Western hemisphere provides a dramatic example of transport of a virus into a new ecosystem. The history of clinical disease due to West Nile virus first in Africa, then the Middle East and Asia, and recently in Europe suggests not only a change in the epidemiology of the virus, but also the evolution of more neurovirulent strains of the virus. The remarkable range of susceptible mosquito vectors and the wide range of warm-blooded avian and mammalian hosts make suppression of the zoonosis problematic.

## African Origin

West Nile virus was originally isolated in 1937 from the blood of a febrile woman in the West Nile province of Uganda [1]. Investigators from the Rockefeller Foundation and the US Navy Research Unit in Cairo, Egypt subsequently showed serologic evidence of widespread infection of children in Egypt and Sudan and established that the virus in northern Africa cycled between a variety of species of birds, including crows, pigeons, sparrows, and herons, and several species of *Culex* mosquitoes [2]. Virus was recovered from the blood of children with minor febrile illnesses, but a clear association with disease was lacking [3].

In the 1950s, West Nile virus was linked definitively to disease during epidemics of dengue-like illnesses in Israel. The acute febrile illness was often accompanied by lymphadenopathy and rash. Virus was recovered from blood during the acute phase, and development of antibody was demonstrated during convalescence. Occasional patients were noted to have nuchal rigidity, and a spinal fluid pleocytosis in these patients documented meningitis as a complication of West Nile fever [4]. Frank encephalitis, however, was not recorded in Israel until the 1960s [5].

In an ironic twist in history, the first documented cases of severe encephalitis due to West Nile virus were not in Africa or the Middle East, but in New York City in 1952. They resulted from experimental, not natural, infection. At the Sloan-Kettering Institute, Southam and Moore [6] inoculated 95 cancer patients with the Egypt 101 strain of West Nile virus based on their hypothesis that this agent might have selective cytolytic effects on rapidly replicating neoplastic cells. Nine of these patients developed signs of encephalitis, virus was recovered from spinal fluid of three, and an autopsy showed that encephalitis may have contributed to one patient's death.

## Spread to Asia and Europe

West Nile virus was related to occasional febrile illnesses in India during the 1960s and 1970s. In 1984, three fatal cases of childhood encephalitis were reported with virus recovery from brain [7]. During the same decades, sporadic

cases and small outbreaks of West Nile fever with occasional cases of encephalitis were reported in and around the Mediterranean basin and in Eastern Europe [8]. An outbreak in Algeria in 1994 involved 50 illnesses, including 20 cases of encephalitis with eight fatalities, primarily in children [9]. This heralded a major change in the epidemiology and neurovirulence of the virus.

The first big epidemic occurred near Bucharest, Romania in the summer and early autumn of 1996. Over 800 patients were admitted to hospitals with apparent nervous system infections; of those who had appropriate serologic studies, 80% were confirmed as having West Nile virus infections. The case-fatality rate was almost 10% [10]. Monitoring from 1997 through 2000 uncovered only 39 cases of West Nile fever in the greater Danube valley of southern Romania; the virus has persisted, but for unexplained reasons epidemic disease has not recurred [11]. In 1999, a similar major epidemic occurred in Volgograd, Russia, with over 800 admissions to hospitals for nervous system infections; 84 cases were classified as severe encephalitis and 40 patients died [12].

In the year 2000, epidemic West Nile fever recurred in Israel. Over 300 patients were hospitalized, over 70% had central nervous system involvement, and 35 died [13]. In contrast with previous outbreaks in Israel, this one was associated with more severe disease, a higher rate of nervous system involvement, and higher morbidity in the elderly [14].

## Arrival in the United States

During the last week of August, 1999, the New York City Department of Health received several inquiries about encephalitis and paralytic disease in the borough of Queens. On August 29, an investigation of hospital admissions in north Queens identified eight cases of encephalitis originating from a 16-square-mile area. The patients ranged from 58 to 87 years of age; no common exposure was uncovered, and there were no reported illnesses in family members. All patients, however, had spent evening hours in outdoor activities, such as gardening or smoking on the porch. These factors suggested a mosquito-borne disease, and mosquito larvae of *Culex* species were found in old tires, rain barrels, and a partially excavated pool in the neighborhood. On September 2, the State Health Department reported serologic results on patients suggesting infection with St. Louis encephalitis virus. Within the week, education and mosquito control programs were begun [15••,16•].

