Lack of Evidence of Increased West Nile Virus Disease Severity in the United States in 2012

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Abstract. In the United States, West Nile virus (WNV) causes annual seasonal outbreaks that fluctuate in size and scope. There was a large multistate outbreak of WNV in 2012, with more human disease cases reported nationally than any year since 2003. We evaluated national surveillance data to determine if the higher number of WNV cases reported in 2012 was associated with changes in the epidemiology or severity of disease compared with 2004–2011. Despite an increased incidence of neuroinvasive disease in 2012, national surveillance data showed no evidence of changes in epidemiology or increased disease severity compared with the previous 8 years.

INTRODUCTION

West Nile virus (WNV), a mosquito-borne flavivirus, was first detected in the Western hemisphere in 1999; by 2005, WNV activity had been detected in all 48 contiguous states. WNV is the leading cause of domestically acquired arboviral disease in the United States, with more than 13,000 cases of neuroinvasive disease and more than 1,200 deaths reported from 1999 to 2011. WNV causes annual seasonal outbreaks that fluctuate in size and scope. National incidence of WNV neuroinvasive disease peaked in 2002 and 2003 during the initial spread of the virus westward. From 2004 through 2011, sporadic cases and smaller outbreaks continued to occur, but national incidence generally declined. In 2012, there was a large multistate outbreak of WNV, with the highest number of cases reported since 2003. We evaluated national surveillance data to describe the 2012 WNV outbreak and determine if the higher number of WNV cases reported in 2012 was associated with changes in the epidemiology or severity of disease.

METHODS

Data collection. WNV disease is a nationally notifiable condition. State and metropolitan health departments report cases to the Centers for Disease Control and Prevention (CDC) through the ArboNET surveillance system. Using standard definitions that include clinical and laboratory criteria, human disease cases are classified as neuroinvasive disease or non-neuroinvasive disease. Because of the considerable morbidity associated with neuroinvasive disease cases, detection and reporting is assumed to be more consistent and complete than for non-neuroinvasive disease cases. WNV presumptive viremic donors (PVDs) are identified through universal screening of the blood supply; case definitions and reporting practices for PVDs vary by jurisdiction and blood services agency. Some PVDs develop clinical illness after donation and are classified as disease cases if they meet the clinical and laboratory criteria in the national case definition.

Data routinely collected in ArboNET for human disease cases and PVDs include patient demographics, county and state of residence, date of illness onset or blood donation, case status (i.e., confirmed, probable, suspect, or not a case), clinical syndrome (e.g., encephalitis, meningitis, acute flaccid paralysis, uncomplicated fever), and outcome (hospitalization or fatality). Cases reported as encephalitis, meningitis, or acute flaccid paralysis are classified as neuroinvasive disease cases; others are considered non-neuroinvasive disease cases. Acute flaccid paralysis can occur with or without encephalitis or meningitis; for this analysis, cases reported as acute flaccid paralysis (with or without another clinical syndrome) were classified as acute flaccid paralysis only and not included in the other clinical syndrome categories.

Data analysis. Simple proportions were generated to describe demographic characteristics, frequencies of clinical classifications, and outcomes for confirmed and probable WNV disease cases reported to CDC with illness onset in 2012. Because of variability in reporting of non-neuroinvasive disease cases, incidence calculations were limited to neuroinvasive disease cases. Incidence rates per 100,000 population and rates by state, county, age group, and sex were calculated using U.S. Census Bureau population estimates for July 1 of 2012. Simple proportions were also calculated to describe demographic characteristics of PVDs reported to CDC with blood donation dates in 2012.

To determine if disease in 2012 was more severe than in recent years, we calculated incidence, distribution of age, sex, and clinical syndrome, hospitalization rates, and case-fatality ratios for WNV neuroinvasive disease cases reported in 2004–2011 and 2012. Hospitalization rates and case-fatality ratios were also calculated for WNV non-neuroinvasive disease cases reported from 2004–2011 and for 2012. Although WNV has been a nationally notifiable disease since 2001, data before 2004 were not included because of changes to national surveillance in that year, including a new national case definition and first collection of data regarding hospitalization and occurrence of acute flaccid paralysis. For 2004–2011, incidence rates per 100,000 population were calculated using U.S. Census Bureau population estimates for July 1 for each year and the average annual incidence was calculated from the annual rates. For WNV PVDs reported in 2004–2011 and 2012, we calculated incidence, age and sex distribution, and the percentage meeting the case definition for WNV disease. To determine if the 2012 values were different from what would be expected based on previous years, we assumed that the 2004–2011 data were a (possibly correlated) sequence of random variables and tested the data for distributional assumptions of normality and autocorrelation. We calculated 95% prediction intervals (PI) for 2012 based on distributional...
characteristics and values of the 2004–2011 data and compared them to the observed 2012 data.

