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EPIDEMIOLOGIC ASPECTS OF A ST. LOUIS ENCEPHALITIS EPIDEMIC IN JEFFERSON COUNTY ARKANSAS, 1991

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Abstract. In 1991, the first epidemic of St. Louis encephalitis (SLE) ever reported in Arkansas resulted in 25 cases in Pine Bluff (attack rate: 44 per 100,000; 95% confidence interval [CI] 28–65). To identify risk factors for SLE viral infection and risk factors for neuroinvasive illness, we conducted a community-based, cross-sectional study of noninfected and asymptomatically infected persons and a case-control study of asymptomatically and symptomatically infected persons. The SLE viral infection rate was similar in all age groups and in all studied census tracts. Risk factors for asymptomatic infection included: living in a low income household (relative risk [RR] = 2.6, 95% CI 1.1–6.0), sitting outside in the evening (RR = 2.1, 95% CI 1.0-4.8), and living in homes with porches (RR = 2.9, 95% CI 0.9–9.3) or near open storm drains (RR = 2.2, 95% CI 1.0–4.9). Compared with asymptomatically infected persons, symptomatic persons were older (odds ratio [OR] for age ≥ 55 years = 13.0, 95% CI 1.2–334) and more likely to have a previous history of hypertension (OR = 8.5, 95% CI 1.1–72). Our results indicate that advanced age is the most important risk factor for developing encephalitis after infection with SLE virus. Hypertension and vascular disease may predispose to neuroinvasive disease, but this epidemiologic study has not ruled out the confounding effects of age.

Saint Louis encephalitis (SLE) is the leading cause of epidemic viral encephalitis in the United States. Less than 1% of SLE viral infections are clinically apparent.[1–3] Illness ranges in severity from a simple febrile headache to meningoencephalitis, with an overall case-fatality ratio of 5–15%.[4–6] Although the ecology, vectors, and transmission cycles of SLE are well understood, few epidemiologic studies have examined risk factors for human infection or for development of neuroinvasive disease after infection has occurred. Previous studies have suggested that advanced age is the most important host factor affecting risk for neuroinvasive disease.[2, 4, 7, 8] Hypertension also has been suspected to increase risk of progression to symptomatic encephalitis and risk of death.[7–10] However, previous studies have been uncontrolled, or failed to compare SLE patients with asymptomatically infected persons.

To identify risk factors for infection, we conducted a neighborhood serosurvey in Pine Bluff, Arkansas, during the first outbreak of SLE reported in Arkansas. Using case-control methods, we compared asymptomatically infected persons identified in the serosurvey with SLE patients to identify risk factors for progression to neuroinvasive SLE.

MATERIALS AND METHODS

Outbreak investigation

In early August 1991, three SLE cases in residents of Pine Bluff (population 57,000) in Jefferson County, Arkansas were reported to the Arkansas Department of Health. During the subsequent two weeks, ten additional patients with SLE sought medical attention, and an investigation of the outbreak was initiated.

To identify additional cases of SLE (active case-finding), we reviewed medical records of patients with neurologic complaints treated at the Jefferson Regional Medical Center from July through August 1991. Additional cases were sought by screening all cerebrospinal fluid (CSF) samples collected at the Jefferson Regional Medical Center from July through September 1991 for SLE virus–specific IgM and by interviewing infection-control nurses at hospitals in and around Jefferson County. A suspected case was clinically defined as a febrile illness (temperature > 38°C) in

a patient with signs or symptoms of neuroinvasive disease, such as headache, delirium, coma, or new onset of seizures. A confirmed case was defined as compatible clinical manifestations in a patient with SLE virus–specific IgM in the CSF or serum[11] or a four-fold or greater change in antibody titer to SLE virus by hemagglutination antibody inhibition, complement fixation, or indirect immunofluorescence assays.[12]