Also in August, a seemingly unrelated disease outbreak was noted in the Bronx involving deaths of crows and a number of exotic birds at the Bronx zoo. Because St. Louis encephalitis outbreaks are not accompanied by deaths of the avian hosts, no connection was obvious, even though the dead birds had encephalitis on pathologic examination [17]. A virus was recovered from birds sent to the National Veterinary Services Laboratory, and the virus was subsequently identified as West Nile virus [18]. This led to a reexamination of the human encephalitis outbreak. Virus isolates from patients and more specific serologic studies both showed that the human encephalitis outbreak was indeed caused by West Nile virus and not the serologically cross-reactive St. Louis encephalitis virus. Archived serum specimens from geographically scattered cases of St Louis encephalitis from the prior 3 years were re-examined and these studies confirmed that all were St Louis encephalitis virus infections [19•]. West Nile virus had not gone undetected in previous years, but had indeed arrived in 1999.

During the 8 weeks of the New York City outbreak (August 2 to September 24), 59 patients were hospitalized with West Nile virus infections and seven died [16•].

In October, a household-based seroepidemiologic survey indicated that between 2% and 6% of people in the outbreak epicenter had been infected. Recent febrile illnesses were reported by seropositive persons 20% more frequently than by seronegative persons, suggesting that several thousand persons may have had symptomatic infection. Based on these data, less than 1% of those infected had developed encephalitis [20].

Virus was recovered from a variety of species of mosquitoes and birds, but the mosquito *Culex pipiens* appeared to be the principal vector, and crows, blue jays, and many other birds appeared to be the primary vertebrate and amplifying hosts. A number of equine illnesses and deaths were reported but they were late in the epidemic, suggesting that horses, like humans, are dead-end hosts [21]. Bats, raccoons, cats, chipmunks, and other mammals have been found with antibodies, but are thought to represent incidental hosts.

## Overwintering and Subsequent Spread

Some observers assumed that the first frost would end the North American incursion of West Nile virus, unless it could spread sufficiently far to the south. But surprisingly, searches of the New York sewers, subways, and old historic sites turned up inactive mosquitoes, and in midwinter West Nile virus was recovered from mosquitoes found on the walls of old Fort Totten in Queens [22]. An alternate mode of overwintering was suggested when the virus was recovered in February from a dead red-tailed hawk in Westchester County, at a time and place where no mosquito should be feeding. This finding raised the unorthodox idea of prey-to-predator transmission [23]. Whatever the mechanism, West Nile virus successfully overwintered in the inhospitable New York climate.

Staten Island was the center of the outbreak in 2000. By autumn of 2000, 21 patients in New York, New Jersey, and Connecticut had been reported with West Nile virus encephalitis, but only two died. Although the number of patients was diminished, the area of virus activity spread over a 12-state area, from New Hampshire to North Carolina [24].

