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Denis Nash

*CUNY School of Public Health*

Farzad Mostashari

*New York City Department of Health*

Annie Fine

*New York City Department of Health*

James Miller

*New York City Department of Health*

Daniel O'Leary

*Centers for Disease Control and Prevention*

*See next page for additional authors*

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**Authors**

Denis Nash, Farzad Mostashari, Annie Fine, James Miller, Daniel O'Leary, Kristy Murray, Ada Huang, Amy Rosenberg, Abby Greenberg, Margaret Sherman, Susan Wong, and Marcelle Layton

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## THE OUTBREAK OF WEST NILE VIRUS INFECTION IN THE NEW YORK CITY AREA IN 1999

DENIS NASH, PH.D., M.P.H., FARZAD MOSTASHARI, M.D., M.S.P.H., ANNIE FINE, M.D., JAMES MILLER, M.D., M.P.H., DANIEL O'LEARY, D.V.M., KRISTY MURRAY, D.V.M., ADA HUANG, M.D., AMY ROSENBERG, M.D., ABBY GREENBERG, M.D., MARGARET SHERMAN, R.N., SUSAN WONG, PH.D., AND MARCELLE LAYTON, M.D.,  
FOR THE 1999 WEST NILE OUTBREAK RESPONSE WORKING GROUP\*

### ABSTRACT

**Background** In late August 1999, an unusual cluster of cases of meningoencephalitis associated with muscle weakness was reported to the New York City Department of Health. The initial epidemiologic and environmental investigations suggested an arboviral cause.

**Methods** Active surveillance was implemented to identify patients hospitalized with viral encephalitis and meningitis. Cerebrospinal fluid, serum, and tissue specimens from patients with suspected cases underwent serologic and viral testing for evidence of arboviral infection.

**Results** Outbreak surveillance identified 59 patients who were hospitalized with West Nile virus infection in the New York City area during August and September of 1999. The median age of these patients was 71 years (range, 5 to 90). The overall attack rate of clinical West Nile virus infection was at least 6.5 cases per million population, and it increased sharply with age. Most of the patients (63 percent) had clinical signs of encephalitis; seven patients died (12 percent). Muscle weakness was documented in 27 percent of the patients and flaccid paralysis in 10 percent; in all of the latter, nerve conduction studies indicated an axonal polyneuropathy. An age of 75 years or older was an independent risk factor for death (relative risk adjusted for the presence or absence of diabetes mellitus, 8.5; 95 percent confidence interval, 1.2 to 59.1), as was the presence of diabetes mellitus (age-adjusted relative risk, 5.1; 95 percent confidence interval, 1.5 to 17.3).

**Conclusions** This outbreak of West Nile meningoencephalitis in the New York City metropolitan area represents the first time this virus has been detected in the Western Hemisphere. Given the subsequent rapid spread of the virus, physicians along the eastern seaboard of the United States should consider West Nile virus infection in the differential diagnosis of encephalitis and viral meningitis during the summer months, especially in older patients and in those with muscle weakness. (N Engl J Med 2001;344:1807-14.)

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IN late August 1999, a specialist in infectious diseases contacted the New York City Department of Health about two patients with encephalitis at a hospital in northern Queens. A preliminary epidemiologic investigation at the nearby hospitals identified six additional cases of encephalitis. These eight cases occurred among previously healthy persons 58 to 87 years of age<sup>1</sup> who presented with a febrile illness followed by changes in mental status. All but one had severe muscle weakness. Four had flaccid paralysis requiring ventilatory support, and three were thought to have atypical Guillain-Barré syndrome.<sup>2,3</sup> Hematologic and biochemical tests of patients' cerebrospinal fluid suggested viral infection as the cause.

The eight patients with encephalitis all lived in a 41.6 km<sup>2</sup> (16 mi<sup>2</sup>) area in northern Queens. Interviews with the patients' families revealed no obvious common exposures. However, all patients had reportedly engaged in outdoor activities (e.g., gardening) around their homes in the evenings. An environmental investigation revealed the presence of culex mosquito breeding sites and larvae in many of the patients' yards and neighborhoods. On the basis of these

From the Communicable Disease Program, New York City Department of Health, New York (D.N., F.M., A.F., J.M., M.L.); the Epidemic Intelligence Service, Epidemiology Program Office, Division of Applied Public Health Training, State Branch (D.N., F.M.), and the Division of Bioterrorism Preparedness (K.M.), Centers for Disease Control and Prevention, Atlanta; the Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colo. (D.O.); the Westchester County Department of Health, New Rochelle, N.Y. (A.H., A.R.); the Nassau County Department of Health, Mineola, N.Y. (A.G., M.S.); and the New York State Department of Health, Albany (S.W.). Address reprint requests to Dr. Nash at the New York City Department of Health, HIV/AIDS Surveillance Program, 346 Broadway, Rm. 706, New York, NY 10013, or at dnash@health.nyc.gov.

