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West Nile fever: Here to stay and spreading

■ ABSTRACT

The ultimate extent of West Nile virus's range in North America is uncertain but is likely to expand in 2001. Spread chiefly by night-biting *Culex* mosquitoes, the virus results in infection that most often is asymptomatic or causes a self-limited febrile illness. The elderly, however, are prone to develop neurologic manifestations, including potentially fatal encephalitis.

■ KEY POINTS

Birds are the primary "amplifying" hosts of West Nile virus, and many bird species are capable of this role.

Common symptoms include myalgia, headache, fatigue, and arthralgia. The elderly are at highest risk for neurologic symptoms.

Testing serum samples in both the acute and the convalescent stages is important to confirm West Nile virus disease, yet it is often not done.

The use of repellents is especially important for the elderly, as they are at markedly disproportionate risk of developing severe disease.

WEST NILE VIRUS is the cause of the latest and most well-publicized of the emerging infectious disease, West Nile fever, and it appears to be here to stay. It has been a source of anxiety in affected areas, particularly New York City and the northeastern United States, since the first cases were reported in 1999.

Although fewer severe human cases were reported in 2000 than in 1999, the virus survived the winter and demonstrated an impressive ability to spread geographically in 2000, a phenomenon most authorities expect to continue in 2001.^{1,2} Movement of the virus to states and provinces adjacent to areas already affected is likely this year, with more extensive spread possible.

This article briefly reviews the background of West Nile virus disease, its chief manifestations, and current guidelines for preventing the disease in humans.

■ ANOTHER EMERGING INFECTIOUS DISEASE

Much attention has been given to so-called emerging infectious diseases—illnesses either previously undescribed or presenting in areas where they were not known to be endemic. Since the mid-1970s, these have included acquired immunodeficiency syndrome (AIDS), Lyme disease, Ebola virus infection, ehrlichiosis, dengue fever, hantavirus pulmonary syndrome, new-variant Creutzfeldt-Jakob ("mad cow") disease, and Nipah virus encephalitis.

In the late summer of 1999, West Nile virus, previously not reported in the Western Hemisphere, was added to this list when it caused an outbreak of meningoencephalitis in the New York City area. Initially, it was

unclear whether the virus would establish itself in North America, but this now appears to be the case.

■ CLASSIFICATION AND LIFE CYCLE

West Nile is an RNA virus of the flavivirus family, which includes members ranging from dengue to hepatitis C. West Nile belongs to the Japanese encephalitis complex, which also includes the agents of St. Louis encephalitis and Murray Valley encephalitis.

The only primary “amplifying” hosts (ie, able to sustain naturally occurring infection) are birds, with many bird species capable of this role. Even though migratory birds have long been suspected as critical agents in outbreaks of this and other arthropod-borne viruses (“arboviruses”), the link remains conjectural because of the difficulty in determining the intensity and duration of viremia in naturally infected wild birds. Old World birds infected with West Nile virus have traditionally shown little or no evidence of disease. A variety of mammalian species may be infected, but all, including humans, exhibit brief, low-level viremia and appear to serve only as “dead-end” hosts.

Many types of ornithophilic mosquitoes act as vectors for the spread of West Nile virus, although certain species seem most important in transmission, chiefly of the *Culex* genus (*C. pipiens* in Europe, *C. univittatus* in Africa).

■ PREVIOUS REPORTS OF WEST NILE FEVER

The virus was initially isolated from the blood of a febrile, mildly ill woman in the West Nile region of Uganda in 1937 and was noted by the original investigators to cause encephalitis in rhesus monkeys.³ During the ensuing 15 years, the disease was found to be endemic in Egypt and the cause of sporadic summertime epidemics in Israel.⁴

Serologic evidence of disease was found in up to 60% of people in specific age groups in the Nile Delta during early studies, with approximately 40% of adults from the same region seropositive in a more recent report.^{4,5} Attack rates in closed (especially military) populations in Israel in the 1950s were sometimes impressively high (60% or greater).^{4,6}

Over time the distribution of human West Nile infection was found to include much of Africa and the Middle East, as well as parts of Europe, the former Soviet Union, and the Indian subcontinent, with sporadic reports of outbreaks from areas with little or no previously recognized disease.⁷⁻⁹

Clinical manifestations

West Nile fever was initially considered a universally mild, self-limited disease, marked by several days of fever and other “flu-like” symptoms. Marberg and colleagues⁶ described a group of 70 members of the Israeli armed forces hospitalized with West Nile fever in 1953. In addition to fever, the illness was characterized by headache (80%), ocular pain (45%), backache (40%), and diarrhea (30%). Other stigmata of disease included lymphadenopathy (90%), conjunctival injection (60%), rash (50%), and splenomegaly (20%).

