St. Louis Encephalitis Virus Disease in the United States, 2003–2017

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Abstract. St. Louis encephalitis virus (SLEV), an arthropod-borne flavivirus, can cause disease presentations ranging from mild febrile illness through severe encephalitis. We reviewed U.S. national SLEV surveillance data for 2003 through 2017, including human disease cases and nonhuman infections. Over the 15-year period, 198 counties from 33 states and the District of Columbia reported SLEV activity; 94 (47%) of those counties reported SLEV activity only in nonhuman species. A total of 193 human cases of SLEV disease were reported, including 148 cases of neuroinvasive disease. A median of 10 cases were reported per year. The national average annual incidence of reported neuroinvasive disease cases was 0.03 per million. States with the highest average annual incidence of reported neuroinvasive disease cases were Arkansas, Arizona, and Mississippi. No large outbreaks occurred during the reporting period. The most commonly reported clinical syndromes were encephalitis ($N = 116$, 60%), febrile illness ($N = 35$, 18%), and meningitis ($N = 25$, 13%). Median age of cases was 57 years (range 2–89 years). The case fatality rate was 6% (11/193) and all deaths were among patients aged > 45 years with neuroinvasive disease. Nonhuman surveillance data indicated wider SLEV activity in California, Nevada, and Florida than the human data alone suggested. Prevention depends on community efforts to reduce mosquito populations and personal protective measures to decrease exposure to mosquitoes.

INTRODUCTION

St. Louis encephalitis virus (SLEV), an arthropod-borne virus (arbovirus), was first recognized as a cause of viral encephalitis in 1933 during an outbreak involving more than 1,000 cases in St. Louis, MO.^{1,2} Although the geographic range of the virus extends from Canada to Argentina, almost all human cases have been reported in the United States.³ St. Louis encephalitis virus is maintained in nature in a mosquito–bird–mosquito transmission cycle, with humans considered dead-end hosts.² In the decades following its recognition, two different transmission patterns became apparent. In the western United States, where *Culex tarsalis* was the primary vector, SLEV transmission was endemic, causing sporadic cases. By contrast, the virus exhibited greater epidemic potential in the eastern United States where it was transmitted primarily via *Culex pipiens*, *Culex quinquefasciatus*, and *Culex nigripalpus*.^{2,4}

St. Louis encephalitis virus is a member of the *Flavivirus* genus, which includes West Nile, Japanese encephalitis, and dengue viruses. The incubation period for SLEV infection is approximately 5–15 days. Although most SLEV infections are asymptomatic, disease presentations can range from mild febrile illness through severe encephalitis. There are no vaccines to prevent or medications to treat SLEV infections.

Since 2003, SLEV disease cases have been reported to the Centers for Disease Control and Prevention (CDC), through ArboNET, the national arboviral disease surveillance system. Two previous reports briefly described SLEV neuroinvasive disease cases reported during 1999–2007 and pediatric cases reported during 2003–2012.^{5,6} We reviewed all national SLEV surveillance data for 2003–2017, including neuroinvasive and nonneuroinvasive disease cases and nonhuman infections, and examined trends in the epidemiology of identified SLEV disease cases.

METHODS

Data sources and case definition. St. Louis encephalitis virus disease cases are reported to ArboNET by state health departments according to a standardized national arboviral disease case definition that includes clinical and laboratory criteria.⁷ Cases with encephalitis, meningitis, acute flaccid paralysis, or other acute signs of neurologic dysfunction are collectively referred to as neuroinvasive disease cases; others are considered nonneuroinvasive disease cases.

A confirmed SLEV disease case has laboratory evidence of disease based on one or more of the following: 1) detection of SLEV virus, antigen, or nucleic acid, in tissue blood, cerebrospinal fluid (CSF), or other body fluid, 2) 4-fold or greater change in SLEV quantitative antibody titers in paired sera, 3) SLEV immunoglobulin (Ig) M antibodies in serum with confirmatory SLEV-neutralizing antibodies, or 4) SLEV IgM antibodies in CSF and a negative result for other IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred. A probable case has SLEV IgM antibodies in serum and/or CSF but with no other testing.⁷

In addition to data on human disease cases, ArboNET collects data on veterinary disease cases and infections in mosquitoes, dead birds, and sentinel animals (e.g., chicken flocks). Nonhuman arboviral surveillance is voluntary and performed variably across different jurisdictions. Data typically reported to ArboNET for nonhuman arboviral infections include species, state and county of collection, and date of symptom onset or specimen collection.