Other authors were Grant L. Campbell, M.D., Ph.D., John T. Roehrig, Ph.D., and Duane J. Gubler, Sc.D. (Centers for Disease Control and Prevention, Fort Collins, Colo.); Wun-Ju Shieh, M.D., M.P.H., Ph.D., and Sherif Zaki, M.D., Ph.D. (Centers for Disease Control and Prevention, Atlanta); and Perry Smith, M.D. (New York State Department of Health, Albany).

\*The other members of the Working Group are listed in the Appendix.

findings, an arthropod-borne virus (arbovirus) was suspected as the cause of this cluster of cases of encephalitis.

When specimens were tested for arboviruses that are common in eastern North America, specimens from all eight patients had positive results on enzyme-linked immunosorbent assay (ELISA) for IgM antibody against St. Louis encephalitis virus, a common flavivirus that is enzootic in North America. The laboratory, clinical, and epidemiologic data indicated that the outbreak in New York City was most consistent with an outbreak of St. Louis encephalitis, and mosquito-control measures were instituted rapidly.<sup>1,4,5</sup>

Before and during the investigation of the encephalitis cluster, an epizootic disease associated with the death of substantial numbers of birds was occurring in the New York City area. These deaths were initially assumed to be unrelated to the outbreak in humans, because St. Louis encephalitis virus does not normally kill its avian reservoir hosts. An independent investigation of dead birds by veterinarians and wildlife specialists in September found pathological evidence of multiorgan involvement, including encephalitis, but specimens obtained at necropsy tested negative for common avian pathogens. Four weeks after the recognition of the outbreak in humans, a flavivirus, later identified as West Nile virus, was isolated from tissue specimens obtained from American crows in Westchester County and a Chilean flamingo in a nearby zoo<sup>6</sup> and was subsequently determined to be the common cause of the encephalitis outbreaks among both birds and humans.<sup>7,8</sup>

West Nile virus belongs to the Japanese encephalitis serogroup of flaviviruses that includes the St. Louis encephalitis, Kunjin, and Murray Valley encephalitis viruses, each of which is antigenically closely related to West Nile virus.<sup>9</sup> This report summarizes the findings of an epidemiologic investigation of the 1999 outbreak of West Nile virus disease in the New York City metropolitan area, which was the first documented occurrence of this virus in the Western Hemisphere.

## METHODS

### Surveillance Methods

Hospitals in New York City and neighboring counties were asked to report any suspected cases of viral infections of the central nervous system. Counties were asked, through weekly broadcast-facsimile alerts, to report all suspected cases. Patients with suspected cases were defined as those who were hospitalized on or after August 1, 1999, with a presumptive diagnosis of viral encephalitis (indicated by fever, altered mental status or other cortical signs, and abnormal findings on analysis of cerebrospinal fluid), aseptic meningitis (fever, meningeal signs, and abnormal findings on analysis of cerebrospinal fluid), or Guillain-Barré syndrome associated with fever. The abnormal findings in cerebrospinal fluid that were considered to be indicative of a viral infection were a protein concentration of at least 40 mg per deciliter or a white-cell count of at least 5 per cubic millimeter, a negative Gram's stain, and a negative bacterial culture.

In addition, active surveillance to identify patients who met the clinical criteria included weekly telephone inquiries to adult and pediatric clinical staff in up to nine specialty areas (e.g., infectious disease and neurology) at each hospital. Specimens of cerebrospinal fluid and serum were requested from patients who met the clinical criteria. A serum specimen obtained during the convalescent phase was requested if an initial specimen, which had been obtained within eight days after the onset of illness from any patient who met the clinical criteria, tested negative for antibodies against West Nile virus. For patients who had been discharged, serum samples from the convalescent phase were obtained during home visits.

### Laboratory Methods

Samples of serum and cerebrospinal fluid were tested with an IgM-capture ELISA and an indirect IgG ELISA for antibodies against the West Nile and St. Louis encephalitis viruses.<sup>10,11</sup> In addition, specimens of cerebrospinal fluid and tissue were tested by standard reverse-transcriptase polymerase chain reaction (RT-PCR) and real-time RT-PCR (TaqMan, PE Applied Biosystems, Foster City, Calif.)<sup>12</sup>; we also attempted to isolate virus from clinical specimens and conducted immunohistochemical analysis of them.<sup>13</sup>