The disease was typically abrupt in onset, lasted 3 to 5 days in most patients, and left some patients with a prolonged period of weakness and fatigue.⁶ The experience of others has largely confirmed the signs and symptoms outlined in this report, with most illness characterized by an incubation period of 2 to 6 days, followed by onset of fever and a variety of constitutional complaints. The fever may have a biphasic pattern similar to dengue fever (acute illness lasting several days, spontaneous remission, then recurrence). Rash, when present, is generally maculopapular or roseolar. Pain with eye movement, lymphadenopathy, gastrointestinal complaints, and myalgias are all commonly reported. Laboratory studies are generally nonspecific, although lymphopenia is usually noted. Subclinical and minimally symptomatic infections are common.^{4,10,11}

Neurologic manifestations

In the 1950s, West Nile virus showed that it could cause neurologic disease, although rarely. Investigators at Memorial Sloan-Kettering Cancer Center, hoping that the virus might have an antitumor effect, experimentally infected patients who had advanced cancer. They found that 9 of 78 evaluable patients developed evidence of encephalitis (altered mental status, abnormal deep tendon

Encephalitis
is only the
tip of the
iceberg



reflexes, and “abnormal twitching”), but most patients did not have significant muscular weakness. Presumably, the frequency of neurologic symptoms in these patients was at least partially explained by their underlying malignancies.¹²

An outbreak of West Nile fever occurred in two nursing homes in Israel in 1957, with 12 cases of suspected meningoencephalitis, 4 of which were fatal.¹³ Apart from a limited number of published cases, however, neurologic involvement in West Nile fever continued to be largely unappreciated for many years. More recently, however, multiple larger outbreaks of meningoencephalitis have occurred, prompting greater awareness of more severe disease.

Larger outbreaks of meningoencephalitis

An outbreak of West Nile fever took place in several Algerian oases in 1994, with 50 cases of neurologic involvement and 8 deaths.⁹ An outbreak of meningoencephalitis due to West Nile virus occurred in southern Russia late in the summer of 1999, with 1,000 cases and 40 deaths.¹⁴ The best-described large epidemic took place in August 1996 in the vicinity of Bucharest, Romania, with 352 laboratory-confirmed cases of meningoencephalitis and 17 deaths, all in patients over age 50. The most common neurologic presentations were confusion, depressed sensorium, and generalized weakness. Other common features were abnormal (increased or decreased) muscle tone, hyperreflexia, ataxia, cranial nerve palsies, and seizures; 13% of patients were comatose during their illness.⁸

An outbreak of West Nile fever in Israel in late summer of 2000 resulted in at least 12 cases of fatal meningoencephalitis and reportedly caused many people with only mild viral illnesses or merely mosquito exposure to report to emergency departments, putting a tremendous strain on the emergency care system.¹⁵

■ WEST NILE VIRUS IN THE UNITED STATES

West Nile virus was first detected in the Western Hemisphere in 1999, when an epidemic occurred in the New York City area. Two patients presenting concurrently with

encephalitis to a hospital in Queens prompted a physician there to contact the New York City Department of Health, which quickly recognized six patients with mental status changes, profound weakness, and an axonal pattern on electromyography. New cases continued to appear, with eight of the earliest-reported cases occurring in people living in a 4-square-mile area of northern Queens and southern Bronx.

An arbovirus was suspected as the cause, and serum and cerebrospinal fluid (CSF) from patients were consistent with St. Louis encephalitis virus by immunoglobulin M (IgM) capture enzyme-linked immunosorbent assay (ELISA).¹⁶ However, bird “die-offs” had been noted, beginning shortly before the onset of human cases, affecting exotic birds at the Bronx and Queens zoos and also native crows. Avian mortality is not a feature of St. Louis encephalitis virus infection, prompting suspicion that infection was due to another flavivirus. Subsequent genomic analysis of the virus at the US Centers for Disease Control and Prevention (CDC) and at the University of California-Irvine confirmed that it was in fact West Nile virus.^{16,17}

Although it remains unclear how West Nile virus migrated to the Western Hemisphere, a number of theories have been proposed. These include introduction via mosquitoes, birds in the pet trade, migratory birds, an infected human, or even an act of bioterrorism.

