ECONOMIC AND SOCIAL IMPACTS OF LA CROSSE ENCEPHALITIS IN WESTERN NORTH CAROLINA

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Abstract. La Crosse encephalitis (LACE), a human illness caused by a mosquito-transmitted virus, is endemic in western North Carolina. To assess the economic and social impacts of the illness, 25 serologically confirmed LACE case patients and/or families were interviewed to obtain information on the economic costs and social burden of the disease. The total direct and indirect medical costs associated with LACE over 89.6 life years accumulated from the onset of illness to the date of interview for 24 patients with frank encephalitis totaled $791,374 (range = $7,521–175,586), with a mean ± SD per patient cost of $32,974 ± $34,793. The projected cost of a case with lifelong neurologic sequelae ranged from $48,775 to $3,090,798 (n = 5). For the 25 LACE patients, 55.15 (54.83%) of the 100.59 cumulative life years (CLYs) were impaired to some degree. Disability adjusted life years (DALYs) were calculated to measure the productive life years lost to LACE. Approximately 13.00 DALYs were accumulated over 100.59 CLYs of study. Projected DALYs for case patients (n = 5) with lifelong neurologic sequelae ranged from 12.90 to 72.37 DALYs. An Impact of La Crosse Encephalitis Survey (ILCES) was used to measure the social impact of LACE over time for case patients and their families. The ILCES scores demonstrated that the majority of the social burden of the illness is borne by the five patients with lifelong neurologic sequelae. The socioeconomic burden resulting from LACE is substantial, which highlights the importance of the illness in western North Carolina, as well as the need for active surveillance, reporting, and prevention programs for the infection.

INTRODUCTION

La Crosse encephalitis (LACE), a predominantly pediatric illness caused by La Crosse (LAC) virus, a mosquito-transmitted bunyavirus of the California serogroup viruses. Historically, most cases of LACE have been reported from the midwestern states. However, LACE is endemic in North Carolina and increasingly recognized in Tennessee, Virginia, and West Virginia. An average of 73 cases is reported annually in the United States by the Centers for Disease Control and Prevention. Between 1996 and 1997, North Carolina ranked eighth in the nation for LACE cases, accounting for 2.8% of the 252 cases reported over the two-year period. During the same time period, LACE was the most frequently reported arthropod-borne encephalitis in the United States. The first death reported in North Carolina from LACE occurred in the summer of 2000 (Communicable Disease Mortality Statistic, North Carolina Department of Health and Human Services, Epidemiology Section). The fatality rate of LACE is low, approximately 0.5% of cases.

Mild LAC virus infection is often misdiagnosed as “flu” or a “summer cold”; therefore, the true incidence of mild or subclinical infections is presently unknown, but estimated to be as great as 300,000 infections per year in the United States. Retrospective serologic surveys indicate that the ratio of inapparent-to-apparent LAC virus infections in children ranges from 26:1 to 1,571:1. Antibody prevalence increases with age, reaching 35% by adulthood in some endemic areas.

In western North Carolina, serum donors living off of the Cherokee Indian Reservation had LAC virus antibody prevalences ranging from 1.8% for the youngest age group (< 15 years old) to 16.7% for the oldest group (75–100 years old) surveyed. On the Reservation for the same age groups, seroprevalence increased markedly from 16.7% to 53.9%. All reported cases of LACE in North Carolina, beginning in 1964, occurred in the Blue Ridge Mountain area of the western part of the State, with the majority of cases reported in or around the Cherokee Indian Reservation area of Jackson and Swain counties.

Transmission of LAC virus is widespread in the southern Appalachian region, including western North Carolina, eastern Tennessee, and southeastern West Virginia. While the clinical manifestations of LAC virus infection have been adequately characterized, the economic and social impacts of LACE have not been clearly defined. In Illinois, the average cost of hospitalization per case of LACE in the early 1980s varied between $3,967 and $5,750 with an average of 12 cases per year. Other costs associated with LACE, such as follow-up medical costs, indirect medical costs, and social costs, were not included in this study. Furthermore, no attempt was made to project future economic or social burdens resulting from sequelae. For some case patients, residual effects have imposed lifelong impairments. Reported residual effects of the illness include recurrent seizures, difficulties in school, behavioral problems, attention deficit disorder, and mild mental retardation.