### Definitions

The finding of any of the following was considered to represent laboratory evidence of recent infection with West Nile virus<sup>14</sup>: the isolation by culture of West Nile virus or the amplification by RT-PCR of West Nile virus RNA from human-tissue specimens; the demonstration of IgM antibodies against West Nile virus in cerebrospinal fluid by IgM-capture ELISA; an increase by more than a factor of four in the titer of neutralizing antibody specific for West Nile virus, as measured by the plaque-reduction neutralization assay in paired serum or cerebrospinal fluid samples obtained at appropriate times; or the detection in a single serum specimen of both IgM and IgG antibodies against West Nile virus on ELISA (and, for IgG, confirmed by a plaque-reduction neutralization assay). Patients with a single serum sample in which only IgM antibodies to West Nile virus were detected were classified as having a probable recent infection. Patients with a single serum specimen in which only IgG antibodies to West Nile virus were detected were also classified as having a probable recent West Nile virus infection acquired in the New York area if the antibodies were confirmed by plaque-reduction neutralization assay to be specific to West Nile virus and if the patient had no history of recent travel to an area where the virus was endemic.

Patients were classified as having hypertension, diabetes mellitus, coronary artery disease, alcoholism, or immunosuppression if a history of these conditions was noted in their medical record. Patients were also classified as having a history of immunosuppression if any of the following conditions were present: cancer, human immunodeficiency virus (HIV) infection, treatment with corticosteroids, or alcoholism. Patients with encephalitis were classified as having muscle weakness if neurologic examinations revealed flaccid paralysis, decreased strength, or hyporeflexia.

### Collection and Analysis of Epidemiologic and Clinical Data

Interviews were conducted with the patients or their proxies to ascertain the epidemiologic and demographic risk factors for arboviral infection. The medical records of all hospitalized patients with laboratory evidence of West Nile virus infection were reviewed with the use of a standardized form for abstracting information from medical charts. If a sign or symptom was not specifically noted in the medical record, it was considered to be absent.

The attack rates of West Nile virus disease per million population, stratified according to age and borough or county, were calculated with the use of 1990 U.S. Census data.<sup>15</sup> The crude relative risks and the relative risks adjusted according to the Mantel-Haenszel method were calculated to examine the associations of age, history of immunosuppression, and the presence or absence of coronary artery disease, diabetes, or hypertension with the severity of disease and mortality. Statistical analyses were performed with the use of SAS software for Windows and Macintosh.<sup>16,17</sup>

## RESULTS

### Arboviral Outbreak Surveillance

Reports on 719 patients with clinical syndromes of meningitis and encephalitis were received by the health departments in New York City (589 patients), Nassau County (70 patients), and Westchester County (60 patients), including 71 patients younger than 18 years old. In 62 of these 719 patients (9 percent), there was laboratory evidence of recent West Nile virus infection. Three of these patients had a mild illness, with symptoms that consisted of only fever and headache, which did not result in hospitalization. This report focuses on the 59 hospitalized patients with West Nile virus infection.

Cerebrospinal fluid specimens were available from 32 of the 59 patients: 30 of these (94 percent) were positive for IgM antibodies against West Nile virus. Serum specimens were also obtained from 29 of the 30 patients with IgM-positive cerebrospinal fluid specimens; all of these serum specimens were IgM-positive. The two patients with IgM-negative cerebrospinal fluid specimens had IgM-positive serum specimens. Of the 19 cerebrospinal fluid specimens that were obtained from patients within eight days after the onset of illness, 17 (89 percent) were positive for IgM antibodies against West Nile virus.

For 27 of the patients, no cerebrospinal fluid specimen was available; viral infection in these patients was confirmed on the basis of the finding of IgM antibodies in the serum. The serologic diagnosis in patients from whom no cerebrospinal fluid specimens had been obtained was confirmed by plaque-reduction neutralization assay. No cases were positive by isolation of virus from brain tissue or cerebrospinal fluid specimens. Among the specimens with sufficient quantity to allow for real-time RT-PCR testing, 16 of 28 cerebrospinal fluid specimens (57 percent) and 4 of 28 serum specimens (14 percent) were positive for West Nile virus genome. In all the patients who died in whom autopsies were performed, the brain tissue was positive for West Nile virus antigen on immunohistochemical analysis, and positive for West Nile virus genome on real-time RT-PCR.

### Epidemiologic Characteristics

The median age of the hospitalized patients was 71 years (range, 5 to 90), and most of them (88 percent) were at least 50 years old (Table 1). The overall attack rate of clinical West Nile virus infection was at least 6.5 cases per million population. The most cases (32) and the highest rate of hospitalization (16.4 per million population) occurred in the New York City borough of Queens. The onset of illness ranged from August 2 through September 24, 1999 (Fig. 1), with the peak of the outbreak occurring in mid-to-late August. The attack rate of clinical infection increased sharply with age, and the attack rate in per-

sons 50 years old or older was almost 20 times as high as that in persons younger than 50 years old (rate ratio, 19.6; 95 percent confidence interval, 17.9 to 21.6). Of the 59 hospitalized patients, 44 resided in New York City, 14 lived in two adjacent counties of New York state, and 1 was a tourist from Canada who arrived in New York City on September 1, departed on September 5 after visiting Queens, and became ill on the airplane (which suggests an incubation period of less than five days).

