West Nile Virus: A Primer for the Clinician

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This paper provides the clinician with an understanding of the epidemiologic and biological characteristics of West Nile virus in North America, as well as useful information on the diagnosis, reporting, and management of patients with suspected West Nile virus infection and on advising patients about prevention. Information was gathered from the medical literature and from national surveillance data through May 2002. Since the identification of West Nile virus in New York City in 1999, enzootic activity has been documented in 27 states and the District of Columbia. Continued geographic expansion is likely. Overall, one in 150 infections results in severe neurologic illness. Advanced age is by far the most important risk factor for neurologic disease and, once disease develops, for worse clinical outcome. Surveillance has identified 149 persons with West Nile virus–related illness in 10 states. Encephalitis is more commonly reported than meningitis, and concomitant muscle weakness and flaccid paralysis may provide a clinical clue to the presence of West Nile virus infection. Peak incidence occurs in late summer, although onset has occurred from July through December. Immunoglobulin M antibody testing of serum specimens and cerebrospinal fluid is the most efficient method of diagnosis, although cross-reactions are possible in patients recently vaccinated against or recently infected with related flaviviruses. Testing can be arranged through local, state, or provincial (in Canada) health departments. Prevention rests on elimination of mosquito breeding sites; judicious use of pesticides; and avoidance of mosquito bites, including mosquito repellent use.

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Four centuries of travel and commerce have led to the North American importation of several important vector-borne human pathogens, including dengue, yellow fever, malaria, and plague. The 1999 appearance of the West Nile virus in New York City may prove to be the best-documented introduction of a new, vector-borne human pathogen into the United States in the past century (1). It remains unknown how the West Nile virus came to North America. However, because it first appeared in a major international gateway, travel and commerce may have played a role. The virus's rapid geographic expansion and subsequent persistence in newly established enzootic areas in North America indicate that West Nile virus has become a permanent fixture of the U.S. medical landscape. Key features of the West Nile virus in North America are indicated in **Table 1**.

EPIDEMIOLOGY

West Nile virus was first isolated and identified in 1937 from an infected person in the West Nile district of Uganda (2). Until 1999, the virus was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe (3). Since 1937, infrequent human outbreaks, mainly associated with mild febrile illnesses, were reported mostly in groups of soldiers, children, and healthy adults in Israel and Africa (4–7). However, one notable outbreak in Israeli nursing homes in 1957 was associated with severe neurologic disease and death (8). Since the mid-1990s, the frequency and apparent clinical severity of West Nile virus outbreaks have increased (4). Outbreaks in Romania (1996) (9), Russia (1999) (10), and Israel (2000) (11) involved hundreds of persons with severe neurologic disease. It is unclear if this apparent change in disease severity and frequency is due to differences in the circulating virus's virulence or to changes in the age structure, background immunity, or prevalence of other predisposing chronic conditions in the affected populations (12).

A large outbreak of West Nile virus infection has yet to occur in the United States. However, national surveillance has documented persons with illness caused by West Nile virus, mostly encephalitis and meningitis, each year since 1999 (62 persons in 1999, 21 in 2000, and 66 in 2001) (13). These persons have been identified over an expanding geographic area (1 state in 1999, 3 in 2000, and 10 in 2001) (**Figure 1**). From 1999 to 2001, illness onset ranged from 13 July to 7 December, with peak incidence in late August and early September (**Figure 2**).