RESULTS

A total of 5,674 WNV disease cases, including 2,873 (51%) neuroinvasive disease cases were reported in 2012. WNV disease cases peaked in mid-August with 5,199 (92%) cases having illness onset during July through September. Although the epidemic peak occurred in August for all regions, southern states reported a larger proportion of cases with illness onset before August (34%) than central (12%) and northern states (16%) (Figure 1). Cases were reported from all 48 contiguous states, the District of Columbia, and Puerto Rico; none were reported from Alaska or Hawaii. Although 976 (31%) of 3,143 U.S. counties reported at least one disease case, 1,427 (25%) cases were reported from just seven counties: Dallas, Texas (N = 396); Tarrant, Texas (259); Denton, Texas (183); Cook, Illinois (174); Los Angeles, California (163); Travis, Texas (151); and Harris, Texas (101). A third of all disease cases were Texas residents.

Demographic characteristics and clinical outcomes. Among the 2,801 non-neuroinvasive WNV disease cases, the average age was 51 years (interquartile range (IQR): 39–64 years) and 53% were male. A total of 805 (29%) patients with non-neuroinvasive disease were hospitalized and 16 (1%) died. Of the 16 patients who died, 13 (81%) were ≥75 years of age.

Among the 2,873 neuroinvasive disease cases, the average age was 57 years (IQR: 46–72 years) and 60% were male. Almost half of all cases occurred in persons aged ≥60 years. Most (93%) patients with neuroinvasive disease were hospitalized and 270 (9%) died. Hospitalization rates were above 85% in all age groups but were higher among patients aged ≥50 years (96%) than among those <50 years of age (88%). The case-fatality ratio increased with increasing age with 190 (23%) of 818 patients ≥70 years of age dying compared with 80 (4%) of 1,943 patients 20–69 years of age and 0 of 112 patients <20 years of age.

Of the 2,873 WNV neuroinvasive disease cases, 1,615 (56%) had encephalitis, 1,038 (36%) had meningitis, and 220 (8%) had acute flaccid paralysis (Table 1). Among the 220 patients with acute flaccid paralysis, 183 (83%) also had encephalitis or meningitis. Males accounted for about 60% of cases for each of the neuroinvasive disease syndromes. The average age of meningitis patients (49 years; IQR 36–62) was lower than that of encephalitis patients (62 years; IQR 52–75) or acute flaccid paralysis patients (61 years; IQR 50–72). Hospitalization rates were above 90% for all clinical syndromes. Case-fatality ratios were highest among cases classified as encephalitis (14%) or acute flaccid paralysis (10%); 2% of meningitis cases were fatal. Hospitalization rates and case-fatality ratios increased with increasing age for each syndrome.

![Figure 1](image-url)
Neuroinvasive disease incidence by location. Neuroinvasive disease cases were reported from 693 (22%) counties in 47 states, the District of Columbia, and Puerto Rico. Over 50% of all cases were reported from five states: Texas, California, Illinois, Louisiana, and Michigan; 29% were reported from Texas alone. No neuroinvasive disease cases were reported from Alaska, Hawaii, or Oregon. State-level incidence ranged from 0.06 (Washington) to 7.4 per 100,000 population (South Dakota). Seven states had incidence > 2 per 100,000 population: South Dakota (7.4), North Dakota (5.6), Mississippi (3.5), Louisiana (3.4), Texas (3.2), Oklahoma (2.7), and Nebraska (2.3). Counties with the highest incidences were clustered in West South Central and West North Central regions (Figure 2).