Data analysis. We reviewed confirmed and probable cases of human SLEV disease and nonhuman infections reported to ArboNET from 2003 through 2017. We analyzed human data on state and county of residence, age, gender, race, ethnicity, clinical syndrome, date of illness onset, hospitalization, and mortality. Nonhuman data were analyzed on species type, and state and county of collection. We analyzed the data using Excel version 2016 (Microsoft Corp, Redmond, WA) and SAS statistical software version 9.4 (SAS Institute, Cary, NC). Maps were made using ArcGIS version 10.5.1 (Esri, Redlands, CA). Categorical variables were described as counts and proportions, and continuous variables were described by median

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and range. Incidence rates were calculated using neuroinvasive disease case counts, which are considered the most accurate indicator of SLEV activity in humans due to the associated morbidity, and annual population estimates from the U.S. Census Bureau.⁸

RESULTS

From 2003 through 2017, 198 counties in 33 states and the District of Columbia reported SLEV activity in a human or nonhuman species in one or more years (Figure 1). Among the 198 counties with any SLEV activity identified during the 15-year period, 81 (41%) reported infections in humans only, 94 (47%) reported infections in nonhuman species only, and 23 (12%) reported infections in both human and nonhuman species. Overall, mosquito infections were reported from 76 counties in 15 states, sentinel chicken infections from 57 counties in 11 states, and dead bird infections from two counties in Nevada. There were no veterinary disease cases reported. Among the 117 counties that reported infections in nonhuman species, 61 (52%) were located in Nevada, California, Arizona, or Florida.

A total of 193 human cases of SLEV disease were reported from 104 counties in 31 states and the District of Columbia. One hundred forty-eight (77%) cases were classified as neuroinvasive disease, and 45 (23%) were classified as nonneuroinvasive disease (Table 1). Of all cases reported, 141 (73%) were confirmed and 52 (27%) were probable. The median age of cases was 57 years (range 2–89 years); median age was similar for neuroinvasive disease cases (median = 57 years) and nonneuroinvasive disease cases (median = 56 years). One hundred sixty-two (84%) cases occurred in patients aged ≥ 40 years. One hundred seven (55%) cases were male.

The most commonly reported clinical syndromes were encephalitis ($N = 116$, 60%), febrile illness ($N = 35$, 18%), and meningitis ($N = 25$, 13%). There were five (3%) cases of acute flaccid paralysis. One hundred eleven (58%) cases were

hospitalized, 25 (13%) were not, and hospitalization status was unknown for 57 (30%). Among the 136 cases for whom hospitalization status was known, 95 (93%) of 102 neuroinvasive disease cases were hospitalized compared with 16 (47%) of 34 nonneuroinvasive disease cases. Overall, 11 (6%) cases died; all deaths were among patients aged > 45 years with neuroinvasive disease. The case fatality rate was the highest in patients aged ≥ 70 years (5/41; 12%).

Although cases occurred in almost all months, 144 (75%) cases had onset of illness from July through September, with a peak in August (Figure 2). Five states reported almost 70% of all cases: Arizona ($N = 42$; 22%), Texas ($N = 38$; 20%), Louisiana ($N = 19$; 10%), Mississippi ($N = 17$; 9%) and Arkansas ($N = 15$; 8%). Overall, 11 (6%) cases were reported as acquired out of state, including five that were the only cases reported for those states (Kentucky, Maryland, New Hampshire, Ohio, and Washington). Blood transfusion was reported to be the probable route of infection for one case.

From 2003 through 2017, a median of 10 SLEV disease cases (range 1–49) were reported per year (Figure 3). The largest peak in cases occurred in 2003 ($N = 49$) and a smaller peak in 2015 ($N = 23$). In 2003, 18 (37%) cases were residents of Texas, including 14 cases in northwest Texas, and the remainder were residents of 12 other states across the country. Conversely, the peak in 2015 reflected a focal outbreak, with 91% ($N = 21$) of cases reported from Maricopa County in Arizona. In the 15-year period from 2003 to 2017, the national average annual incidence of reported neuroinvasive disease cases was 0.03 per million (range 0.003–0.15 cases per million). The states with the highest average annual incidence of reported neuroinvasive disease cases were Arkansas (0.35 cases per million), Arizona (0.32), and Mississippi (0.29).