Interviews were completed with 56 of the 59 patients (95 percent). Only three (5 percent) reported having traveled outside the United States (to Aruba, St. Martin, and Canada) during the month before the onset of illness. Only 18 patients (32 percent) recalled being bitten by mosquitoes during the month before the onset of illness.

### Clinical Characteristics

Of the 59 patients, 37 (63 percent) had encephalitis, 17 (29 percent) had meningitis without encephalitis, and 5 (8 percent) had illness characterized by fever and headache (Table 2). The mean duration of symptoms before hospitalization was 5.3 days. Nearly all the patients presented with fever (90 percent; temperature range, 36.5°C to 40.2°C); other symptoms included weakness (56 percent), nausea (53 percent), vomiting (51 percent), headache (47 percent), altered mental status (46 percent), and stiff neck (19 percent). A rash was reported in 11 patients (19 percent) and was described as an erythematous macular, papular, or morbilliform eruption involving some combination of the neck, the trunk, and the arms and legs.

Underlying chronic medical conditions included hypertension (in 42 percent of the patients), diabetes mellitus (in 20 percent), coronary artery disease (in 20 percent), and a history of known immunosuppression (in 14 percent) (Table 2). The immunosuppression was caused by cancer (in five patients), HIV infection<sup>18</sup> (in one patient), the use of prednisone for asthma (in one patient), and alcoholism (in one patient).

Complete blood counts on admission showed no substantial abnormalities (Table 3). However, the cerebrospinal fluid findings were typical of a viral infection: pleocytosis (mean cerebrospinal fluid white-cell count, 38.2 per cubic millimeter; range, 0 to 525) and an elevated protein concentration (mean, 104.2 mg per deciliter; range, 38 to 899).

Computed tomographic scans of the brain were obtained for 43 patients (73 percent); they showed no evidence of acute disease (Table 4). Magnetic resonance imaging of the brain was performed in 16 patients (27 percent); in 5 of these patients (31 percent), the scans showed an enhancement of the leptomeninges, the periventricular areas, or both.

Muscle involvement was documented by neurologic examination as decreased muscle strength (in 27

**TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF 59 PATIENTS HOSPITALIZED WITH WEST NILE VIRUS INFECTION IN THE NEW YORK CITY AREA IN 1999 AND POPULATION ATTACK RATES.**

CHARACTERISTIC	NO. OF PATIENTS (%)	POPULATION AT RISK*	RATE OF INFECTION PER MILLION POPULATION	RATE RATIO (95% CI)†
Age (yr)				
0–19‡	2 (3)	2,324,081	0.9	1.0
20–29	1 (2)	1,553,981	0.6	0.8 (0.2–3.7)
30–39	3 (5)	1,549,111	1.9	2.3 (1.1–4.6)
40–49	1 (2)	1,177,190	0.8	1.0 (0.2–4.9)
50–59	9 (15)	867,331	10.4	12.1 (9.1–15.9)
60–69	13 (22)	814,838	16.0	18.5 (15.2–22.6)
70–79	18 (31)	534,785	33.7	39.1 (33.8–45.3)
≥80	12 (20)	281,054	42.7	49.6 (40.1–61.5)
Age category (yr)				
≥50	52 (88)	2,498,008	20.8	19.6 (17.9–21.6)
<50‡	7 (12)	6,604,363	1.1	1.0
Sex				
Male	31 (53)	4,289,988	7.2	1.2 (1.0–1.6)
Female‡	28 (47)	4,812,383	5.8	1.0
Race				
White	41 (69)	5,983,901	6.9	2.4 (1.3–4.4)
Nonwhite‡	9 (15)	3,118,470	2.9	1.0
Unknown	9 (15)	—	—	—
Borough or county of residence				
New York City				
Brooklyn (Kings)‡	3 (5)	2,300,664	1.3	1.0
Bronx	9 (15)	1,203,789	7.5	5.7 (4.1–8.0)
Manhattan	1 (2)	1,487,536	0.7	0.5 (0.1–2.8)
Queens	32 (54)§	1,951,599	16.4	12.6 (11.4–13.9)
Staten Island (Richmond)	0	379,999	0.0	—
New York State				
Nassau	6 (10)	1,287,348	4.7	3.6 (2.3–5.7)
Westchester	8 (14)	874,866	9.1	7.0 (4.9–10.1)

\*Population figures are from the 1990 U.S. Census.