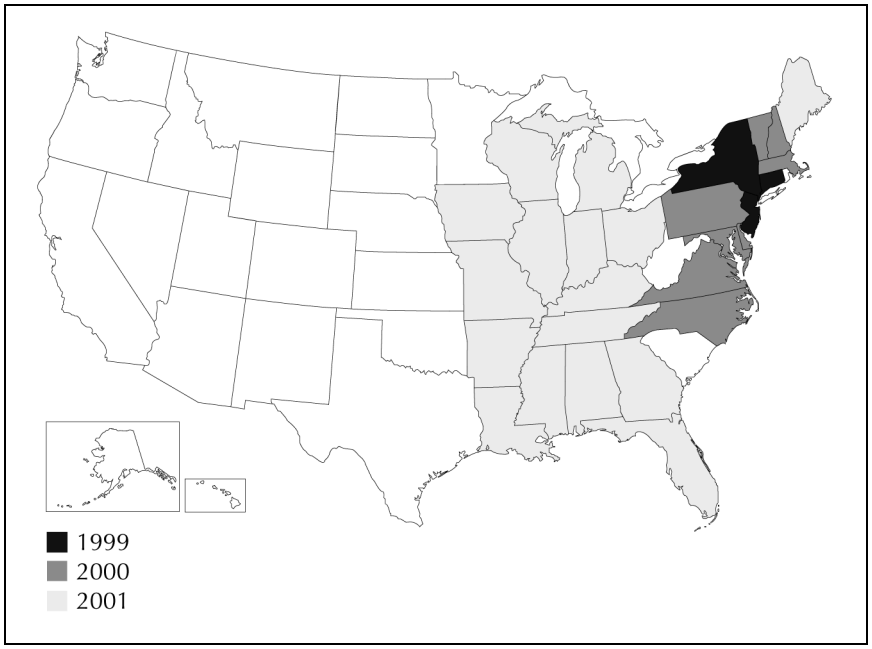


**Figure 1.** Spread of West Nile virus in the United States from 1999 to 2001.

The first epidemiologic observations in 2001 were ominous. The first case was in Georgia, far to the south of prior spread, and the woman died. Human surveillance identified 48 cases of encephalitis or meningitis, with the largest numbers in New York and Florida. By the end of the season in 2001, the virus had been recovered in 27 states and the District of Columbia (Fig. 1). It had spread north to Canada, south to Florida and the Cayman Islands, and west across the Mississippi to Arkansas, Iowa, and Missouri. Although crows remained the most important sentinel bird, with their deaths heralding the virus spread, over 80 species of birds and 22 species of mosquitoes have been shown to be infected. In 2002, West Nile virus has continued to spread, with all 41 states east of the Continental Divide and four Canadian provinces reporting the virus in animals or humans by September 1. The greatest concentration of human disease has been in Louisiana, Mississippi, Texas, and Illinois, with over 400 cases of illness and 20 deaths from encephalitis across the country. West Nile virus seems solidly established in North America, and its spread to the West Coast and South America over the next few years seems inevitable [25].

## How Did It Cross the Atlantic Ocean?

Arboviruses are geographically restricted by the regional distribution of vectors and natural hosts [26]. For example, Colorado tick fever virus is transmitted only by *Dermacenter andersoni*, the Rocky Mountain wood tick, so infections are restricted to the Rocky Mountain region. On occasion, arboviruses are transported into a new area. In 1957, a tick-bone virus appeared abruptly in the Kyasanur Forest of Mysore State in India. This virus proved to be related to Russian Spring-Summer encephalitis virus of Siberia. This remarkable transposition was accredited to ticks riding on migratory birds that crossed the Himalayas.

Transatlantic transport of an African arbovirus is believed to have happened in the 17th century, when yellow fever virus and possibly it vector, *Aedes aegypti*, came to the Americas from Africa [27]. It has been postulated that the virus and mosquito came on sailing ships of the slave trade, with larvae breeding in the tubs of water and virus being cycled between mosquitoes and sailors and slaves. The speed and frequency of modern transportation make such a complex scenario unnecessary. The nucleic acid sequence similarity of all North American isolates suggests a common origin [28], so it is assumed that West Nile virus in the Western Hemisphere was transported in 1999 by a single person, bird, or mosquito.

Modern airline travel allows any tropical virus to be in anyone's hometown within the preclinical incubation period. Nevertheless, in contrast with yellow fever virus, West Nile virus does not produce a prolonged or high titered viremia in humans, so humans are an unlikely source of subsequent arthropod infection. Intentional human transport as an act of terrorism has been posited, but West Nile virus, with its complex ecology, would not seem a weapon of choice [15••].

A bird could have transported the virus. Few migration pathways cross the Atlantic, but European birds are occasionally blown across in storms [29]. Pigeons, known to be susceptible hosts, do ride across on freighters, where they are fed by the crews. A smuggled bird is more likely. All birds in the Bronx zoo had undergone long quarantines, but there is a sizable traffic in exotic, undeclared birds.

The likeliest courier of West Nile virus is a mosquito. Jet planes arriving from overseas often have viable mosquitoes in the overhead bins. The sequence of the American isolates is most closely related to that of an Israeli isolate

from a dead goose in 1998 (99.8% identity match) [30•]. An infected female mosquito, after a brief flight on an international jet, may have found a crow at Kennedy airport in New York City and started the whole scenario.