DISCUSSION

During the 15-year period from 2003 to 2017, 193 cases of SLEV disease, including 148 cases of neuroinvasive SLEV disease, were reported to ArboNET, predominantly from southern

FIGURE 1. Counties reporting St. Louis encephalitis virus (SLEV) activity to ArboNET, United States, 2003–2017. *Human disease cases reported by state and county of residence.

TABLE 1

Characteristics of SLEV disease cases, United States, 2003–2017

	SLEV disease cases (N = 193)	
	No.	(%)
Age group, in years		
0–9	4	(2)
10–19	6	(3)
20–29	8	(4)
30–39	13	(7)
40–49	36	(19)
50–59	42	(22)
60–69	43	(22)
70–79	28	(15)
≥ 80	13	(7)
Gender		
Male	107	(55)
Female	84	(44)
Unknown	2	(1)
Race		
White	126	(65)
Black	22	(11)
Unknown	45	(23)
Ethnicity		
Non-Hispanic	110	(57)
Hispanic	18	(9)
Unknown	65	(34)
Clinical syndrome		
Neuroinvasive		
Encephalitis	116	(60)
Meningitis	25	(13)
Acute flaccid paralysis*	5	(3)
Other neuroinvasive presentation†	2	(1)
Nonneuroinvasive	45	(23)
Hospitalized		
Yes	111	(58)
No	25	(13)
Unknown	57	(30)
Fatality		
Yes	11	(6)
No	178	(92)
Unknown	4	(2)

SLEV = St. Louis encephalitis virus.

* Of the five cases with acute flaccid paralysis, three also had encephalitis and one had meningitis.

† Symptoms for one case included headache, myalgia, neck stiffness, arthralgia, fatigue, and altered mental status and for another case included headache, nausea, myalgia, arthralgia, paresis, fatigue, altered mental status, and chills.

states. Most cases and all deaths were among patients aged ≥ 40 years. Annual case numbers were generally low and no large outbreaks occurred.

The epidemiology of SLEV disease in the United States has changed since it was first recognized as a cause of viral encephalitis in 1933. Previously, SLEV disease was the leading cause of arboviral disease in the United States and caused periodic large outbreaks in the southeastern and central United States at intervals up to approximately 10 years.^{2,9} Outbreaks often resulted in hundreds of reported cases, with the largest outbreak in 1975 resulting in about 2,000 reported cases.¹⁰ The last major outbreak occurred in Florida in 1990 with > 200 cases reported.¹¹ In the following years, only smaller outbreaks were reported.^{5,12,13} During the period of our review, the only notable SLEV activity was a small outbreak in Texas in 2003 and a localized outbreak in Maricopa County, Arizona, in 2015. Overall, case numbers were low with a median of only 10 reported cases per year. West Nile virus (WNV) and La Crosse virus are now the leading causes of arboviral encephalitis in the United States.¹⁴

The reasons for the changing SLEV epidemiology are unclear. Some researchers have suggested that SLEV was competitively displaced in parts of the United States by the introduction of WNV.³ St. Louis encephalitis virus and WNV share the same *Culex* species mosquito vectors and avian hosts. Studies suggest WNV-infected birds develop sterilizing immunity to both WNV and SLEV, but birds previously infected with SLEV can still develop viremia if infected with WNV.³ Thus, the spread and continued circulation of WNV might have resulted in fewer avian hosts susceptible to SLEV, reducing SLEV transmission to humans.

Another contributing factor to the low reported case numbers might be laboratory testing practices. St. Louis encephalitis virus testing is available at CDC and some state health department and commercial laboratories. However, because both incidence and awareness of WNV disease are substantially higher than SLEV disease, SLEV testing might not routinely be requested. In addition, cross-reactivity between WNV and SLEV antibodies can occur with standard diagnostic tests, requiring confirmatory neutralizing antibody testing to determine the infecting flavivirus. If only WNV testing is conducted, or if confirmatory testing is not conducted on an initially seropositive WNV sample, SLEV disease cases might remain undetected or be misdiagnosed as WNV disease cases.