Neighborhood serosurvey

To identify risk factors for SLE infection in the resident population, we performed a cluster-sampled serosurvey of three Pine Bluff census tracts (10, 13, and 16). On the basis of their respective populations, the three tracts were proportionally allotted 30 starting points in the serosurvey.[13] Questionnaires were used to collect demographic data, symptoms of SLE during the six weeks before the serosurvey, medical history, measures of possible mosquito exposure, and knowledge of mosquito avoidance behavior. An adult caretaker completed the personal questionnaire for children five years old or younger. A premise inspection identified mosquito breeding sites, the presence of mosquito larvae at these sites, potential points of mosquito entry into the house, resting sites for mosquitoes, and the type and density of vegetation cover. Sera were tested for SLE virus–specific antibodies by IgM-capture[11] and IgG-capture enzyme-linked immunosorbent assay (ELISA) (Marfin AA, unpublished data) at the Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention (CDC) (Fort Collins, CO). Recent infection was defined by the presence of SLE virus–specific IgM, and previous SLE infection was defined by the presence of SLE–specific IgG without IgM.

Case-control study

To identify risk factors for progression to neuroinvasive disease, we compared 21 recently infected but asymptomatic serosurvey participants with nine SLE patients from census tracts 10, 13, and 16 identified by active case-finding. A questionnaire eliciting medical history was administered by telephone or by face-to-face interviews to case-patients and controls, respectively. If the case-patient was dead or incapacitated, a related household member was asked to provide the information.

Statistical analysis

Population-based rates were calculated using the 1990 U.S. Census for Jefferson County, Arkansas.[14] Ninety-five percent confidence limits for these population-based rates were calculated using EPISTAT software (Epistat Services, Richardson, TX).[15] Odds ratios with exact confidence intervals, relative risks with Taylor series confidence intervals, Mantel-Haenszel adjustments, and Fisher's exact test (two-tailed) were calculated using Epi-Info software (USD, Inc., Stone Mountain, GA).[16]

RESULTS

Descriptive epidemiology

Symptomatic St. Louis encephalitis was confirmed in 25 Pine Bluff residents, resulting in an overall crude attack rate of 44 cases per 100,000 (95% confidence interval [CI] 28–65). Cases had onsets of illness during a six-week period from July 14 through August 23, 1991. Three additional cases were confirmed in residents of Jefferson and surrounding counties. In 14 (50%) of 28 cases, onset of illness occurred before the first case was reported to the state health department. Four (14%) of the 28 patients died, and four others were left with profound neurologic deficits. The ages of the patients ranged from five weeks to 85 years (median age 54 years).

Cases of encephalitis occurred predominantly in the city of Pine Bluff (Figure 1). Thirteen cases were in residents of adjacent census tracts 10, 12, and 13. The resulting crude attack rate for these three tracts (128 per 100,000; 95% CI 68–218 per 100,000) was five times greater than the rate for residents of other Pine Bluff census tracts combined (relative risk [RR] = 5.0, 95% CI 2.3–10.9).

As in previous SLE outbreaks, risk of neuroinvasive SLE was correlated with the age of the patient.[4, 8] The attack rate in persons 55 years of age and older was 107 per 100,000, which was four times greater than the attack rate in younger persons (RR = 4.2, 95% CI 1.9–9.3) (Table 1). Neither sex nor race was associated with increased risk of illness.