†CI denotes confidence interval.

‡This group served as the reference population.

§This group includes a Canadian tourist who became ill after visiting relatives in Queens.

percent of patients) and hyporeflexia (in 32 percent) and was more common among the patients with encephalitis. Diffuse, flaccid paralysis occurred in 10 percent of the patients, with no discernible ascending or descending pattern of progression. Abnormal findings consistent with an axonal polyneuropathy were noted in 8 of the 10 patients who underwent electrophysiologic testing, with decreased nerve conduction velocity of motor or sensory nerves or both and diminished compound muscle action potentials and fibrillation potentials on electromyography.

Among the 589 patients with suspected West Nile virus infection reported in New York City, those with encephalitis accompanied by muscle weakness were more likely to be seropositive for West Nile virus (27 percent) than were patients with encephalitis alone (14 percent) or aseptic meningitis (6 percent) ( $P$  for trend  $<0.001$ ).

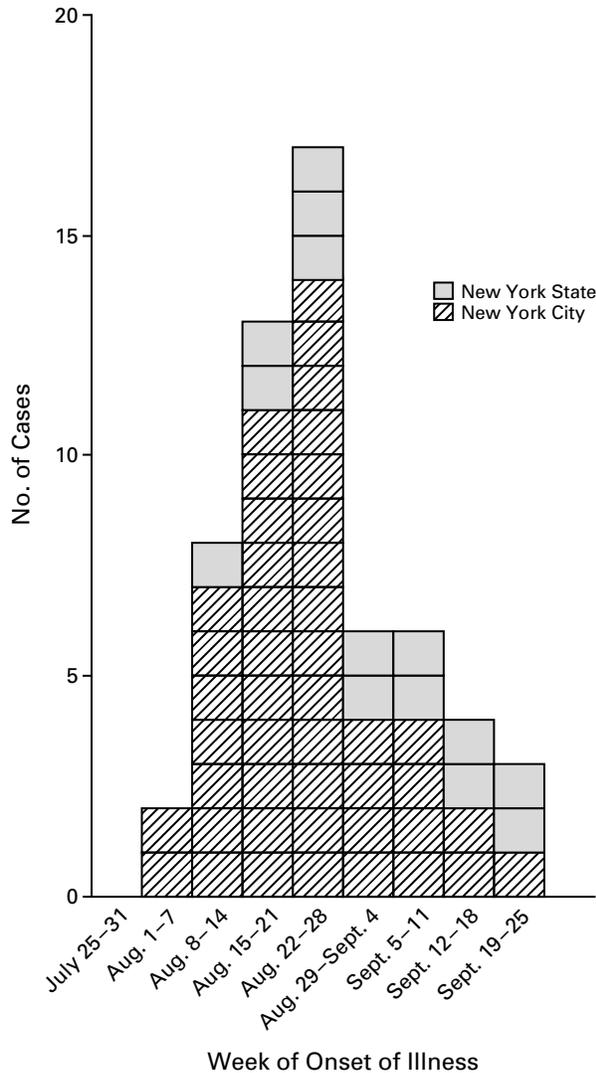
#### Factors Predictive of Disease Severity and Prognosis

The analyses of potential risk factors for severe disease (defined as encephalitis with muscle weakness)

and death are shown in Table 5. Only an age of 75 years or older was associated with a significantly higher likelihood of having encephalitis with muscle weakness (relative risk, 2.7; 95 percent confidence interval, 1.3 to 5.8). Of the 59 patients, 7 died, for an overall case fatality rate of 12 percent. Among the patients with encephalitis who also had muscle weakness, the case fatality rate was 30 percent, with six of the seven deaths occurring in patients with encephalitis and muscle weakness. An age of 75 years or older was the factor most strongly associated with death (relative risk adjusted for the presence or absence of diabetes mellitus, 8.5; 95 percent confidence interval, 1.2 to 59.1). The presence of diabetes mellitus was also significantly associated with death, even after adjustment for age (age-adjusted relative risk, 5.1; 95 percent confidence interval, 1.5 to 17.3).

#### Pathological Findings

Autopsy reports on the four patients from New York City who died, as well as immunohistochemical analysis of cortical tissue, showed only minimal evi-



**Figure 1.** Numbers of Patients Hospitalized with West Nile Virus Infection (Epidemic Curve) in the New York City Metropolitan Area in 1999.

Hatched boxes represent patients who resided in New York City, and light gray boxes represent patients who resided in other parts of New York State.

dence of viral inflammation in brain tissue.<sup>13</sup> Evidence of West Nile virus infection was more likely to be found in the brain stem than in other sites in the brain or in extraneural tissue. In the most severe case, there was evidence of scattered microglial nodules; perivascular and perineuronal inflammation, primarily confined to the medulla and the cranial-nerve roots, was also present.<sup>19</sup> One patient was found on postmortem examination to have hemorrhagic pancreatitis. Autopsy did not reveal evidence of hepatitis or myocarditis.