Neuroinvasive disease incidence by age and sex. The incidence of neuroinvasive disease increased with increasing age, ranging from 0.06 per 100,000 among persons aged <10 years to 2.87 among those ≥70 years of age. Similarly, the incidences of encephalitis and acute flaccid paralysis increased with increasing age (Figure 3). The incidence of meningitis increased with increasing age among persons aged <40 years but was stable among persons aged ≥40 years. Neuroinvasive disease incidence was higher among males (1.1 per 100,000 population) than among females (0.7), especially among persons aged ≥70 years, where the incidence in men was almost twice as high as that in women. Similar differences by sex were observed among the various neuroinvasive disease syndromes (i.e., encephalitis, meningitis, and acute flaccid paralysis).

PVDs. A total of 703 PVDs were reported to CDC in 2012. WNV PVDs had a similar seasonal trend as disease cases, with 91% having blood donation dates during July through September. The average age of PVDs was 47 years (IQR: 34–59 years) and 59% were male. Among the 703 PVDs, 11 (2%)
met the case definition for neuroinvasive disease and 87 (12%) met the case definition for non-neuroinvasive disease; these 98 patients were included in the disease case counts.

**Epidemiology and disease severity in 2012 compared with previous seasons.** The incidence of reported WNV neuroinvasive disease (0.92 cases per 100,000 population) was higher than expected based on data from 2004 to 2011 (average annual incidence 0.31; 95% PI 0.01–0.61) (Figure 4). The average age of cases was 57 years in both 2012 and 2004–2011 (95% PI: 55–59 years) and 60% were male during both time periods (95% PI: 55–64%). The distribution of clinical syndromes for neuroinvasive disease cases was similar in 2012 compared with 2004–2011 (encephalitis [56% in 2012 versus 58% for 2004–2011; 95% PI: 53–62%], meningitis [36% in both periods; 95% PI: 29–44%], and acute flaccid paralysis [8% in 2012 versus 6% for 2004–2011; 95% PI: 2–11%]).

The hospitalization rate for neuroinvasive disease cases was higher in 2012 (93%) than 2004–2011 (88%) but was within the expected 95% PI (75–100%) based on data from the previous 8 years and was similar to rates for each of the last 4 years (mean: 95%; range: 93–97%) (Figure 5). The case-fatality ratio was 9% in both 2012 and 2004–2011 (95% PI: 6–11%). The average age of fatal neuroinvasive disease patients was similar in 2012 (74 years) and 2004–2011 (mean: 73 years; 95% PI: 70–77 years). Similar to what was seen among neuroinvasive disease cases, the hospitalization rate for non-neuroinvasive disease cases was higher in 2012 (29%) than 2004–2011 (22%) but was within the expected

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**Figure 4.** Annual incidence of West Nile virus neuroinvasive disease, by year—United States, 2004–2012. *95% prediction interval for 2012 based on 2004–2011 data.

**Figure 5.** Hospitalization rates and case-fatality ratios for West Nile virus neuroinvasive disease, by year—United States, 2004–2012 *95% prediction interval for 2012 based on 2004–2011 data.
95% PI (12–37%) and was similar to the rates for the last 4 years (mean: 29%; range: 25–37%). The case-fatality ratio was similar in 2012 (0.6%) and 2004–2011 (0.5%; 95% PI: 0–1%). The average age of fatal non-neuroinvasive disease patients was similar in 2012 (80 years) and 2004–2011 (mean: 79 years; 95% PI: 69–88 years).

The incidence of reported WNV PVDs in 2012 (0.22 cases per 100,000 population) was higher than expected based on data from 2004–2011 (average annual incidence 0.08; 95% PI 0.001–0.16). The average age of WNV PVDs was similar in 2012 (47 years) and 2004–2011 (46 years; 95% PI: 43–50 years). Fifty-nine percent of PVDs were male in both time periods (95% PI: 52–66%). The percent of PVDs meeting the case definition for WNV disease in 2012 (14%) was lower than expected based on data from 2004–2011 (25%; 95% PI: 16–34%). The percent meeting the case definition for neuroinvasive disease in 2012 (2%) was similar to that for 2004–2011 (1%) and was within the expected 95% PI (1–8%).