Rapid public health response to the 1999 New York City outbreak

Mosquito control measures were quickly initiated, involving the entire city by September 11. The public health response also included free distribution of more than 300,000 cans of mosquito repellent containing diethyltoluamide (DEET) and nearly 1 million informational leaflets, as well as widespread educational efforts directed through the mass media. The last reported case of the 1999 epidemic presented on September 16, suggesting that aggressive intervention may have been instrumental in controlling the outbreak.¹⁶

A total of 61 human cases of meningoencephalitis were reported from August 5 to September 16, with 7 deaths.¹⁸ An institution

**Bird die-offs
accompany
West Nile fever
outbreaks**

The spread of West Nile fever in the United States

- Virus activity in 1999 and 2000
- Virus activity in 2000 only

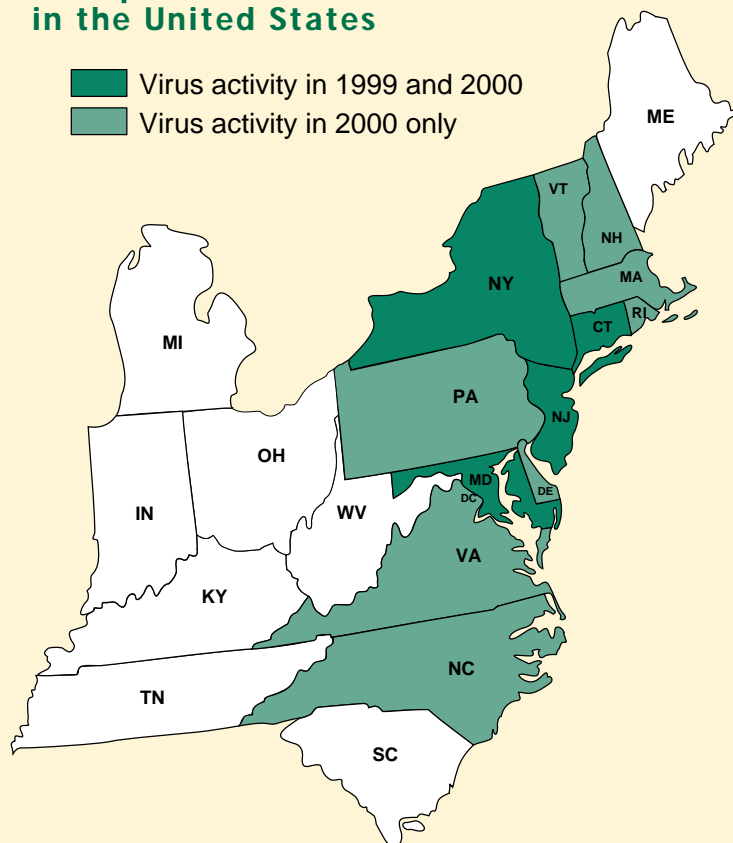


FIGURE 1

in northern Queens reported its experience with 8 of the patients, including 6 with frank encephalitis: 5 of the 6 with encephalitis presented with profound weakness; all were over age 50, all but one demonstrated CSF pleocytosis, and all had lymphopenia. A common factor was spending considerable time outdoors.¹⁹ Lymphopenia appeared to be a consistent feature and has been suggested as an aid in differentiating West Nile virus-related encephalitis from other encephalitides.^{20,21}

Postmortem studies

Of the 7 people who died in the 1999 outbreak, 4 underwent postmortem study by the Office of the Chief Medical Examiner of New York City. All demonstrated microglial nodules with a predilection for the brainstem and also involving the thalamus, cerebellum, and cortex. Three cases showed perivascular mononuclear

infiltrates. This contrasts with St. Louis encephalitis virus infection, which typically displays much more cerebral involvement, and with Eastern and Western equine encephalitis virus infections, which show much more fulminant changes pathologically.²²

Ability of West Nile virus to survive the winter

Many experts hoped that the winter months would spell the end of the West Nile virus in North America. Surveillance of mosquitoes at a variety of sites in early 2000 found no live virus. However, West Nile virus RNA was found in several mosquito pools, suggesting the virus had not been contained (the ability of the virus to spread via vertical transmission within mosquitoes had previously been observed),²³ and by early summer of 2000, surveillance revealed birds and mosquito pools infected with West Nile virus in New York City. The first human case was diagnosed in Staten Island, New York, in mid-July.