ECOLOGY

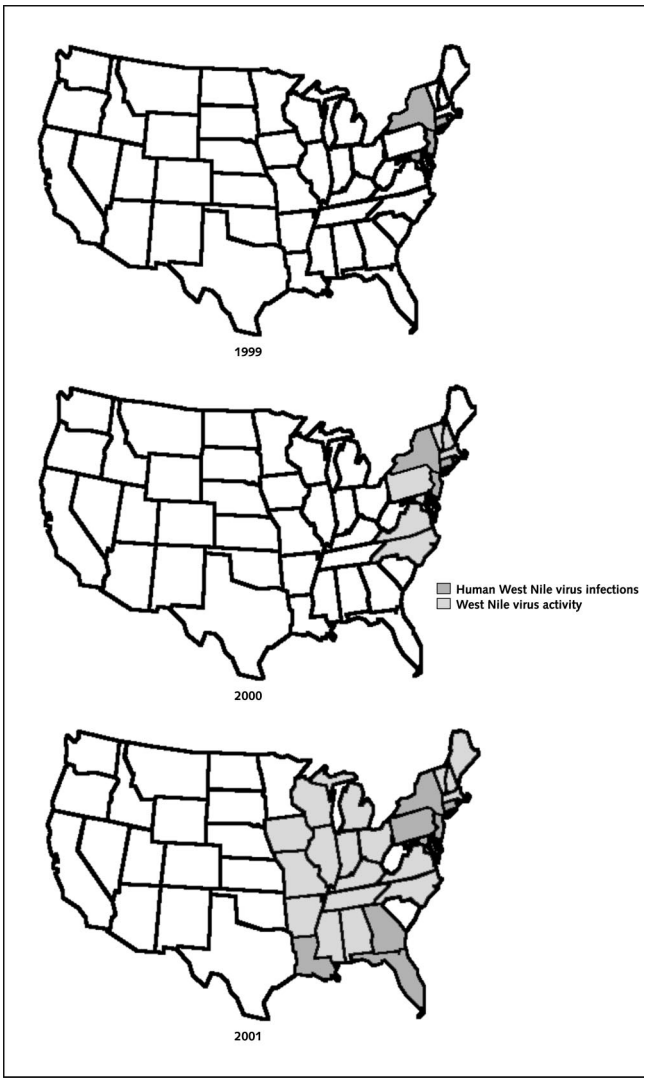
In the Eastern Hemisphere, West Nile virus is maintained in an enzootic cycle involving culicine mosquitoes and birds (3, 14). Evidence to date suggests a similar cycle in North America (**Figure 3**) (4). After passing through three aquatic stages (egg, larva, pupa), adult mosquitoes begin to emerge in the spring in temperate regions. Viral

Table 1. **Key Clinical Facts about West Nile Virus in North America***

West Nile virus infection is a mosquito-borne infection with rapidly expanding geographic distribution.
One in 5 infected persons develops mild febrile illness; 1 in 150 develops meningitis, encephalitis, or both.
Advanced age is by far the greatest risk factor for severe neurologic disease, long-term morbidity, and death.
Presence of West Nile virus–infected birds, onset of meningitis or encephalitis in late summer or early fall, and profound muscle weakness provide important diagnostic clues.
IgM antibody-capture ELISA testing of CSF or serum is the most efficient diagnostic method; testing is available through state and local health departments; false-positive results may occur after other flaviviral infections or vaccinations.
Rapid reporting of possible cases to health departments is essential to guide public health control efforts.

* CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay.

Figure 1. **States reporting epizootic activity and human infections of the West Nile virus, 1999–2001.**



amplification occurs in the bird–mosquito–bird cycle until early fall, when female mosquitoes begin diapause and infrequently bite. Many environmental factors affect this viral amplification cycle (for example, weather or climate, host and vector predators and parasites, and host immune status). When environmental conditions promote significant amplification, sufficient numbers of "bridge vector" mosquitoes—mosquitoes that bite both humans and birds—become infected in late summer and then pose an infection threat to humans. Year-round transmission is possible in more tropical climates. Through spring 2002, West Nile virus had been detected in 29 North American mosquito species; this number will undoubtedly increase as the virus spreads into new ecologic habitats. Although *Culex pipiens, Culex restuans*, and *Culex quinquefasciatus* are probably the most important maintenance vectors in the eastern United States, it is unknown which species are most responsible for transmission to humans (15).

While arboviral maintenance cycles are normally not apparent, dramatic avian mortality rates have accompanied outbreaks in humans in Israel and the United States (4, 16). Particularly high mortality rates have been noted among American crows (*Corvus brachyrhynchos*) and other North American corvids (ravens, jays, and other crows). In the northeastern United States, deaths in crows have increased markedly shortly before human cases have developed (17). Surveillance systems involving testing dead birds, sentinel chickens, and ill horses for West Nile virus have demonstrated rapid geographic spread in the United States (4 states in 1999, 12 states and the District of Columbia in 2000, 27 states and the District of Columbia in 2001) and into Canada (southern Ontario in 2001) (**Figure 1**). Up-to-date maps showing the U.S. distribution of West Nile virus are available at www.cdc.gov/ncidod/dvbid/westnile/surv&control.htm and at http://cindi.usgs.gov/hazard/event/west_nile/west_nile.html.