To address the lack of a comprehensive economic and social analysis of LACE, we interviewed North Carolina case patients or their families to collect information on direct monetary costs resulting from inpatient and outpatient medical procedures, and the cost of lost workdays and other indirect expenses incurred during and after the illness. Furthermore, we estimated the social impact imposed by LACE on case patients, case patients’ families, and the community.

MATERIALS AND METHODS

Study population. We identified 63 LACE patients from case records provided by the Epidemiology Section of the North Carolina Department of Health and Human Services and positive serology reports of LAC virus infection from the North Carolina State Laboratory of Public Health. Case patients from years 1989 to 2001 were contacted by mail and asked to participate in a study of the socioeconomic impacts
of LACE. We received 29 positive replies from which 25 interviews were conducted. Four positive repliers either declined to be interviewed the day before the interview (n = 1) or did not appear at prearranged interview sites (n = 3). A protocol for the study was reviewed and approved by the Institutional Review Board at North Carolina State University (Human Use Protocol Institutional Review Board # 01XM). Interviews were conducted with informed consent with adult case patients (n = 2) or the parent(s)/guardian(s) of case patients (n = 23) less than 18 years of age. All interviews were conducted between June 2001 and April 2002.

Disease severity. Each case patient who participated in the study was categorized by severity of his/her illness using a classification scheme modified from Gundersen and Brown. Case patients were categorized so that variance in disease manifestations could be related to the direct and indirect medical expenses and social costs of the illness. Our premise was that the economic costs and social burden imposed by LACE would increase with the severity of the disease. The three categories of LACE severity used were as follows: 1) frank encephalitis with no sequelae (NS): LACE with no observable residual sequelae; 2) frank encephalitis with intermediate or long-term sequelae (IS): LACE with non-neurologic residual sequelae resolving in 1–5 years; 3) frank encephalitis with lifetime sequelae (LS): LACE with neurologic residual sequelae (primarily seizures) projected to be lifelong by the attending physician.

Each case patient was initially classified from information gathered during interviews. Attending physicians confirmed the classification of patients who were placed into the LS category. All patients reported by their parent(s)/guardian(s) to exhibit educational/social sequelae that were not diagnosed medically were placed into the IS category. Patients with no patient or parent-reported residual effects were placed into the NS category.

Survey questionnaire. Information on the socioeconomic impacts of LACE was collected using a standardized questionnaire. Questions were posed to characterize the social and work roles of household members, to obtain a travel history for each case patient a minimum of two weeks prior to onset of illness, and to assess three major categories of cost. The first category was direct medical costs. These are monetary costs of resources used directly in the treatment process. Direct medical costs included emergency professional transport of the patient, hospitalization, medication, follow-up medical care and procedures, all therapy and medical equipment, and educational costs. The second category was indirect medical costs. These are the monetary value of lost productivity as well as lost school time resulting from the disease. Indirect medical costs included lost workdays and lost wages, lost school days, and private transportation costs associated with the medical care of the patient during hospitalization and recovery from LACE. The third category was social costs. These are the impacts of the illness on the patient, family, and community due to the patient’s impairment. These impacts included non-monetary quantitative and qualitative estimates of the burden of the disease.

Monetary cost estimates. All costs incurred by each case patient between the age at onset of LACE and the date-of-interview are reported in 2001 U.S. dollars. All dollar costs and estimates from other studies have also been converted to 2001 dollars for comparison purposes. Conversions of dollar costs were made using the consumer price index “all urban consumers” population group with the appropriate categories of costs. As “strongly recommended” by the Bureau of Labor Statistics, escalation calculations were made using annual percent changes that were not seasonally adjusted.

Costs were calculated using billing statements provided by the study participants or health care facilities. In the event billing records were not available for particular services, an estimate based on the minimum fee for that service for case patients from the same geographic area was applied as the costs of that service. Billing information for seizure medication was available only for one participant. To estimate the cost of medication for all case patients, a neurologist provided an estimate of the average weekly cost of seizure medication for a typical LACE case patient. This cost rate was applied to the number of weeks of seizure medication use reported during interviews. Emergency transport costs were calculated from records provided by the participants or air/ground ambulance companies.