Intensive mosquito control efforts already underway in New York City perhaps at least partially explain why West Nile fever in humans was not more widespread in 2000.²⁴ Despite the spread of West Nile "activity" (infected birds, mosquitoes, humans, other mammals) to 8 new states in 2000 (FIGURE 1), the number of severe human cases was lower than in 1999: 22 cases and 2 deaths reported as of early 2001, vs 62 cases and 7 deaths in 1999.²⁵ Whether these low numbers represent successful public health efforts, natural fluctuation of the disease (well documented in other parts of the world), or both, remains unclear.

That the reported cases of severe neurologic disease are only the tip of the iceberg is clear. A serosurvey of the most heavily affected area of Queens in 1999 revealed that 2.6% of individuals had been recently infected with West Nile virus, with less than 1% of seropositive persons developing severe neurologic manifestations. The 2000 Staten Island serosurvey revealed a low incidence of infection (0.46%), which may reflect the less concentrated distribution of human disease last season, with an estimated 1 in 157 infected individuals exhibiting evidence of meningoencephalitis.^{26,27}

**TABLE 1****Clinically significant arthropod-borne virus (arbovirus) encephalitides in North America**

VIRUS	DISTRIBUTION	AGE AFFECTED	MORTALITY RATE	AMPLIFYING HOST	RATIO OF INFECTION TO ENCEPHALITIS
West Nile	Northeast US	Over 50	5% to 10%	Birds	150:1
St. Louis	Throughout US, but especially the Ohio and Mississippi valleys	All ages	Up to 20% in the elderly	Birds	200:1
Western equine	Western North America	All ages	5%	Birds	1,000:1
Eastern equine	Atlantic and Gulf coasts	All ages	30% to 50%	Marsh birds	20:1
La Crosse	Midwest	Under 15, 90% males	1%	Chipmunks, squirrels	25:1

The 1999 Queens serosurvey found that 30% of seropositive persons recalled a febrile illness in the preceding 3 months compared with 11% of seronegative persons. In seropositive persons describing a recent febrile illness, common symptoms included myalgia (100%), headache (89%), fatigue (87%), and arthralgia (76%). The case ratio of subclinical to clinical disease was approximately 4:1.²⁸

■ DIFFERENTIAL DIAGNOSIS OF WEST NILE ENCEPHALITIS

The differential diagnosis of West Nile meningoencephalitis, depending on the severity of the case, is that of either aseptic meningitis or encephalitis. Patients with West Nile fever presenting as aseptic meningitis are not distinguishable clinically from those with other forms of aseptic meningitis.

The preponderance of cases of aseptic meningitis during “West Nile season” (summer and early fall) has been enteroviral in origin. More severe disease is most likely to be confused with encephalitides caused by other arboviruses (TABLE 1) or herpes simplex virus. Many other conditions may present in similar fashion; these include infectious agents (enteroviruses, adenovirus, mumps, lymphocytic choriomeningitis virus, rabies, cytomegalovirus, Epstein-Barr virus, varicella-

zoster virus, human immunodeficiency virus, and others), post-infectious encephalitides, and noninfectious conditions (central nervous system vasculitis, sarcoidosis, systemic lupus erythematosus).

■ LABORATORY CONFIRMATION OF WEST NILE VIRUS INFECTION

Laboratory confirmation of West Nile virus infection can be carried out in several ways. For example, early in the course of disease the virus can be isolated from blood or CSF; however, the CDC has recommended this be done only in laboratories that meet CDC laboratory biosafety level 3 criteria.¹⁸

Serologic testing techniques

Typically, proof of West Nile virus infection is accomplished with serologic testing. Techniques now in use are IgM capture ELISA, plaque reduction neutralization (the most specific serologic test), complement fixation, and hemagglutination-inhibition. The IgM capture ELISA has good sensitivity for acute disease, although its specificity is less clear. Some investigators have found it highly specific, although this was not the case in the 1999 New York outbreak. There is general agreement that the IgG ELISA for West Nile virus cross-reacts with other flaviviruses, making it less specific.²⁹

IgM capture ELISA is a sensitive test for acute disease

Obtaining serum from the patient in both the acute and convalescent stages of infection may be necessary to confirm acute disease in endemic areas. This was illustrated by the 1999 Queens serosurvey, in which 55% of seropositive patients still had detectable IgM antibody by ELISA 6 months later.²⁶ Infected persons typically have West Nile virus serum IgM antibodies by the 8th day of illness. IgM antibodies are essentially always positive in the CSF by that time in cases of meningoencephalitis, and may be present as early as the first day of illness. Nearly 100% of those infected show IgG antibodies in serum by 3 weeks after onset of illness.