VIROLOGY

West Nile virus is a single-stranded RNA virus of the family *Flaviviridae*, genus *Flavivirus*. The E-glycoprotein is the viral hemagglutinin and mediates virus–host cell binding. As the most immunologically important structural protein, the E-glycoprotein elicits most virus-neutralizing antibodies. West Nile virus is a member of the Japanese encephalitis virus serocomplex, which contains several medically important viruses associated with human encephalitis: Japanese encephalitis, St. Louis encephalitis, Murray Valley encephalitis, and Kunjin virus (an Australian subtype of West Nile virus). The close antigenic relationship of the flaviviruses, particularly those belonging to the Japanese encephalitis complex, accounts for the serologic cross-reactions observed in the diagnostic laboratory (18).

West Nile virus can be divided genetically into two lineages. Only viruses of lineage 1 have been definitely associated with human disease. The West Nile virus responsible for the 1999 outbreak in New York City was a lineage 1 virus that circulated in Israel from 1997 to 2000, suggesting viral importation into North America from the Middle East (19, 20). Of interest, both birds and humans have died of West Nile virus infection only in the United States and Israel to date; the reason for this is not known. Since 1999, very few genetic changes have occurred in the variant of West Nile virus circulating in the United States.

CLINICAL FEATURES

The incubation period of West Nile virus, although not precisely known, probably ranges from 3 to 14 days. Most human infections are not clinically apparent. A serosurvey conducted during the 1999 New York City epidemic indicated that approximately 20% of persons infected with West Nile virus had developed West Nile fever and only half of these had visited a physician for this illness (21). The frequencies of various symptoms and signs asso-

ciated with West Nile fever during recent outbreaks are poorly defined because surveillance has focused on patients with neurologic disease. In earlier outbreaks, the disease was described as a febrile illness of sudden onset, often accompanied by malaise, anorexia, nausea, vomiting, eye pain, headache, myalgia, rash, and lymphadenopathy; these symptoms generally lasted 3 to 6 days. Among the 6 symptomatic persons positive for IgM antibody who were identified in the 1999 New York City serosurvey, all reported myalgia, 5 reported fatigue, 5 had headache, and 4 had arthralgia (21).

Although recent outbreaks of West Nile virus seem to be associated with increased morbidity and mortality, severe neurologic disease remains uncommon. Two serosurveys conducted in New York City in 1999 and 2000 showed that approximately 1 in 150 infections resulted in meningitis or encephalitis, a result consistent with a 1996 Romanian serosurvey indicating that 1 in 140 to 320 infections led to these diseases (9, 21, 22). Advanced age is by far the most significant risk factor for severe neurologic disease after infection; risk increases markedly among persons 50 years of age and older. An analysis of attack rates per million persons during the 1999 New York City outbreak showed that compared with persons 0 to 19 years of age, the incidence of severe neurologic disease was 10 times higher in persons 50 to 59 years of age and 43 times higher in those at least 80 years of age (1). In addition, the household-based serosurvey in New York City showed that incidence of West Nile virus infection was fairly uniform according to age (21). These results indicated that the higher incidences of severe neurologic disease among older persons were not attributable simply to differences in mosquito exposure. A similar finding was noted during the 1996 Romanian outbreak (9).