The costs of rehabilitative services (speech, physical, and occupational therapy) required by one case patient were provided by the North Carolina State Department of Education and the North Carolina Developmental Evaluation Center responsible for providing care for this patient. Other educational services provided for LACE patients (n = 3) during recovery included tutors and home schooling. A standard hourly tutor rate ($35/hour), obtained from a faculty team leader in a Wake County, North Carolina school district, was applied to estimate private tutor costs. Other services, such as in-school reading specialists and other specialized education services, were estimated by calculating the hourly wage of a first year educational professional responsible for each particular service. Hourly wages were calculated using entry-level salary (without local supplements) and benefits package information provided by the Wake County, North Carolina Department of Education. No direct medical billing information was available for one case patient included in the study. As a result, reported direct medical costs are calculated from billing information of 24 case patients.

Indirect medical costs included all monetary expenditures related to the disease, but not associated with the direct medical costs. Estimates of days lost because of the disease included days of school and/or work missed during hospitalization, as well as recovery, and follow-up care for the patient and/or family members. Dollar estimates for lost workdays were calculated by multiplying the number of days missed by a reported daily wage. The daily wage was calculated by dividing the weekly hours worked by five (five work days per week) and then multiplying the reported hourly wage by the average number of hours worked per day. In the case of variances in normal work schedule (n = 1), a daily work wage estimate was recorded and multiplied by the number of days of work missed due to LACE. One case patient and all members of the case patient’s family were retired during the time of illness and recovery. This family was not included in the analysis of lost work days. Lost school days were documented if the illness occurred during the local school year. Days ill or in recovery from LACE over vacations and/or weekends were not included as lost school days.

Indirect medical transport costs were calculated using reported number of round trips and round trip mileage from the case patient’s residence to the care facility. Costs were calcu-
lated by multiplying reported mileage by the 2001 North Carolina state allowance for mileage ($0.345/mile).17 Private transport costs included trips made during hospitalization, rehospitalization, or follow up care visits and medical therapy.

**Cost estimates for LS class case patients.** Estimates of the annual direct costs for treatment of patients with projected lifelong neurologic sequelae were obtained from their attending neurologists. For three of these five case patients, an annual office visit and seizure medication were noted as the minimum level of medical care required. Long-term physical therapy was projected to be needed only for the two youngest patients with severe sequelae. One of these patients is expected to require rehabilitative therapy until the age of 18 and will then need lifelong services similar to those described for the other three LS class patients. The other patient is projected to need lifelong rehabilitative therapy. Due to the severity of neurologic sequelae, this patient will require services provided by a state residential care facility after the age of 21. Four state-owned and operated residential medical care facilities servicing people with severe to profound mental retardation were contacted and asked to provide an estimate of the annual cost of residential care. The resulting average cost ($124,030) was used to estimate the annual cost of care for the annual cost of residential care. The resulting average cost of ($124,030) was used to estimate the annual cost of care for the lifetime of the patient after 21 years of age. Because of the profound level of physical and mental impairment resulting from sequelae, employment will almost certainly not be obtained in the patient’s lifetime. Lost earnings are part of the total estimated economic loss from an illness.18 To estimate the loss of income due to LACE, the mean annual income reported for North Carolina was applied for an average working life of 47 years (age 18–65 years) with a 5% annual discount rate.19 Estimates of lost earnings did not include the value of benefit packages or other employee incentives. A 5% discount rate over time was applied to projected direct and indirect medical costs for patients exhibiting lifelong sequelae.18

**Estimation of social costs.** Social costs were documented using four different methods.

**Impaired life years.** These are the total number of life years impaired in any manner by LACE. Impaired life years provide a measure of overall gross impairment caused by LACE for each case patient in the study.

**Disability adjusted life years (DALYs).** These are an estimate of the number of productive life years lost due to an illness or health condition. DALYs, developed as the unit of measure for the “Global Burden of Disease Study” initiated in 1992 by the World Health Organization, have been used to quantify the social cost of disease and injury worldwide.20 The DALYs reported in this study were calculated using different combinations of parameter values for an age-weighting function (β), a discount rate (r), and an age-weighting modulation factor (K).20,21 These parameters (r, K, and β) were set at standard DALY values or 0, while two different values of life expectancy were used in the calculation of projected DALYs for patients experiencing lifelong sequelae. The two different life expectancies were the standard DALY (SDALY) life expectancy (80 years for males and 82.5 years for females) and a United States DALY (USDALY) based on life expectancies reported in United States Life Tables from the National Vital Statistics Reports.22 The resulting combinations produced the following four DALY (r, K, and β) measures for cases projected to experience lifelong sequelae: 1) standard DALY = SDALY (0.03, 1, 0.04); 2) standard “0” DALY = SDALY (0, 0, 0); 3) United States DALY = USDALY (0.03, 1, 0.04); and 4) United States “0” DALY = USDALY (0, 0, 0). Application of different types of DALYs23–25 will allow results of our study to be compared with other economic studies of mosquito-borne diseases.