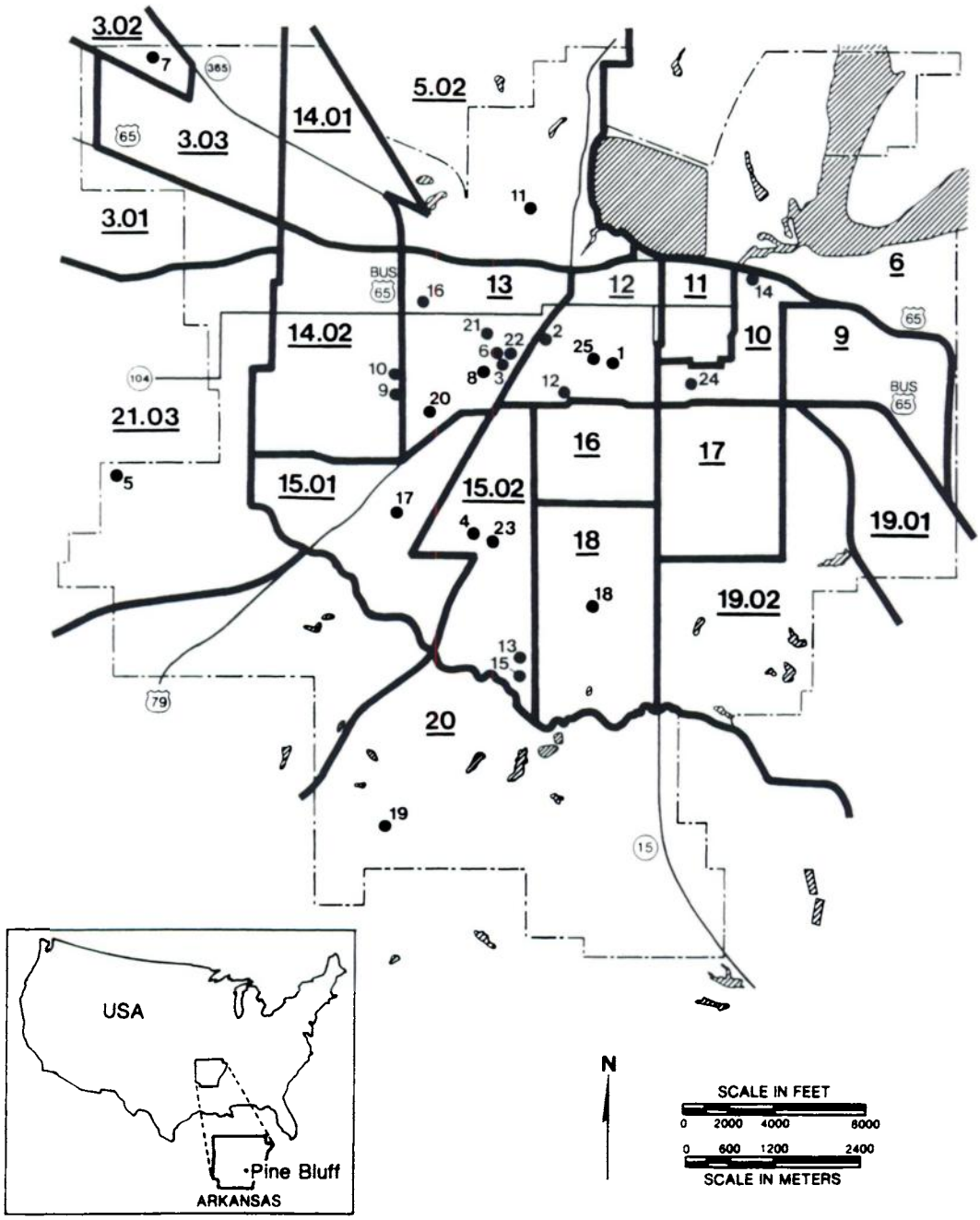

FIGURE 1. Map of Pine Bluff, Arkansas, showing residences of St. Louis encephalitis cases (●), July through August 1991. Cases are sequentially numbered by the date of onset of illness. Census tracts are shown with bold lines and numbers.

TABLE 1

Cases and crude attack rates of St. Louis encephalitis, by sex, race, and age of patient, in Pine Bluff, Jefferson County, Arkansas, July–August 1991

	Cases (%)	Attack rate per 100,000 (95% CI)*
Females	15 (60)	48 (27–80)
Males	10 (40)	38 (18–71)
Black	15 (60)	49 (27–81)
White	10 (40)	38 (18–71)
Age (years)†		
0–20	3 (12)	15 (3–44)
21–54	8 (32)	33 (14–66)
≥55	14 (56)	107 (58–180)

* Based on 1990 Census data.[14] CI = confidence interval.
† χ^2 for linear trend = 13.7, $P < 0.001$.