## Clinical Signs and Neurovirulence

West Nile virus disease is more severe and life threatening in the elderly, a phenomenon long recognized with the related St. Louis encephalitis virus. In New York, 88% of those hospitalized were at least 50 years of age [16•]. The majority of infections are asymptomatic or characterized by a few days of fever, headache, myalgia, and arthralgias. A maculopapular or roseolar rash may be seen.

The neurologic complications seen in the United States have been characterized by a predilection to involve the brainstem and spinal cord. Flaccid paralysis resembling poliomyelitis or Guillain-Barré syndrome has been described, as well as hyporeflexia and urinary retention [16•,31]. Electromyography has shown decreased motor amplitudes, suggesting motor axonopathy [32]. Neuropathologic studies showed intense inflammation, microglial nodules, neuronal necrosis, and neuronophagia, particularly in the brainstem, with associated inflammation within cranial nerves [33].

The recent experiences in the Middle East, Romania, Russia, and the United States suggest the evolution of new, more virulent West Nile strains associated with higher rates of serious neurologic infection and human mortality, as well as higher mortality in birds and horses [25,34]. The West Nile fever originally recognized in North and East Africa was a dengue-like disease primarily of children. Possibly, widespread childhood infection gave rise to immunity in adulthood, where infections are fraught with neurologic complications. Yet in a major South African epidemic, the lack of neurologic complications was notable [35]. In Central Africa, a yellow fever-like illness with fulminant fatal hepatitis has been described, further supporting the idea that different strains with varied tissue tropisms are circulating in different regions of the world [36].

## Diagnosis and Treatment

Diagnosis can be made by detecting West Nile-specific immunoglobulin M (IgM) in serum or cerebrospinal fluid using an IgM-capture enzyme-linked immunosorbent assay. Alternatively, a fourfold or greater increase in IgG can be shown between the acute and convalescent phase of illness. Real-time polymerase chain reaction testing for West Nile sequences have also been used for diagnosis [16•,19•,37].

Treatment involves supportive care. No drug has proved effective against any flavivirus infection, although ribavirin does inhibit West Nile virus replication in cell cultures [38]. Steroids may aid in the control of brain edema, but a placebo-controlled study of high-dose dexamethasone in Japanese encephalitis showed no beneficial or adverse effect on clinical course or mortality [39].

## Prevention

Vector control by clearing stagnant urban water, spraying, screening, repellent use, and protective clothing has some benefit at the time of outbreaks. Because West Nile virus has a wide variety of competent vectors, disease control similar to the clearance of yellow fever in Cuba by *Aedes aegypti* eradication would not be fully effective. Vaccine development is the reasonable long-term solution.

Effective vaccines have been developed and widely used against other flaviviruses, including yellow fever, Japanese encephalitis virus, and tick-borne encephalitis virus. The current risk-benefit ratio may not yet justify the development of a vaccine against West Nile virus. However, with the increasing geographic spread and the potential of huge outbreaks with many fatalities as in Romania and Russia, development of vaccines seems prudent.

Inactivated and subunit vaccines are easy to develop, have a reasonable safety record, and can be used in humans and animals. The main disadvantage of these vaccines is the need for multiple doses to elicit and sustain an effective immune response. Their use to control an impending outbreak is limited. DNA vaccines have the theoretical advantage of simple development, and a West Nile DNA vaccine has already been tested in horses and mice [40]. Their effectiveness in species other than mice have been limited, and the regulatory concerns, mode of administration, possible need for adjuvants, and other problems will slow development of a human DNA vaccine. Live vaccines similar to yellow fever vaccine can provide rapid, long-term protection after a single injection [41••]. Chimeric live virus vaccines incorporating the envelope protein genes for West Nile virus into yellow fever 17D vaccine virus [41••] and into dengue virus [42] are being tested.

## Conclusions

As West Nile virus spreads across the Western hemisphere, both its distribution and virulence need to be carefully monitored. The morbidity and mortality caused by this infection are still modest in the United States, but the potential to be a major public health threat is real.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Smithburn KC, Huges TP, Burke AW, Paul JH: **A neurotropic virus isolated from the blood of a native of Uganda.** *Am J Trop Med Hyg* 1940, **20**:471–492.