The DALYs calculated for the cumulative life years (CLY) of study, the time period between the onset of illness and the date of the interview, are not dependent on life expectancies. Therefore, only two sets of DALYs, DALY [0.0,0] and DALY [0.03,0,0.04], are reported for case patients during the study period. Since disability weight tables for calculating DALYs resulting from LACE are currently unavailable, base disability weights20 were used for calculation of all DALY types reported in this study. Disability weights reported during the interview for LS class patients were approved by their current-attending neurologists and have been used to calculate projected DALYs.

**Impact of La Crosse encephalitis scale (ILCES).** This is a measurement of the social impact of LACE over time for case patients and their families. The ILCES was developed from the Impact of Pediatric Epilepsy Scale.26 Adult case patients or parent(s)/guardian(s) of adolescent case patients were asked to rate how familial and case patient quality of life (QOL) attributes had been affected by LACE at the time of the interview. The major QOL attributes included in the ILCES were family relationships, family and case patient’s social life, and the case patient’s self esteem and school life. Participants rated QOL attributes as being affected a lot, some, a little, or not at all in a positive or negative way. To quantify these responses, a positive or negative rank score was assigned to each rating (a lot = 3 or −3; some = 2 or −2; a little = 1 or −1; not at all = 0). As a component of the ILCES, an overall QOL rating for each case patient was made on a scale of 1 to 6, with a score of 6 being the highest rating of quality of life.

**Stressors.** These are incidents or conditions that cause or add to the social/psychological impact of an event.27 When the survey questionnaire was completed, each adult case patient (n = 2) or parent/guardian (n = 32) of an adolescent case patient was asked to identify the most stressful event experienced during the acute and convalescent phases of the illness. Each response was recorded, and the audio recordings were subsequently transcribed. Stressors were identified after all taped statements had been transcribed.

**Data analysis.** Descriptive statistics were calculated (Microsoft Excel 2000; Microsoft Corp., Seattle, WA) for the dataset. With simple linear regression (PROC REG 1999–2001; SAS Institute, Cary, NC), we examined total ILCES scores for case patients to determine if the social impacts of LACE changed significantly over time (years since onset of illness). Comparisons among sequelae class means for the CLY of study for case patients and selected cost figures were performed using the nonparametric Kruskal-Wallis test (PROC NPARIWAY 1999–2001; SAS Institute). Pairwise comparisons of means were performed using one-sided Wilcoxon rank sum tests (PROC NPARIWAY). The Bonferroni method was used to control for experimentwise error (α = 0.05/k = 0.05/3 = 0.0167) for pairwise comparisons between sequelae classes. The association between selected cost variables and case patients’ real ages (ages at onset of LACE) was tested using a one-sided Kendall tau-b rank cor-
relation procedure (PROC CORR 1999–2001; SAS Institute) at a significance level of $\alpha = 0.05$.

**RESULTS**

**Epidemiology of La Crosse encephalitis.** The case patients included in our study represent 19 (40%) of 47 of all physician-reported LACE cases in NC between 1989 and 2001. Additionally, six serologically confirmed, but unreported case patients with onset of illness within the same time period were recruited into our study. The mean ± SD age of all LACE case patients was 12.65 ± 17.0 years (median = 9.40 years, n = 25), and the mean ± SD age for study participants <16 years of age was 7.97 ± 4.41 years (median = 8.17 years, n = 23). Adult case patients were 56.01 and 76.97 years of age. The large majority (80%) of study participants were male. The majority (18 of 25) of cases in our study occurred in late summer (August and September). Twenty-one (84%) of 25 case patients resided in the mountains of North Carolina. Travel histories of all LACE case patients but one correspond to LAC virus infection in the mountains of North Carolina. The travel history of the one case patient is consistent with the claim of having been infected in the western Piedmont in Forsyth County, North Carolina.