Among hospitalized persons with West Nile virus infection in the United States (1999), Romania (1996), and Israel (2000), encephalitis–meningoencephalitis was more frequently reported than meningitis (62%, 60%, and 58%

Figure 2. **Week of symptom onset for persons reported to have West Nile virus infection, 1999–2001.**

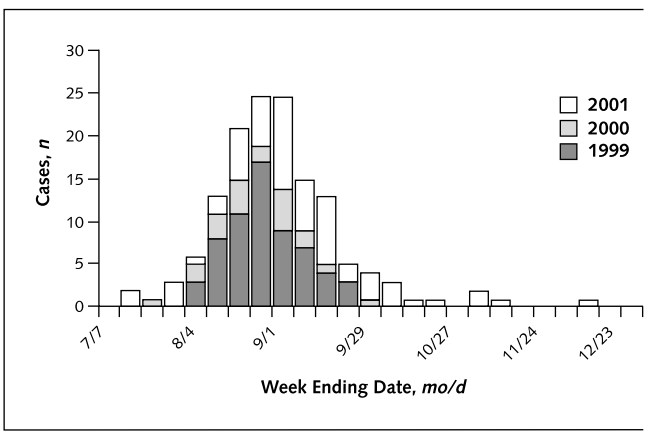
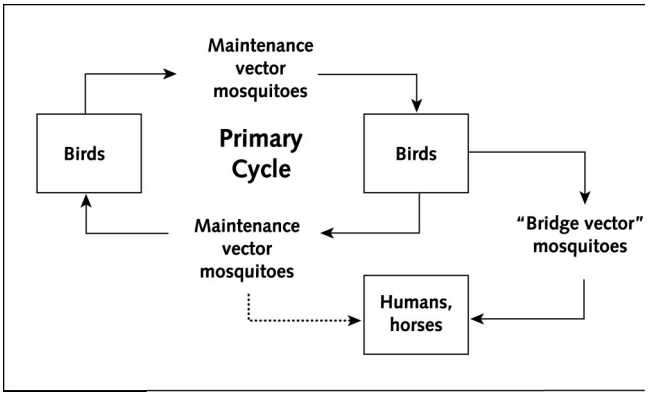


Figure 3. **Transmission cycle of West Nile virus.**



compared with 32%, 40%, and 16%, respectively) (1, 9, 11). More than 90% of patients hospitalized during these outbreaks had fever; weakness, gastrointestinal symptoms, headache, and changes in mental status were common reported symptoms (**Table 2**). A skin rash, present in a minority of patients, was described as an erythematous macular, papular, or morbilliform eruption involving the neck, trunk, arms, or legs (1, 23).

Approximately half of the hospitalized U.S. patients had severe muscle weakness. This symptom may provide a clinical clue to the presence of West Nile virus, particularly in the setting of encephalopathy (1, 23). Approximately 10% of patients in the New York outbreak had complete flaccid paralysis. In fact, several patients had such profound weakness that they were first thought to have the Guillain–Barré syndrome (24, 25). However, most studied persons with clinical presentations consistent with the Guillain–Barré syndrome had pleocytosis as well as electromyography and nerve-conduction velocity studies indicating both axonal and demyelinating lesions, with axonal changes most prominent (26). These findings would be unusual for the Guillain–Barré syndrome. Neurologic presentations other than encephalitis or meningitis, which occur more rarely, include ataxia and extrapyramidal signs, cranial nerve abnormalities, myelitis, optic neuritis, polyradiculitis, and seizures. Myocarditis, pancreatitis, and fulminant hepatitis have been described in outbreaks occurring before 1990.

Clinical Outcome and Treatment

Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% in Romania (1996) to 12% in New York (1999) and 14% in Israel (2000) (1, 9, 11). Case fatality rates have remained constant among U.S. patients in 2000 and 2001 (13). Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. For hospitalized persons older than 70 years of age, case fatality rates were 15% in Romania and 29% in Israel; in New York, persons 75 years of age and older were nearly nine

Table 2. **Symptoms of West Nile Virus Reported among Hospitalized Patients during Outbreaks in New York State (1999), Romania (1996), and Israel (2000)**

Symptom*	Location		
	New York State (*n* = 59)	Romania (*n* = 393)	Israel (*n* = 233)
	← % →		
Fever	90	91	98
Weakness	56		
Nausea	53		
Vomiting	51	53	31
Headache	47	77	58
Changes in mental status	46	34†	40†
Diarrhea	27		19
Rash	19		21
Cough	19		
Stiff neck	19	57	29
Myalgia	17		15
Arthralgia	15		
Lymphadenopathy	2		10

* Some listed symptoms were not reported in Romania and Israel.
† Reported as confusion.

times more likely to die than younger persons (1, 9, 11). Encephalitis with severe muscle weakness and change in the level of consciousness were also prominent clinical risk factors predicting death. Limited data suggest that certain preexisting conditions, such as diabetes mellitus or immunosuppression, may be independent risk factors for death (1, 11). In one study of induced West Nile infections in patients with cancer, prolonged viremia and severe illness were more common among those with hematologic malignancies than among those with other types of cancer (27).