TABLE 2

*Mosquito minimum infection rates and St. Louis encephalitis (SLE) attack rates, by census tract, in Pine Bluff, Arkansas, 1991**

Census tract	*Culex quinquefasciatus* SLE viral infection rate (95% CI)†	Attack rate (95% CI)‡
9	4.7 (1.0–13.7)	0
10	3.3 (0.9–8.4)	92 (11–330)
13	1.1 (0.2–3.1)	191 (77–390)
16	0.0	0
18	1.9 (0.1–11.1)	30 (1–170)

* CI = confidence interval.
† SLE viral infection rate per 1,000 *Cx. pipiens quinquefasciatus*.
‡ Rate per 100,000 residents.

Vector infection rates

During the last two weeks of the outbreak, an entomologic survey was performed in the three serosurvey census tracts and two additional Pine Bluff tracts (Table 2).[17] Although SLE viral infection rates in *Culex pipiens quinquefasciatus* were similar in the five tracts, clinical attack rates differed significantly between these five tracts ($\chi^2 = 16.1$, degrees of freedom = 4, $P = 0.003$).

Neighborhood serosurvey

In a neighborhood serosurvey of census tracts 10, 13, and 16, we collected serum samples from 214 persons in 130 households. Race and age distributions of survey respondents closely approximated those of the underlying survey population, but the proportion of females in the sample (63%) was significantly greater than in the survey population.

Of the 214 survey participants, 32 (15%) had SLE viral-specific IgG without specific IgM, indicating previous SLE viral infection. Previously infected persons were older (RR = 2.5 for age ≥ 55 years, 95% CI 1.3–4.8), and a greater proportion was white than black (RR = 2.3, 95% CI 1.2–4.4). Annual household income, census tract of residence, and sex were not associated with previous SLE viral infection. The 32 persons infected with SLE virus before the 1991 outbreak were not considered in further analyses.

Of the remaining 182 susceptible persons, 21 (11.5%) had SLE virus-specific IgM, indicating recent SLE virus infection. None had been ill with a headache and fever during the six weeks before the serosurvey, and all were considered to be asymptomatically infected.

Although the risk of developing symptomatic SLE increased with age, the risk of acquiring infection during the outbreak was not significantly different between persons < 55 years of age and those ≥ 55 years of age (Table 3). Neither race nor sex was associated with increased rates of symptomatic or asymptomatic infection. Although attack rates in tracts 13 and 10 were significantly greater than in tract 16 ($P < 0.01$, by Fisher's exact test for each comparison) (Table 2), rates of asymptomatic infection in these tracts were not significantly different (tract 10 = 10.9%, tract 13 = 13.8%, tract 16 = 9.9%).

Several environmental and household factors were associated with recent SLE infection (Table 3). Socioeconomic status, measured by annual household income and years of education, was inversely related to recent SLE infection (Table 3). The risks associated with low household income and low educational achievement in adults were independent of each other. Other factors associated with risk of infection included living in a house near an open storm drain (RR = 2.2, 95% CI 1.0–4.9), and living in a house with an unscreened porch (RR = 2.9, 95% CI 0.9–9.3). Stratification by income showed that these risks were not equally distributed across the survey population, suggesting an interaction with household income.

Several environmental conditions identified as risk factors in previous studies were not associated with an increased risk of asymptomatic infection in this study. Residence in houses with open foundations, without screens or with screens in poor repair, with nearby standing water, or

TABLE 3

Risk factors for asymptomatic S. Louis encephalitis viral infection in 182 susceptible persons in Pine Bluff, Arkansas, August 1991