2. Work TH, Hurlbut AS, Taylor RM: **Indigenous wild birds of the Nile Delta as potential West Nile virus circulating reservoirs.** *Am J Trop Med Hyg* 1955, **4**:872–887.
3. Melnick JL, Paul JR, Riordan JT, *et al*: **Isolation from human sera in Egypt of a virus apparently identical to West Nile virus.** *Proc Soc Exp Biol Med* 1951, **77**:661–665.
4. Marberg K, Goldblum N, Sterk VV, Jasinska-Klingberg W, Klingberg MA: **The natural history of West Nile fever: clinical observations during an epidemic in Israel.** *Am J Hyg* 1956, **64**:259–269.
5. Pruzanski W, Altman R: **Encephalitis due to West Nile fever virus.** *World Neurol* 1962, **3**:524–527.
6. Southam CM, Moore AE: **Induced virus infections in man by the Egypt isolates of West Nile virus.** *Am J Trop Med Hyg* 1954, **3**:19–50.
7. George S, Gourie-Devi M, Rao JA, Prasad SR, Pavri KM: **Isolation of West Nile virus from the brains of children who had died of encephalitis.** *Bull World Health Org* 1984, **62**:879–882.
8. Hubalek Z, Halouzka J: **West Nile fever—a reemerging mosquito-borne viral disease in Europe.** *Emerg Infect Dis* 1999, **5**:643–650.
9. Le Guenno B, Bougermouth A, Azzam T, Bouakaz R: **West Nile: a deadly virus?** *Lancet* 1996, **348**:1315.
10. Tsai TF, Popovici F, Cernescu C, Campbell GL, Nedelcu NI: **West Nile encephalitis epidemic in southeastern Romania.** *Lancet* 1998, **352**:767–771.
11. Ceianu CS, Ungureanu A, Nicolescu G, *et al*: **West Nile virus surveillance in Romania.** *Viral Immunol* 2001, **14**:251–262.
12. Platonov AE, Shipulkin GA, Shipulina OY, *et al*: **Outbreak of West Nile virus infection, Volgograd region, Russia, 1999.** *Emerg Infect Dis* 2001, **7**:128–132.
13. Weinberger M, Pitlik SD, Gandacu D, *et al*: **West Nile fever outbreak, Israel, 2000: epidemiological aspects.** *Emerg Infect Dis* 2001, **7**:686–691.
14. Chowers MY, Lang R, Nassar F, *et al*: **Clinical characteristics of West Nile fever outbreaks, Israel, 2000.** *Emerg Infect Dis* 2001, **7**:675–678.
15. •• Fine A, Layton M: **Lessons from the West Nile viral encephalitis outbreak in New York City, 1999: implications for bioterrorism preparedness.** *Clin Infect Dis* 2001, **32**:277–282.

This is a personal, first-hand account of the discovery and response to the 1999 New York City outbreak.

16. • Nash D, Mostashari F, Fine A, *et al*: **The outbreak of West Nile virus infection in the New York City area in 1999.** *N Engl J Med* 2001, **344**:1807–1814.

A more detailed analysis of the 1999 New York City outbreak, including diagnostic criteria, clinical features, and pathologic findings.

17. Steele KE, Linn MJ, Schoepp RJ, *et al*: **Pathology of fatal West Nile virus infections in native and exotic birds during the 1999 outbreak in New York City.** *Vet Pathol* 2000, **37**:208–228.
18. Centers for Disease Control and Prevention: **Outbreak of West Nile-like viral encephalitis—New York, 1999.** *MMWR* 1999, **48**:845–849.
19. • Gubler DJ, Campbell GL, Nasci R, *et al*: **West Nile virus in the United States: guidelines for detection, prevention, and control.** *Viral Immunol* 2000, **13**:469–475.

The surveillance, laboratory diagnosis, control, and research priorities are reviewed.