Additional ecologic or other unknown factors also could be contributing to the changing epidemiological pattern of SLEV disease. With an increasingly long period since the last large SLEV outbreak in 1990, it seems unlikely that an outbreak of the magnitude seen in the past will occur again. However, the extent, timing, and nature of any reemergence cannot confidently be determined. In 2015, for example, in addition to the small outbreak in Arizona, SLEV activity unexpectedly was detected through mosquito and sentinel chicken surveillance in southern California after an apparent 11-year absence.¹⁵ Sequencing showed > 99% nucleotide homology between the 2015 California and Arizona isolates, and with a 2005 Argentinian isolate, suggesting a possible introduction of SLEV to the United States from South America at an unknown time.¹⁵

The 2015 outbreak of SLEV disease in Arizona, as well as being the only SLEV disease outbreak reported during the past decade, was also the first known concurrent outbreak of SLEV and WNV disease in the United States.¹⁶ The simultaneous circulation of SLEV and WNV led to the challenge of correctly diagnosing infections, as both viruses have similar clinical presentations and cross-react serologically. Although medical treatment of the two infections does not differ, correctly identifying SLEV disease cases is critical to SLEV surveillance, monitoring epidemiologic trends, and for determining causality of individual patients' infections. During this outbreak, probable SLEV transmission via blood transfusion also was recognized for the first time.¹⁷ Although this was not unexpected given previous occurrences of WNV transmission via blood transfusion, it was the first time SLEV transmission by transfusion had been documented.^{18,19}

Similar to previously published surveillance data and research studies, our review showed the greatest burden of disease was in older age groups.^{2,3} Studies have demonstrated that infection rates are similar among all age groups but that progression to symptomatic disease is more common

FIGURE 2. St. Louis encephalitis virus disease cases by month of illness onset, United States, 2003–2017 ($N = 192$)*. *Month of onset missing for one case.

FIGURE 3. St. Louis encephalitis virus disease cases by year and clinical presentation, United States, 2003–2017.

in older people.^{2,3} The risk of severe and fatal disease also has been shown previously to be higher in older age groups.^{2,12}

The nonhuman surveillance data reported to ArboNET were primarily from mosquito and sentinel chicken infections. Experimental infection studies indicated few birds produce elevated viremia and succumb to infection, so dead birds with possible SLEV infection are likely infrequently tested.²⁰ The nonhuman surveillance data indicated wider SLEV activity than the human data alone suggested, particularly in California, Nevada, and Florida. One explanation for the low incidence of human disease cases in these states could be related to diagnostic testing and surveillance biases. If providers are not aware of virus circulation in their area, they may not consider SLEV infection in their differential diagnosis. In addition, population immunity might be a factor in long-term residents of endemic areas, such as parts of California.^{21–24} Different exposure risks for human and animal populations or factors relating to locations of mosquito and animal testing are other possible explanations.

The findings in this review are subject to several limitations. First, ArboNET is a passive surveillance system that is dependent on clinicians considering the diagnosis of SLEV disease, obtaining the appropriate diagnostic test, and reporting positive results to public health authorities. Therefore, diagnosis and reporting are likely incomplete, and the incidence of SLEV disease is likely underestimated, particularly for cases of nonneuroinvasive disease. Second, because ArboNET does not require information regarding clinical signs and symptoms or laboratory findings (e.g., cerebrospinal fluid findings), misclassification of the various neurologic syndromes caused by SLEV (i.e., encephalitis, meningitis, and other neurologic presentations) cannot be detected. Finally, nonhuman surveillance data are reported voluntarily and are subject to greater variability in detection and reporting between jurisdictions.

St. Louis encephalitis virus outbreaks appear to have decreased in both intensity and frequency, and disease incidence during the past 15 years has been relatively low. However, SLEV disease can be a severe disease, especially among older people, and prevention measures remain important.

Health-care providers should consider SLEV infections 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. Prevention depends on community and household efforts to reduce vector populations (e.g., applying insecticides and reducing breeding sites) and personal protective measures to decrease exposure to mosquitoes (e.g., use of repellants and wearing protective clothing). Based on the epidemiology described here and in previous reports, efforts to prevent SLEV disease should primarily target older adults in southern states.

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