	No. (%) seropositive	Total tested	Relative risk (95% confidence limit)
Age (years)			
≥55	8 (15)	54	1.5 (0.6–3.3)
<55	13 (10)	127	
Sex			
Female	14 (12)	119	1.0 (0.4–2.5)
Male	7 (11)	63	
Race			
Black	19 (12)	156	1.5 (0.4–6.1)*
White	2 (8)	26	
Annual household income			
≤$10,000	10 (23)	43	2.6 (1.1–6.0)
≥$10,000	9 (9)	101	
Education level†			
<10th grade	8 (24)	34	2.9 (1.2–7.0)
≥10th grade	8 (8)	97	
Sit outside in the evening			
≥once per week	12 (17)	70	2.1 (1.0–4.8)
<once per week	9 (8)	112	
Knowledge of mosquito avoidance beahvior‡			
Yes	12 (9)	136	0.4 (0.2–0.9)
No	8 (22)	35	
Evening yard work			
≥once per week	7 (12)	56	1.1 (0.5–2.6)
<once per week	14 (11)	126	
Walk in the evening			
≥once per week	13 (13)	101	1.3 (0.6–3.0)
<once per week	8 (10)	81	

* $P = 0.75$ (two-tailed result, by Fisher's exact test).
† For persons ≥17 years old.
‡ For persons ≥6 years old.

without air conditioning was not associated with an elevated risk of infection.

Personal behaviors that may have increased exposure to peridomestic mosquitoes were also associated with an increased risk of asymptomatic infection. Persons who sat outside in the evening at least once a week were more likely to be infected during the outbreak than those who never sat outside (Table 3). Risk associated with sitting outside in the evening was independent of proximity to an open storm drain, the presence of an unscreened porch, and annual household income. Evening outdoor activities, such as neighborhood walks or gardening, and use of mosquito repellents were not associated with risk of infection.

Knowledge of mosquito avoidance behaviors was associated with a reduced risk of infection (Table 3). In stratified analyses, the protective function of this knowledge was independent of the actual time spent sitting outside in the evening, household income, and highest educational achievement.

Case-control study

When nine symptomatically infected residents of tracts 10, 13, and 16 were compared with 21 asymptomatically infected residents, race and sex were not risk factors, but advanced age was associated with increased risk of neuroinvasive infection. Encephalitis occurred more frequently in infected persons ≥ 55 years than in younger infected persons (odds ratio [OR] = 13.0, 95% CI 1.2–620, $P = 0.02$ by Fisher's exact test).

Among other host factors potentially associated with increased susceptibility to neuroinvasive SLE, only hypertension was a significant risk factor. Six (67%) of nine persons with encephalitis had a previous history of hypertension, compared with only four (19%) of 21 persons who were asymptomatically infected (OR = 8.5, 95% CI 1.1–7.2, $P = 0.03$ by Fisher's exact test). The small number of cases precluded stratifying these data by age, which may have been a confounding variable. A previous history of diabetes mellitus, cerebrovascular disease, moderate-to-severe head trauma, or seizure disorder was not associated with an increased risk.

DISCUSSION

This outbreak of St. Louis encephalitis was the first reported in Arkansas. We estimated from the serosurvey that 6,700 residents (11.5%) were infected during the outbreak, but despite the large number of infections that occurred, encephalitis developed in only 25 persons (asymptomatic: symptomatic infection ratio = 268:1). Although it is well-established that clinical encephalitis rarely occurs after SLE infections, little is known about host-associated risk factors that predispose to neuroinvasive infections. We used case-control methods to identify host factors associated with developing more serious illness after SLE viral infection.

More than half of the symptomatic St. Louis

encephalitis cases in this outbreak were in persons 55 years or older. Infection rates were not significantly different between older and younger persons, but as has been previously reported,[2, 4, 8] risk of progression to symptomatic encephalitis was more than four times greater among older persons.

Age-related conditions associated with disruptions of the brain vascular barrier may facilitate viral entry into the brain with the subsequent development of encephalitis. In the case-control analysis comparing asymptomatically and symptomatically infected persons, risk of encephalitis was associated with a history of hypertension. Previous studies showed that a family history of hypertension was a risk factor and that hypertension was associated with a fatal outcome of SLE.[2, 7] Although our observations suggest that preexisting hypertension increases the risk of developing encephalitis, too few asymptomatically infected persons could be enrolled to eliminate potentially confounding factors associated with age. An important age-related factor that was not studied is the relative decrease of immunologic competence in the elderly. In other flaviviral infections of the central nervous system, preexisting antibody or a vigorous antibody response to infection prevents or modulates the severity of illness.[18-21] Persons with an impaired immunologic response due to age, medication, or other chronic disease may be more susceptible to neuroinvasion and to more severe illness.