The mean ± SD number of CLYs elapsed from the date of onset of illness to the date of interviews for case patients was 5.91 ± 5.28 years (n = 4), 3.75 ± 2.78 years (n = 16), and 3.40 ± 3.61 years (n = 5) for the NS, IS, and LS sequelae classes, respectively. These mean CLYs of study were not significantly different ($P = 0.4338$, $\chi^2 = 1.671$, degrees of freedom [df] = 2, by Kruskal-Wallis test).

**Direct impacts. Medical costs.** Participant families (n = 25) reported annual incomes ranging from $\leq 10,000$ to $\geq 110,000$ with a median income of $40,000$. Medical costs for 23 (92%) of 25 case patients were paid for by health insurance. Medicare or Medicaid was the sole health insurance provider for 10 (43.5%) of the 23 participants. The direct medical costs over 89.60 CLYs for 24 patients were $26,328 ± $27,291 expended per case patient. Total direct medical costs increased with the severity of sequelae with mean estimates of $16,462, $21,176, and $48,736 for the NS, IS and LS classes, respectively. However, differences in cost estimates were not statistically significant ($P = 0.4221$, $\chi^2 = 1.725$, df = 2, by Kruskal-Wallis test). The mean ± SD length of hospitalization for all participants (n = 24) was 10.9 ± 11.1 nights, with a mean ± SD cost (n = 24) of $20,097 ± $17,888. The two youngest patients in our study were re-hospitalized for a mean ± SD of 2.5 ± 0.71 nights. Both of these case patients were diagnosed with lifelong sequelae. No other patients in this study were re-hospitalized due to LACE. The cost of re-hospitalization for these two case patients totaled $9,815.

Mean therapy costs for case patients (n = 24) totaled $33,624 (mean ± SD = $1,401 ± $3,283) with the LS class (n = 5) accounting for the majority of estimated costs (mean ± SD = $4,449 ± $6,286). When the individual types of therapy costs were examined, occupational therapy costs and real age were positively associated (n = 24; $t_b = 0.367; P = 0.016$, by Kendall tau-b rank correlation procedure). Likewise, case patients’ real ages and the number of speech therapy sessions during recovery were positively associated (n = 25; $t_b = 0.313; P = 0.0304$).

The LS class case patients averaged significantly more office visits (22.6 ± 21.1 visits over 16.97 CLYs) than the NS class (1.5 ± 0.6 visits over 23.65 CLYs) ($P = 0.0079$, by Wilcoxon rank sum test) and IS class case patients (5.4 ± 4.4 visits over 59.97 CLYs) ($P = 0.0058$). Additionally, the LS class averaged more weeks on seizure medication (199.0 ± 210.1 weeks over 16.97 CLYs) than the IS class (11.1 ± 13.7 weeks over 59.97 CLYs) ($P < 0.001$). The LS class averaged higher mean costs for office visits ($P = 0.0014$) and medication ($P < 0.001$) than the IS class, but not the NS class (office visit: $P = 0.0179$; medication: $P = 0.0667$). Two participants in the study listed the cost of equipment associated with medical care and support of patients as an expense totaling $7,230. Most of the cost ($6,920) was for one patient.

Parent-reported educational expenses (n = 24) totaled $8,727, with a mean ± SD of $364 ± $959 per patient. There was a statistically significant positive association between education expenditures and real age of case patients (n = 24; $t_b = 0.299; P = 0.0384$).

**Projected direct medical costs.** For four of five LS class case patients that were projected to experience similar sequelae, the total estimated lifetime direct medical cost was $289,404 based on U.S. life tables, with an mean ± SD cost of $72,351 ± $29,511 per case patient. Direct medical expenses included seizure medication and an annual neurologic examination for the expected lifetime of each patient. For the most severe case, the estimated lifetime direct medical cost based on U.S. life tables was $2,567,953.

**Projected indirect medical costs.** For all 24 case patients, a total of 1,150 family workdays were missed as a result of LACE, accounting for an estimated loss of $125,733 of income. A mean ± SD of 47.9 ± 78.6 workdays were lost per family, which is equivalent to an estimated mean ± SD loss of $5,030 ± $6,692 per family.