Per CDC guidelines, a positive IgM capture ELISA in serum in conjunction with an appropriate clinical scenario is sufficient to make a diagnosis of “probable” acute or recent West Nile infection. Definite diagnosis requires viral isolation, CSF positive for IgM capture antibody, or a fourfold or greater increase in antibodies by plaque reduction neutralization testing performed on sera from acute and convalescent stages.

Paired sera should be drawn at least 2 weeks apart. Samples should be sent directly to the appropriate state health department laboratory; the CDC will perform confirmatory testing at the request of state laboratories.²⁸

Collection of acute and convalescent sera is important. Nevertheless, clinicians are notoriously reluctant to do this. If serum from both stages is not tested, then at a minimum serum and CSF from suspected cases should be sent for IgM capture antibody testing.

Polymerase chain reaction techniques have been shown to be sensitive and specific in identifying West Nile virus in mosquito pools and human tissue, but are thus far less useful in human serum.³⁰

■ TREATMENT

Currently, there is no specific therapy for West Nile virus infection. Analgesics and antipyretics may ameliorate symptoms in milder cases. More severe cases may require aggressive supportive care, including mechanical ventilation.

■ PREVENTING WEST NILE FEVER: RECOMMENDATIONS

Control of West Nile infection has been a priority since its initial appearance in the United States in 1999, and it continues to command considerable attention from the public health infrastructure on both national and local levels. In 2000, the CDC and the US Department of Agriculture issued guidelines for control of the virus that involve both surveillance and active control measures. The recommendations include:

- Monitoring West Nile infection in birds, especially dead crows, as they appear to be an excellent sentinel for viral activity
- Monitoring virus activity in mosquito pools
- Passive surveillance (ie, West Nile virus testing) in both humans and horses showing signs of illness
- Serologic testing. State public health laboratories should have the ability to perform on-site serologic testing for West Nile virus, and mosquito control efforts are highly encouraged in areas where the virus is active; these efforts should be aimed particularly at the larval stage
- Public education is strongly encouraged at the local level. This should include elimination of breeding sites from individual yards, as well as use of a DEET-based mosquito repellent during dusk and evening hours (corresponding to the feeding period of *Culex* mosquitoes, the chief vectors of infection in the United States).¹⁸ The use of repellents is especially important for the elderly, as they are at markedly disproportionate risk of developing severe disease.

Conditions that should be reported to a public health authority

In an effort to capture cases of West Nile meningoencephalitis, the New York City Department of Health formulated a list of reportable conditions, a list that should also be helpful in other jurisdictions where the disease may occur. These include:

- Patients with fever, altered mental status, CSF pleocytosis, and weakness
- Suspected cases of viral encephalitis
- Patients with fever and focal neurologic findings



- Patients who are febrile and are presumed to have Guillain-Barré syndrome or acute flaccid paralysis
- Patients with aseptic meningitis.²²

Awareness is key

Most clinically apparent infections take the form of undifferentiated febrile syndromes and thus generally go undiagnosed. Awareness of West Nile disease by clinicians and a high index of suspicion are important in the detection of human cases in previously uninvolved areas.

Preparing for the future

The ultimate importance of West Nile virus infection in the United States and the rest of the Western Hemisphere remains to be determined, but in recent years the virus has shown a tendency to cause epidemics of neurologic disease. Based on the events of 2000, hopes that the virus would fail to gain a permanent foothold here appear to have been unfounded. Given the propensity of migratory birds to spread West Nile virus, its eventual role in the Americas, while uncertain, is likely to be much wider than at present.¹⁷ States with known viral activity to date, as well as nearby states such as Ohio that have thus far been unaffected, have been preparing for the uncertainties of the 2001 West Nile season.³¹

Vaccine research aimed at West Nile virus is ongoing, and there is some interest in specific therapy directed against West Nile virus infection; however, the cornerstone of disease containment will continue to be vector control and public education.^{32,33}

Rapid mobilization of public health resources

Whatever the eventual extent of West Nile virus infection in North America, its presumed spread from the Middle East to this country (the virus strain responsible for the 1999 outbreak has been shown to be essentially identical to a strain isolated in Israel in 1998) demonstrates once again that the world continues to shrink.³⁴ The rapid mobilization of resources in 1999 to identify and control a novel infectious disease agent points out the importance of an adequately trained and funded public health system. An excellent review of the public health "lessons learned" has recently been published by the New York City Department of Health Communicable Disease Program.³⁵ It is safe to assume this is not the last time these capabilities will be called upon.



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