**TABLE 2.** CLINICAL CHARACTERISTICS OF 59 PATIENTS HOSPITALIZED WITH WEST NILE VIRUS INFECTION IN THE NEW YORK CITY AREA IN 1999.

CHARACTERISTIC	No. OF PATIENTS (%)
<b>Syndromes</b>	
Encephalitis	
With weakness	20 (34)
Without weakness	17 (29)
Aseptic meningitis without encephalitis	17 (29)
Fever and headache	5 (8)
<b>Signs and symptoms</b>	
Fever (temperature >37.8°C)	53 (90)
Weakness	33 (56)
Nausea	31 (53)
Vomiting	30 (51)
Headache	28 (47)
Altered mental status	27 (46)
Diarrhea	16 (27)
Rash	11 (19)
Cough	11 (19)
Stiff neck	11 (19)
Myalgia	10 (17)
Arthralgia	9 (15)
Photophobia	8 (14)
Tremor	7 (12)
Slurred speech	5 (8)
Abdominal pain	4 (7)
Focal sensory change	4 (7)
Pharyngitis	3 (5)
Conjunctivitis	2 (3)
Seizures	2 (3)
Lymphadenopathy	1 (2)
<b>Medical history</b>	
Hypertension	25 (42)
Diabetes	12 (20)
Coronary artery disease	12 (20)
Known immunosuppression	8 (14)
Dementia	3 (5)
Head trauma	2 (3)

**TABLE 3.** SELECTED LABORATORY RESULTS FOR 59 PATIENTS HOSPITALIZED WITH WEST NILE VIRUS INFECTION IN THE NEW YORK CITY AREA IN 1999.

VARIABLE	MEAN ±SD	RANGE	NORMAL RANGE
<b>Blood</b>			
White-cell count ( $\times 10^3/\text{mm}^3$ )	10.4±4.9	2.3-30.8	3.2-9.8
Hemoglobin (g/dl)	13.5±1.7	9.0-16.7	11.5-18.0
Hematocrit (%)	39.1±6.0	10.2-50.2	33.0-49.0
Lymphocytes (%)	14.1±7.3	3.0-38.0	>25.0
<b>Cerebrospinal fluid</b>			
Interval between onset and collection (days)	9.3±7.2	0-24	—
Protein (mg/dl)	104.2±117.2	38.0-899.0	15.0-50.0
White-cell count (per $\text{mm}^3$ )	38.2±11.6	0-525	0-10
Lymphocytes (%)	47.4±29.0	4.0-92.0	63.0-99.0
Glucose (mg/dl)	79.8±20.9	46.0-143.0	40.0-80.0

**TABLE 4. HOSPITAL COURSE IN 59 PATIENTS WITH WEST NILE VIRUS INFECTION IN THE NEW YORK CITY AREA IN 1999, ACCORDING TO CLINICAL PRESENTATION.\***

VARIABLE	ALL PATIENTS (N=59)	PATIENTS WITH ENCEPHALITIS (N=37)	PATIENTS WITH MENINGITIS OR OTHER SYMPTOMS (N=22)
	no./total no. (%)		
CT scanning results			
Normal	27/43 (63)	16/31 (52)	11/12 (92)
Atrophy or ischemic changes	16/43 (37)	15/31 (48)	1/12 (8)
Evidence of acute disease	0/43	0/31	0/12
MRI results			
Normal	5/16 (31)	5/13 (38)	0/3
Atrophy or ischemic changes	6/16 (38)	4/13 (31)	2/3 (67)
Meningeal enhancement	5/16 (31)	4/13 (31)	1/3 (33)
Abnormal cranial nerve function	13/59 (22)	11/37 (30)	2/22 (9)
Motor examination findings			
Abnormal strength	16/59 (27)	12/37 (32)	4/22 (18)
Flaccid paralysis	6/59 (10)	4/37 (11)	2/22 (9)
Abnormal deep tendon reflexes	23/59 (39)	16/37 (43)	7/22 (32)
Hyporeflexia	19/23 (83)	15/16 (94)	4/7 (57)
Hyperreflexia	4/23 (17)	1/16 (6)	3/7 (43)
Electromyography and nerve conduction study results			
Axonal neuropathy	8/10 (80)	5/6 (83)	3/4 (75)
Admitted to intensive care unit	19/59 (32)	16/37 (43)	3/22 (14)
Respiratory symptoms			
Required oxygen	19/59 (32)	15/37 (41)	4/22 (18)
Required mechanical ventilation	10/59 (17)	9/37 (24)	1/22 (5)
Treatments			
Plasmapheresis	3/59 (5)	2/37 (5)	1/22 (5)
Intravenous immune globulin	1/59 (2)	1/37 (3)	0/22
Antibiotics	51/59 (86)	36/37 (97)	15/22 (68)
Acyclovir	24/59 (41)	21/37 (57)	3/22 (14)
days			
Length of hospitalization			
Mean	14.8	17.9	12.4
Range	0–82	0–82	3–56