Along with lost workdays and wages, a total of 42,909 (mean ± SD = 1,717 ± 2276, n = 25) miles were traveled using private vehicles during the study period for all LACE patients, which is equivalent to $14,804 (mean ± SD = $593 ± $786, n = 25). The mean ± SD distance traveled for office visits by the LS class (n = 5) class was 1,287.8 ± 1,652.5 miles, which was greater than that of the IS class (218.9 ± 150.4 miles, n = 16) ($P = 0.0073$, by Wilcoxon rank sum test) and the NS class (23.5 ± 13.7 miles, n = 4) ($P = 0.0079$). Mean miles traveled were also significantly greater for the IS class than the NS class ($P = 0.0019$). There was also a significant negative association between miles traveled for office visits and real age of case patient (n = 25; $t_b = -0.28670; P = 0.0233$). The family of the most severely affected case patient spent $21,896 for materials needed for non-medical care.

**Lost school days.** Although the peak incidence of onset of LACE in our study occurred during September, patients could have become ill and recovered when school was not in session. Even so, for all school-aged participants ill while school was in session (n = 20), a total of 686.3 school days were lost with a mean ± SD of 34.3 ± 38.0 days per patient.

**Projected indirect medical costs.** The indirect medical costs for four of the five patients with projected lifelong sequelae could not be estimated. As noted in interviews, patients and families were able to rearrange work schedules to meet required medical appointments, minimizing lost work or school days.
The neurologic sequelae experienced by the most severely affected case patient will almost certainly prevent this case patient from obtaining employment in the future. Any resulting loss of income is a cost of the illness. Although other indirect medical costs will occur over the lifetime of the patient, the frequency or duration of costs such as mileage and parental lost workdays cannot be predicted. Therefore, the sole indirect medical cost included for this case patient is the loss of future income for a projected 47 working years calculated with a 5% discount rate, which is estimated to be $488,501.

**Total direct and indirect medical costs.** The total direct and indirect medical cost associated with LACE for 24 of the 25 case patients was $791,374 for 89.60 CLYs, with a mean ± SD of $32,974 ± $34,793 per case. The LS patients in this study are projected to experience lifelong neurologic sequelae. Using U.S. life tables, the total projected direct and indirect medical cost estimate for patients with lifelong neurologic sequelae is $3,380,202, with a range of cost between $48,775 and $3,090,798.

**Social costs. Impaired life years.** For 25 case patients, 55.15 (54.83%) of 100.59 CLYs were impaired to some degree by LACE. When impairment time was examined by sequelae class, the LS (P = 0.0079) and IS class case patients (P = 0.0025) had a greater mean percent time impaired than NS class case patients (Figure 1).

**Current and projected DALYs.** A total of 13.78 DALYs (0, 0, 0) or 12.66 DALYs (0.03, 1, 0.04) was accumulated over 100.59 CLYs for 25 case patients. These estimates represent a loss of 13.70% and 12.59% of productive life years, respectively, for an annual average of 0.137 DALYs (0, 0, 0) or 0.126 DALYs (0.03, 1, 0.04) per case, respectively. When the percent burden is based on DALY estimates, the LS class (n = 5) (DALYs [0, 0, 0]: P = 0.0079; DALYs [0.03, 1, 0.04]: P = 0.0079) and IS class (n = 16) (DALYs [0, 0, 0]: P = 0.0025; DALYs [0.03, 1, 0.04]: P = 0.0014) experienced a greater mean percent burden than the NS class (n = 4) (Figure 2). Additionally, the LS group experienced a greater mean burden than the IS group (DALYs [0, 0, 0]: P < 0.001; DALYs [0.03, 1, 0.04]: P = 0.0074). For the LS class, projected disability ranged from 12.90 USDALYs (0.03, 1, 0.04) to 72.37 SDALYs (0, 0, 0) per case patient, representing a burden of 17.46–92.00% of a case patient’s remaining life years (Figure 3).

**Impact of La Crosse encephalitis scale.** The regression of ILCES scores against time elapsed since the onset of LACE for each case patient was not significant, indicating that the familial and social burden of LACE did not decrease over time (Figure 4). The mean ± SD total ILCES score was –3.33 ± 8.29, range = –21 to 10) for 24 case patients, reflecting a negative impact of LACE on the case patients and their families. The mean total ILCES scores by sequelae class decreased in relationship to increasing severity of sequelae, indicating that there was an increase in the overall burden associated with a case of LACE with lifelong neurologic sequelae (Figure 5). The LS group was significantly different from the IS (P = 0.0015) and NS (P = 0.0079) groups. The NS class of case patients had a positive ILCES score, indicating their quality of familial life had not been detrimentally affected by LACE.