**DISCUSSION**

There was a large outbreak of WNV in 2012, with more human disease cases reported nationally than any year since 2003. Human disease activity in 2012 was highly focal, with a third of disease cases being reported from Texas and a quarter of cases being reported from just seven counties. National incidence of WNV neuroinvasive disease in 2012 was higher than expected based on recent patterns from 2004–2011. PVD incidence in 2012 was also higher than expected. Despite the increased incidence of neuroinvasive disease and PVDs, national surveillance data showed no evidence of changes in epidemiology or increased disease severity compared with the previous 8 years.

WNV disease incidence previously peaked during 2002 and 2003 when large, regional outbreaks occurred as the virus spread across the country. In recent years, the number of reported cases declined and outbreaks became more focal and sporadic. It is not clear why there was more WNV activity in 2012 than in recent years. Available data suggest that the increased incidence of WNV disease in 2012 was not likely due to genotypic changes in the circulating virus strains. The intensity of transmission to humans is dependent on a number of inter-related factors, including the weather, abundance of birds that maintain the virus, abundance of mosquitoes that spread the virus, and human behavior.

Demographic and clinical characteristics of neuroinvasive disease cases and PVDs were comparable in 2012 and during 2004–2011. The hospitalization rates for neuroinvasive and non-neuroinvasive disease cases were higher in 2012 than during 2004–2011 but were within the prediction intervals based on data from the previous 8 years and were similar to rates for each of the last 4 years. Hospitalization was first reported to ArboNET in 2004; the lower hospitalization rates during 2004–2007 might be related to underreporting during the first years of data collection. The case-fatality ratios for both neuroinvasive and non-neuroinvasive disease cases were similar in 2012 and 2004–2011. In addition, the percent of PVDs meeting the case definition for WNV disease in 2012 was lower than expected based on data from 2004–2011.

As has been previously reported, neuroinvasive disease incidence and mortality were strongly associated with advancing age. In addition, neuroinvasive disease incidence and mortality were higher among males than females, a finding that has also been reported previously. The reasons why males appear at higher risk for developing neuroinvasive disease are unknown but may include behavioral differences that result in different infection rates, reporting biases, or differential prevalence of underlying medical conditions that might be risk factors for the development of neuroinvasive disease after infection. The risk for initial infection with WNV has not been found to be significantly higher among males in serosurveys or studies among blood donors. Similarly, the reasons why men with neuroinvasive disease appear at higher risk of death than women are unknown.

This analysis is subject to a number of limitations. ArboNET is a passive surveillance system dependent on clinicians to consider the diagnosis of WNV disease and obtain appropriate diagnostic tests and on healthcare providers and laboratories to report laboratory-confirmed cases to public health authorities. Reporting to ArboNET is likely incomplete (leading to underestimation of true disease incidence) and may be variable by jurisdiction, and even over time within a jurisdiction. Reported cases of neuroinvasive disease are considered the most accurate measure of WNV disease in humans because of the substantial associated morbidity; the severity of disease increases the likelihood that a patient will seek medical care, have appropriate diagnostic testing performed, and have the illness reported to public health authorities. Although neuroinvasive disease cases are thought to be most consistently reported, there are likely variations in case detection and reporting that could have impacted this analysis. During an outbreak of WNV disease in Arizona, only 40% of patients presenting with a clinically compatible neuroinvasive illness were tested for WNV infection and older persons and those with more severe disease were more likely to be tested, suggesting testing biases. Additionally, because ArboNET does not routinely collect information regarding clinical signs and symptoms or specific laboratory findings (e.g., cerebrospinal fluid findings), misclassification of the various syndromes caused by WNV (i.e., encephalitis, meningo, acute flaccid paralysis, and uncomplicated fever) cannot be detected.

Although it is not possible to predict the timing or location of future WNV activity, sporadic cases and focal outbreaks are likely to continue to occur in the United States. Surveillance programs are essential to identify outbreaks and guide prevention efforts aimed at reducing disease incidence. Healthcare providers should consider WNV infection in the differential diagnosis of cases of aseptic meningitis and encephalitis, obtain appropriate specimens for laboratory testing, and promptly report cases to public health authorities. Because a human WNV vaccine is not available, disease prevention depends on community and household efforts to reduce mosquito populations (e.g., applying insecticides and reducing breeding sites), personal protective measures to decrease exposure to mosquitoes (e.g., use of repellents and wearing protective clothing), and screening of blood donations.

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