Few data exist regarding long-term morbidity after hospitalization for West Nile infection; those that do suggest that many patients have substantial morbidity. Among patients hospitalized in New York and New Jersey in 2000, more than half did not return to their functional level by discharge and only one third were fully ambulatory (23). One-year follow-up of the 1999 New York patients by the New York City Department of Health found frequent persistent symptoms (fatigue, 67%; memory loss, 50%; difficulty walking, 49%; muscle weakness, 44%; and depression, 38%) (28).

Treatment for West Nile virus infection is supportive. Of 19 patients hospitalized in New York and New Jersey in 2000, 5 were admitted to intensive care units and 2 required mechanical ventilation (23). Ribavirin in high doses and interferon-α2b were efficacious against the West Nile virus in vitro; however, controlled clinical trials have not been completed for either agent (29). One comatose patient treated with both ribavirin and interferon-α did not improve (23). In Israel, patients treated with ribavirin had a higher mortality rate than those who did not receive ribavirin, although this difference could have been related to patient selection (11). No controlled studies have examined the use of steroids, antiseizure medications, or osmotic agents in the management of West Nile virus encephalitis.

Laboratory Findings and Diagnosis

During recent outbreaks, total leukocyte counts in peripheral blood were mostly normal or elevated; lymphocytopenia and anemia also occurred (1, 11, 23). Hyponatremia was sometimes present, particularly among patients with encephalitis (11, 23). Examination of the cerebrospinal fluid showed pleocytosis, with leukocyte counts ranging from 0 to 1782 cells/mm^3, usually with a predominance of lymphocytes (1, 11, 23, 25). Protein levels were universally elevated (51 to 899 mg/dL), and glucose levels were normal. Computed tomography of the brain usually showed no evidence of acute disease (1, 11, 23). In approximately one third of patients, magnetic resonance imaging showed enhancement of the leptomeninges, the periventricular areas, or both.

The diagnosis rests on a high index of clinical suspicion and on results of specific laboratory tests. West Nile virus or other arboviral diseases, such as St. Louis encephalitis, should be seriously considered in older adults who have onset of unexplained encephalitis or meningitis in late summer or early fall. The local presence of West Nile virus enzootic activity or other human cases should further raise the index of suspicion. However, because severe neurologic disease due to West Nile virus infection has occurred in persons of all ages and because year-round transmission is possible in more southern states, West Nile virus should always be considered in persons with unexplained encephalitis and meningitis.

The most efficient diagnostic method is detection of IgM antibody to West Nile virus in serum or cerebrospinal fluid. The IgM antibody-capture enzyme-linked immunosorbent assay is optimal for IgM detection because it is simple, sensitive, and applicable to serum samples and samples of cerebrospinal fluid. Among the patients in New York City who were infected in 1999 and 2000 and for whom a sample of cerebrospinal fluid was available, nearly all (95%) had demonstrable IgM antibody (28). Since IgM antibody does not cross the blood–brain barrier, IgM antibody in cerebrospinal fluid strongly suggests central nervous system infection. Ninety percent of serum samples obtained within 8 days of symptom onset were also positive for IgM antibody. Tests of serum or cerebrospinal fluid are available commercially and can be obtained through local, state, or province (in Canada) health departments for patients with encephalitis or meningitis.