20. Mostashari F, Bunning ML, Kitsutani PT, *et al*: **Epidemic West Nile encephalitis, New York, 1999: results of a household-based seroepidemiological survey.** *Lancet* 2001, **358**:261–264.
21. Bunning ML, Bowen RA, Cropp B, *et al*: **Experimental infection of horses with West Nile virus.** *Emerg Infect Dis* 2002, **8**:380–386.
22. Nasci RS, Savage HM, White DJ, *et al*: **West Nile virus in overwintering Culex mosquitoes, New York City, 2000.** *Emerg Infect Dis* 2001, **7**:742–744.
23. Garmendia AE, Van Kruiningen HJ, French RA, *et al*: **Recovery and identification of West Nile virus from a hawk in winter.** *J Clin Microbiol* 2000, **38**:3110–3111.
24. Centers for Disease Control and Prevention: **Update: West Nile virus activity—Eastern United States, 2000.** *MMWR* 2000, **49**:1044–1047.
25. Johnson RT: **West Nile virus in the United States and abroad.** *Curr Top Infect Dis* 2002, **22**:52–60.
26. Johnson RT: *Viral Infections of the Nervous System*, edn 2. Philadelphia: Lippincott-Raven; 1998.
27. Taylor RM: **Epidemiology.** In *Yellow Fever.* Edited by Strode G. New York: McGraw-Hill; 1951:427–538.
28. Ebel GD, Dupuis AP, Ngo K, *et al*: **Partial genetic characterization of West Nile virus strains, New York State, 2000.** *Emerg Infect Dis* 2001, **7**:650–653.
29. Rappole JH, Derrickson SR, Hubalek Z: **Migratory birds and spread of West Nile virus in the western hemisphere.** *Emerg Infect Dis* 2000, **6**:319–328.
30. • Lanciotti RS, Roehrig JT, Deubel V, *et al*: **Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States.** *Science* 1999, **286**:2333–2337.

The sequence analysis of West Nile virus isolates in birds, mosquitoes, and humans in the United States indicates a common origin. The North American strain is most closely related to an Israel isolate found in 1998.

31. Ahmed S, Libman R, Wesson K, Ahmed F, Einberg K: **Guillain-Barre syndrome: an unusual presentation of West Nile virus infection.** *Neurology* 2000, **55**:144–146.
32. Asnis DS, Conetta R, Teixeira AA, Waldman G, Sampson BA: **The West Nile virus outbreak of 1999 in New York: the Flushing Hospital experience.** *Clin Infect Dis* 2000, **30**:413–418.
33. Sampson BA, Ambrosi C, Charlot A, *et al*: **The pathology of human West Nile virus infection.** *Hum Pathol* 2000, **31**:527–531.
34. Meek J: **West Nile virus in the United States.** *Curr Opin Pediatr* 2002, **14**:72–77.
35. McIntosh BM, McGillivray GM, Dickinson DB: **Illness caused by Sindbis and West Nile viruses in South Africa.** *South Afr Med J* 1964, **38**:291–294.
36. Georges AJ, Lesbordes JL, Georges-Courbot MC, Meunier DM, Gonzalez JP: **Fatal hepatitis from West Nile virus.** *Ann Inst Pasteur Virol* 1987, **138**:237–244.
37. Briese T, Glass WG, Lipkin WI: **Detection of West Nile virus sequences in cerebrospinal fluid.** *Lancet* 2000, **355**:1614–1615.
38. Jordan I, Brises T, Fischer N, Lau JY, Lipkin WI. **Ribavirin inhibits West Nile virus replication and cytopathic effect in neural cells.** *J Infect Dis* 2000, **182**:1214–1217.
39. Hoke CH, Vaugh DW, Nisalak A, *et al*: **The effect of high-dose dexamethasone on the outcome of acute encephalitis due to Japanese encephalitis virus.** *J Infect Dis* 1992, **165**:631–637.
40. Davis BS, Chang GJ, Cropp B, *et al*: **West Nile virus recombinant DNA vaccine protects mouse and horse from virus challenge and express in vitro a noninfectious recombinant antigen that can be used in enzyme-linked immunosorbent assays.** *J Virol* 2001, **75**:4040–4047.
41. •• Monath TP: **Prospects for development of a vacine against the West Nile virus.** *Ann NY Acad Sci* 2001, **951**:1–12.

Strategies for vaccine development are concisely presented. The novel technology for developing a chimeric vacine uses yellow fever 17D as a live vector for envelope genes of West Nile virus.

42. Pletnev AG, Putnak R, Speicher J, Wagar EJ, Vaughn DW: **West Nile virus/dengue type 4 virus chimeras that are reduced in neurovirulence and peripheral virulence without loss of immunogenicity or protective efficacy.** *Proc Natl Acad Sci U S A* 2002, **99**:3036–3041.