\*CT denotes computed tomographic, and MRI magnetic resonance imaging. The denominators for CT scanning results, MRI results, and electromyography and nerve conduction study results represent the numbers of patients who underwent those tests. Hyporeflexia and hyperreflexia are subcategories of abnormal deep-tendon reflexes.

## DISCUSSION

West Nile virus is enzootic in Africa, Europe, and Asia. Its typical reservoirs include a wide variety of wild and domestic birds, and the vectors are mosquitoes of the culex species.<sup>20</sup> Most West Nile virus infections in humans are subclinical, with overt disease estimated to occur in approximately 1 of every 100 infections.<sup>21</sup> The incubation period ranges from 3 to 15 days.<sup>22</sup> The resulting illness varies from mild illness (with fever, petechial rash, and headache) to meningoencephalitis,<sup>9</sup> and the likelihood that severe neurologic illness will develop increases with age.<sup>23</sup> Underlying medical conditions (e.g., hypertension) may facilitate the passage of neurotropic flaviviruses across the blood–brain barrier and may predispose

infected persons to neurologic complications.<sup>24–27</sup> In previous outbreaks, the case fatality rate among clinical cases ranged from 4 percent to 13 percent and was highest among elderly persons.<sup>20</sup>

This outbreak represents the first recognized occurrence of West Nile virus in the Western Hemisphere. In areas where it is endemic, West Nile virus usually causes outbreaks of milder febrile illness.<sup>9,28,29</sup> The 1999 outbreak in the New York City area followed a pattern more characteristic of recent outbreaks of encephalitis in areas where the virus is not endemic and where the level of immunity of the population to West Nile virus is lower (e.g., Romania and Russia); in these outbreaks, recognized illness was characterized by severe neurologic disease that affected primarily older adults.<sup>20,30–34</sup> Genetic analysis indicated that the strain of West Nile virus responsible for this outbreak was similar to strains that have caused outbreaks of encephalitis in northern Europe and was nearly identical to a strain that was circulating in Israel in 1998.<sup>7</sup>

In our study, older age was associated with a substantially higher risk of more severe neurologic disease, and both age and the presence of diabetes mellitus were significant risk factors for death. Decreasing immunity is a consequence of aging as well as a complication of diabetes mellitus, and both factors can increase the host's susceptibility to infections.<sup>35–38</sup> The relation we found between diabetes and the fatal outcome of West Nile virus infections requires further study.

The outbreak in the New York City area was unusual because profound muscle weakness was a common complication in the patients with encephalitis. This unusual finding of profound muscle weakness prompted the initial report of a cluster of cases of encephalitis to the New York City Department of Health and ultimately led to the recognition of a regional epidemic and epizootic of West Nile virus infection.

Most of the mosquito pools that tested positive for West Nile virus by RT-PCR and real-time RT-PCR and from which virus could be isolated contained both *Culex pipiens* and *C. restuans* mosquitoes<sup>39</sup>; such pools were found in all the areas where cases occurred among humans except Manhattan. However, West Nile virus infection in birds was much more geographically widespread than indicated by the distribution of the human cases and positive mosquito pools.<sup>40</sup> Infected dead crows were found in areas where no human cases were detected, including the lower Hudson Valley, eastern Long Island, Connecticut, New Jersey, and Baltimore. Serologic studies conducted in live wild birds in September 1999 demonstrated a direct geographic correlation between the rates of West Nile meningoencephalitis in humans and the prevalence of antibody against West Nile virus in birds that were tested in Queens (avian seroprevalence, 50 percent), Westchester County (11 per-

**TABLE 5.** RELATIVE RISKS OF MUSCLE WEAKNESS, ENCEPHALITIS WITH MUSCLE WEAKNESS, AND DEATH ASSOCIATED WITH VARIOUS PROGNOSTIC FACTORS IN 59 PATIENTS HOSPITALIZED WITH WEST NILE VIRUS INFECTION.\*