Two caveats must be considered when interpreting serologic tests. First, because of close antigenic relationships among the flaviviruses, persons recently vaccinated with yellow fever or Japanese encephalitis vaccines or persons recently infected with a related flavivirus (for example, St. Louis encephalitis or dengue) may have positive results on IgM antibody tests for West Nile virus (18). The plaque reduction neutralization test, the most specific test for the

arthropod-borne flaviviruses, can be used to help distinguish false-positive results on IgM antibody-capture enzyme-linked immunosorbent assay or other assays (for example, indirect immunofluorescence and hemagglutination inhibition). The plaque reduction neutralization test may also help distinguish serologic cross-reactions among the flaviviruses, although some degree of cross-reaction in neutralizing antibody may still cause ambiguous results. Second, because most infected persons are asymptomatic and because IgM antibody may persist for 6 months or longer, residents in endemic areas may have persistent IgM antibody from a previous infection that is unrelated to their current clinical illness (28). An increase in West Nile virus–specific neutralizing antibody titer in serum specimens from persons with acute and convalescent disease confirms acute infection.

It is also possible to isolate West Nile virus or to detect viral antigen or nucleic acid in cerebrospinal fluid, tissue, blood, or other body fluids. Although a positive culture or positive results on the nucleic acid amplification test are diagnostic, low sensitivity precludes their use as routine screening tests. Viral culture of cerebrospinal fluid or brain tissue has had very low yield among U.S. patients; results on nucleic acid amplification testing, such as real-time polymerase chain reaction, have been positive in up to 55% of samples of cerebrospinal fluid and 10% of serum samples (28). One autopsy series of four New York patients infected in the 1999 outbreak showed a mostly mononuclear inflammation that formed microglial nodules and perivascular clusters in the white and gray matter. The brainstem, particularly the medulla, was most extensively involved. Cranial nerve roots had mononuclear inflammation in two patients (30).

Table 3. **U.S. National Case Definitions for West Nile Encephalitis***

Possible case of West Nile encephalitis
Febrile illness with neurologic syndrome (ranging from headache to serious neurologic illness [e.g., aseptic meningitis, myelitis, encephalitis]). Suggested specimens (if indicated) for West Nile virus diagnostic studies are the following:
Acute serum sample (collect within 7 days of illness onset)†
Acute CSF sample (collect within 7 days of illness onset)†
Convalescent serum sample (collect 14–21 days after illness onset)†
Probable case of West Nile encephalitis
Febrile illness with neurologic syndrome plus at least one of the following:
Demonstration of West Nile virus IgM antibody in acute serum sample using (MAC-ELISA)
Demonstration of elevated titer of West Nile virus–specific IgG (by ELISA) or HI antibody in a convalescent serum sample relative to titer in an acute serum sample (confirm by PRNT)
Confirmed case of West Nile encephalitis
Febrile illness with neurologic manifestations plus at least one of the following:
Isolation of West Nile virus from tissue, blood, CSF, or other body fluid
Demonstration of West Nile viral antigen or genomic sequences in tissue, blood, CSF, or other body fluid
Demonstration of West Nile virus IgM antibody in an acute CSF sample using MAC-ELISA
Demonstration of fourfold change in PRNT antibody titer to West Nile virus in paired, appropriately timed acute and convalescent serum samples
Demonstration of both West Nile virus–specific IgM (by MAC-ELISA) and IgG (by IgG ELISA or HI antibody titer; confirm by PRNT) in a single serum sample
Non-case of West Nile encephalitis
Febrile illness with neurologic manifestations ranging from headache to aseptic meningitis or encephalitis that does not meet any of the above laboratory criteria. There should be a negative test result for at least one of the following:
IgM antibody to West Nile virus (by MAC-ELISA) in serum or CSF collected 8–21 days after onset of illness
IgG antibody to West Nile virus (by EIA, HI antibody titer, or PRNT) in serum collected 22 days after onset of illness

* CSF = cerebrospinal fluid; EIA = enzyme immunoassay; HI = hemagglutination inhibition; MAC-ELISA = IgM antibody-capture enzyme-linked immunosorbent assay; PRNT = plaque reduction neutralization test.
† All samples should be refrigerated at 4 °C to 8 °C or frozen.