Interventions to reduce infection among older persons are the most specific means of reducing morbidity and mortality from SLE. One possible approach is to target mosquito abatement measures in neighborhoods with a greater proportions of elderly residents. However, in this study, mosquito infection rates did not differ significantly among five census tracts and did not correlate with the attack rates. Although other aspects of vector biology not measured in this study may be important factors affecting human risk, the uniformity of human asymptomatic infection rates in the city suggests that differences in clinical attack rates may reflect the distribution of elderly and others with an increased susceptibility to illness. In the 1990 census,[14] the proportion of elderly (≥ 55 years) in the combined population of census tracts 10 and 13 (26.4%) was significantly greater than in tract 16 (20.8%). Although it is unlikely that increased frequency of persons ≥ 55 years of age solely accounts for the increased clinical attack rate in these two tracts, targeted interventions in neighborhoods with more elderly persons may reduce the number of SLE infections in those most susceptible for progression to encephalitis.

Epidemiologic observations suggest that vector control efforts should be directed at neighborhoods with open storm drains. *Culex pipiens quinquefasciatus* mosquitoes may be more abundant in these locations because they breed in collections of water with high organic content such as those typically found in poorly draining open storm sewers.

The location and circumstances under which persons are bitten by infected mosquitoes are important factors to consider in formulating public health warnings. In previous outbreaks, risk of acquiring infection was associated with absent or inadequate screens and lack of air-conditioning, implying that infection occurred indoors.[3, 10] In this study, sitting outside in the evening and having a porch were independently associated with risk of SLE viral infection, suggesting that infections occurred outside, but near the house. Collectively, these observations are consistent with the behavior of *Cx. pipiens quinquefasciatus,* which exploits peridomestic breeding and resting sites. During an outbreak, public warnings should instruct the public to stay indoors in well-screened or air-conditioned areas and to specifically avoid outdoor evening activity around residential areas. Conversely, outdoor activity in open areas such as parks and ballfields probably does not increase the risk of acquiring infection. Long-term approaches to prevention should focus on eliminating peridomestic breeding sites, such as discarded containers and ditches where water stagnates. Eliminating resting sites such as open foundations under houses and porches also should be encouraged.

This study is the first to document the efficacy of a public health message in reducing SLE infection. Persons who were aware that they should reduce evening outdoor activity had a lower risk of acquiring infection. This protective effect was independent of socioeconomic status. However, assuming a seven-day incubation period for SLE,[22] 90% of the eventual case-patients already had been infected when the public health warnings began. It is likely that some unmeasured variable associated with hearing this public health message was actually associated with the lower risk of infection.

Ideally, early warning systems to detect SLE viral amplification in the enzootic cycle would predict the risk of epidemic transmission before any human cases occurred. However, systems of avian and mosquito surveillance are expensive and difficult to maintain. In communities where enzootic SLE viral activity is not monitored, the occurrence of a human case of SLE may predict subsequent cases of SLE. At least one resident of this two square mile tract became ill in each of the six weeks of this outbreak. In addition, the first and final cases of the outbreak were in persons who lived only two blocks apart. Immediate application of adulticides after the occurrence of the first case may have prevented subsequent cases in the same neighborhood.

Unfortunately, active surveillance of human cases and rapid intervention to control vector mosquitoes after the discovery of an index case will not eliminate all cases of SLE. In this outbreak, half of the epidemic cases had already occurred before the first case was recognized and reported. Our observation that 15% of Pine Bluff residents had been infected before the 1991 outbreak indicates that earlier sporadic and possibly epidemic cases had escaped notice. Thus, a heightened awareness of the disease, improved laboratory diagnosis and a more rapid system of reporting are essential to improving the public health response to SLE outbreaks.

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