When ILCES scores are examined by major categories, mean scores for the LS class were lower than the NS class for social life (P = 0.0079) and self esteem (P = 0.0143). The LS class case patients also had a lower mean score than IS class

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**FIGURE 1.** Mean and median percent time impaired for 25 La Crosse encephalitis (LACE) case patients by sequelae class (NS = no sequelae; IS = intermediate sequelae; LS = lifetime sequelae). Means for percent time impaired followed by a different letter are significantly different at α = 0.05 by a Wilcoxon rank sum test. Error bars show 1 SD from the mean.
case patients for social life \((P/H_{11505} 0.0020)\), school \((P/H_{11505} 0.0043)\), and self esteem \((P/H_{11505} 0.0054)\).

The mean ± SD QOL rating for participants \((n = 24)\) was 5.13 ± 1.26. Notably, the LS class QOL score \((3.6 ± 1.67)\) was significantly lower than that of the IS class \((5.4 ± 0.83) \(P = 0.0059)\) and the NS class \((6.0 ± 0) \(P = 0.0079)\). The IS class was not significantly different from the NS class for QOL rating \((P = 0.1227)\).

Stressors. Lack of information was the primary stressor identified by 26 (76%) of 34 case patient’s parents during the acute phase of illness. After the acute illness, 19 (56%) of 34 participants sited lack of information as still being their primary concern. Other notable stressors reported after the acute phase of illness were lack of medical and mental health follow-up (15%) and lack of community action/response to LACE (12%).

**DISCUSSION**

To our knowledge, our investigation is the first comprehensive socioeconomic analysis of an arboviral disease. Results highlight the substantial disease burden imposed by LACE on the individual, family, and community. It should be noted that the response rate (46%) for LACE case patients or their families who received our invitation to be interviewed and subsequent interview rate (40%) were low, which suggests that a non-response bias may have been introduced into our survey. The smallest number of case patients was assigned to the NS class; the sequelae class for case patients that had no residual effects from the illness. This suggests that families with case patients experiencing residual effects may have been more willing to be interviewed.

In quantifying the socioeconomic impact of LACE, we were limited to billing information provided by participants and/or health care facilities. In general, participants did not keep detailed billing records. Major medical facilities did maintain detailed records, but not all smaller health care providers maintained detailed billing records more than five years past the date of service. Since we used conservative estimates for missing billing information, the U.S. dollar costs reported in our study represent a lower-end estimate of the monetary costs of LACE cases in North Carolina.

Quantifying educational costs was problematic. More than half (13 of 25) of the participants in our study claimed that case patients experienced educational sequelae. Parent-reported educational sequelae were similar to those reported...
in other studies of the residual impacts of LACE on school age patients.\textsuperscript{11,12,28} The cost of all services claimed by participants for case patients with educational sequelae could not be estimated. During interviews, participants explained that teachers provided special attention (one-on-one assistance) and consideration (modified assignments and quizzes) to patients with parent-reported educational sequelae. This action was taken without placing the child in a special education program or officially documenting the services provided for the student. As a result, there were no records available detailing the types or costs of services provided for school age case patients with parent-reported educational sequelae. The time spent for these activities by teachers is a relevant cost, but an estimate of the average time spent in assisting students with educational sequelae could not be made, nor could a cost estimate for time be calculated. Two case patients in the LS class were not yet old enough to attend public school. The severity of sequelae experienced by these patients make it likely that they will be placed in special education and special service programs when they do attend school. These program costs will further increase the overall educational costs resulting from LACE for these patients. Due to our inability to predict specific future educational sequelae and interventions, we were not able to make a dollar estimate for projected educational services.