REPORTING

West Nile virus encephalitis has recently been added to the list of designated nationally notifiable arboviral encephalitides; aseptic meningitis is reportable in some jurisdictions (31). Recommended clinical and laboratory case definitions for West Nile virus are available at www.cdc.gov/ncidod/dvbid/westnile/resources/wnv-guidelines-apr-2001.pdf and are summarized in **Table 3**. Submission of serum specimens or specimens of cerebrospinal fluid to state and local public health laboratories for arboviral diagnosis facilitates rapid diagnosis and reporting. The timely identification of even a single person with acute West Nile virus or other arboviral infection may have substantial public health implications and will probably augment the public health response to reduce the risk for additional human infections. An additional benefit of human West Nile virus surveillance has been increased recognition of other arboviral encephalitides, such as Powassan encephalitis virus in the northeastern United States and Canada (32, 33). Information on how to report persons with suspected West Nile virus infection or how to submit diagnostic samples in the United States is available at www.cdc.gov/ncidod/dvbid/westnile/city_states.htm.

PREVENTION

Although human vaccines for West Nile virus are under development (34), for the foreseeable future West Nile infection prevention will rest on two broad general strategies: 1) reducing the number of vector mosquitoes through actions taken by the public or by municipal authorities, and 2) preventing vector mosquitoes from biting humans by using mosquito repellents; avoiding locations where vector mosquitoes are biting; and using barrier methods, such as window screens or long-sleeved clothing.

Reducing the Number of Mosquitoes

Many vector mosquitoes have a limited flight range and readily breed in containers or other objects containing small pools of water. Thus, homeowners or municipal authorities can greatly reduce mosquitoes in residential or urban areas by draining water from or eliminating mosquito breeding sites. Larvicides can also be applied to still

or stagnant waters that are potential mosquito breeding sites. *Bacillus thuringiensis* var. *israelensis* and *Bacillus sphaericus* are two larvicides in which the active ingredient is a biological organism. Municipal authorities commonly use these products with methoprene, a biochemical regulator that interferes with mosquito maturation, for West Nile virus prevention. None of these products is associated with serious acute or chronic health effects.

The U.S. Environmental Protection Agency–approved organophosphate or pyrethroid formulations are applied in very small volumes by ground or aerial spraying for control of adult mosquitoes. Public health authorities use these "adulticides" for prevention of human West Nile virus infection when epidemiologic evidence suggests impending or continuing human transmission. Serious adverse health events associated with pesticide spraying for West Nile virus control seem rare (28). Minor eye and skin irritation, as well as breathing problems, have rarely been reported with spraying of organophosphates and pyrethroids. Cholinergic symptoms (for example, nausea, vomiting, diarrhea, sweating, and bronchospasm) are associated with high-dose occupational or accidental organophosphate exposure. A cholinesterase level can be obtained to confirm organophosphate poisoning. Exposure to high doses of pyrethroids may cause abnormal facial sensation, dizziness, salivation, headache, vomiting, diarrhea, irritability, pulmonary edema, and seizures. More detailed information about pesticides and other mosquito control measures can be obtained from the U.S. National Pesticide Information Center at www.ace.orst.edu/info/npic/wnv/. Backyard "bug zappers" or carbon dioxide–baited devices have not been proven to significantly reduce exposure to mosquito bites.

Using Mosquito Repellents

An excellent clinician's guide for mosquito repellents has recently been published (35). The most widely used repellent, DEET (N,N-diethyl-3-methylbenzamide), is available in many formulations; however, concentrations higher than 50% show little incremental increase in efficacy and only slightly longer durations of action. Extended-release preparations are available. Products containing 10% to 50% DEET are sufficient under most conditions and can be reapplied according to the manufacturer's instructions. The American Academy of Pediatrics recommends that repellents containing no more than 10% DEET be used on children. DEET is registered for direct application to skin, pets, clothing, tents, bedrolls, and screens. It has a remarkable safety profile, and serious toxicity has been limited to encephalopathy in a few children, most of whom had a history of long-term, excessive use of DEET repellents. DEET is not recommended for infants younger than 2 months of age.

Permethrin, a pyrethroid with repellent and insecticidal characteristics, is found in Environmental Protection Agency–approved repellents that can be applied to clothing, tent walls, mosquito nets, or other fabrics, but not to skin. Many other repellents, such as citronella, are marketed but are not as effective as DEET.

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