FACTOR	RELATIVE RISK (95% CONFIDENCE INTERVAL)		
	MUSCLE WEAKNESS	ENCEPHALITIS WITH MUSCLE WEAKNESS	DEATH
Known history of immunosuppression	1.6 (1.0–2.6)	1.4 (0.4–11.1)	2.1 (0.5–8.1)
Coronary artery disease	1.2 (0.5–2.6)	1.4 (0.7–2.6)	2.0 (0.6–6.6)
Hypertension	1.6 (0.9–2.5)	1.2 (0.6–2.3)	2.1 (0.3–12.2)
Diabetes mellitus	1.0 (0.5–1.9)	1.3 (0.6–2.7)	5.1 (1.5–17.3)
Age $\geq$ 75 yr			
Unadjusted	1.4 (0.8–2.3)	2.7 (1.3–5.8)	8.8 (1.1–68.1)
Adjusted for presence or absence of diabetes mellitus	1.4 (0.8–2.3)	2.4 (1.3–4.6)	8.5 (1.2–59.1)
Muscle weakness	—	—	4.6 (0.7–31.6)
Virus detected by PCR in cerebrospinal fluid†	0.7 (0.3–1.8)	2.3 (0.6–9.0)	1.0 (0.2–5.0)

\*Muscle weakness was defined by evidence of flaccid paralysis, abnormal strength, or hyporeflexia on neurologic examination. The relative risks associated with a history of immunosuppression and with the presence of coronary artery disease, hypertension, and diabetes mellitus have been adjusted for age. PCR denotes polymerase chain reaction.

†Specimens of cerebrospinal fluid from 25 patients were available for testing by real-time reverse-transcriptase PCR.

cent), Nassau County (7 percent), Brooklyn (5 percent), and Staten Island (2 percent).<sup>41</sup>

Recent data suggest that West Nile virus has become enzootic in the northeastern United States. In the winter after the 1999 outbreak, West Nile virus was isolated from overwintering culex mosquitoes collected in Queens.<sup>42,43</sup> Surveillance of birds and mosquitoes during 2000 showed extensive epizootic activity centered in the New York City metropolitan area and extending throughout much of the eastern seaboard, with reports of dead birds that tested positive for West Nile virus from southern Vermont and New Hampshire down to North Carolina. However, a human outbreak of meningoencephalitis during the late summer and early fall of 2000 was limited to New York City (14 cases) and New Jersey (5 cases).<sup>43,44</sup>

West Nile virus will most likely spread beyond the northeast and may cause sporadic cases or outbreaks of West Nile virus disease in other regions of the United States. During the mosquito season (from late spring until the first sustained frost), physicians — especially those along the eastern seaboard — should consider West Nile virus disease in the differential diagnosis of hospitalized patients with encephalitis (especially when it is accompanied by muscle weakness) and viral meningitis (especially in adults).<sup>43</sup> Serologic testing remains the most reliable diagnostic method for West Nile virus infection in humans. Suspected cases should be reported to local public health departments, and appropriate laboratory specimens, including cerebrospinal fluid and serum samples ob-

tained during the acute and convalescent phases, as well as autopsy specimens, should be submitted to state public health laboratories to be tested for West Nile virus. Treatment is supportive.

The 1999 West Nile virus disease outbreak again proves that, with the growing volume of international travel and commerce, exotic pathogens can move between continents with increasing ease. Physicians, veterinarians, laboratory workers, and public health officials must remain vigilant for unexpected outbreaks of imported diseases in the future.

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## APPENDIX

In addition to the authors, the members of the West Nile Outbreak Response working group were as follows: N. Cohen, D. Cimini, A. Ramon, I. Poshni, B. Maldin, A. Inglesby, A. Labowitz, K. Bornschlegel, E. Samoff, M.C. Vargas, R. Bhalla, E. Lee, G. Sacajiu, D. Malebranche, A. Sharma, M. Eisenberg, T. Chernesky, M. Volk, and D. Brown, New York

City Department of Health, New York; H.N. Adel, Westchester County Health Department, New Rochelle, N.Y.; K. Gaffney, G. Terillion, B. Smith, and R. Porter, Nassau County Department of Health and Nassau County Department of Public Works, Mineola, N.Y.; A. Novello, D. White, D. Morse, B. Wallace, G. Brady, L. Grady, and C. Huang, New York State Department of Health, Albany; R. Nasci, N. Komar, D. Martin, R. Lanciotti, A.J. Johnson, J. Velez, C.B. Cropp, N. Karabatsos, and A. Kerst, Centers for Disease Control and Prevention, Fort Collins, Colo.; J. Guarner, Centers for Disease Control and Prevention, Atlanta; B. Fitzsimmons, Department of Neurology, Columbia University School of Medicine, New York; H. Artsob, National Microbiology Laboratory, Health Canada, Winnipeg, Man.; D. Asnis, Flushing Hospital, Queens, N.Y.; and J. Rahal, New York Hospital, Queens, N.Y.

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