The case patients in our study were predominantly (80%) males. The preponderance of males among LACE case patients has been noted in other investigations, and is explained by the greater outdoor activity of males resulting in an increased exposure to mosquitoes.\textsuperscript{7} Two (8%) of the 25 case patients in our study were adults. A similar prevalence rate of adult case patients has been reported.\textsuperscript{5}

The majority of the economic costs of LACE were for direct medical costs during acute illness. National (Medicare and Medicaid) and private sector health insurance paid for the greater part (80–100%) of direct medical costs of case patients (n = 23), indicating that LACE poses a substantial financial burden to health care insurers. The LS class accounted for significantly greater overall mean physical therapy costs than the IS and NS classes, as well as significantly greater mean office costs and seizure medication costs than the IS class, highlighting the increased burden associated with severe sequelae. The higher costs in these expense categories for LS class case patients were not an artifact of a greater number of CLY, because CLY for case patients were not significantly different (\(P > 0.05\)) among sequelae classes. However, the costs of office visits and seizure medication for case patients in the NS and LS classes were not significantly different. This unexpected result is most likely due to the small sample sizes (n = 3 and 2, respectively), resulting in a loss of power in the Wilcoxon rank sum test to detect differences between the LS and NS classes for these costs. The LS class would be expected to incur greater expenses relative to other sequelae classes because LS class case patients will require lifelong office visits and seizure medication, while case patients in other classes are not projected to require seizure medication or office visits over their lifetimes. The positive correlation between occupational therapy costs and educational costs with increasing age of case patient suggests physical impairments and educational sequelae resulting from LACE are more evident or more easily diagnosed in older patients.

Hospitalization costs for LACE case patients in Illinois between 1976 and 1980 were reported by Clark and others.\textsuperscript{10} When these cost figures are transformed to 2001 values, the per case direct medical costs range from $13,967 to $19,320, which is comparable to the overall mean hospitalization costs ($21,107 ± $18,689) in our study. Cases in the NS and IS classes are similar in severity to those in the transient category of eastern equine encephalomyelitis (EEE) cases described by Villari and others.\textsuperscript{18} The mean cost per case in NS and IS classes were $17,353 and $28,117, respectively, which are similar to the estimated mean cost of $35,415 (2001 dollars) of a transient case of EEE.\textsuperscript{18} Cost differences may be explained by our conservative approach in estimating costs or a higher cost of living and medical care in Massachusetts compared with North Carolina.\textsuperscript{15} The most severe case of LACE in our study is projected to experience lower lifetime costs ($3,090,798) compared with the lifetime costs of a residual case of EEE ($4,973,061 in 2001 dollars).\textsuperscript{18} Since the levels of lifetime impairment from these encephalitides are comparable, similar lifelong services will be required for the LACE case patient. The lower lifetime cost estimate for LACE might be accounted for by a lower estimated annual salary and regional differences in costs of health care services.\textsuperscript{15}

Khetsuriani and others estimated costs of hospitalization for encephalitis-related illnesses that occurred in the United States between 1988 and 1997.\textsuperscript{29} The estimated mean ± SEM hospitalization cost ($32,825 ± $1,093) was higher than our estimated mean ± SEM direct medical costs ($26,328 ± $27,291) for LACE. However, the reported median cost ($17,563) is similar to the median direct medical costs ($18,696) for a LACE patient.

The mean ± SD number of nights hospitalized in our study (10.9 ± 11.1 nights) was similar to the duration of hospitalization reported in other studies of LACE.\textsuperscript{10,12,30} The mean ± SD of hospitalization in our study was also similar to mean ± SD number of days of hospitalization for all reported encephalitis cases in the United States between 1988 and 1997 (12 ± 0.6 days).\textsuperscript{29} The two youngest patients in the study, 0.25 and 1.35 years old at onset of illness, required re-hospitalization for a mean ± SD of 2.5 ± 0.71 nights. Both patients were placed in the LS class. No other case patients in
our study were re-hospitalized. Increased burden on LS class case patients is demonstrated by the significantly greater number of mean office visits than the NS and IS classes, as well as a greater number of mean weeks on seizure medication than the IS class. Once again, the LS class is expected to accumulate a significantly greater number of weeks on seizure medication than the NS class due to the LS class case patients’ projected need of lifelong seizure medication.

Lost workdays demonstrated that LACE disrupted the normal family routine of caretakers. In rural Puerto Rico, adult dengue case patients lost an average of five workdays due to illness. For pediatric cases, only mothers lost workdays to care for the child. During a 1977 epidemic of dengue fever in Puerto Rico, affected workers lost an average of 2.75 workdays. Similarly, when a child was ill with dengue fever, parents lost an average of 2.75 workdays. In comparison, a greater number of mean familial workdays were lost due to LACE. Furthermore, in two-parent homes, both parents lost workdays. School age LACE case patients on average also missed a greater number of school days (34.3 days) than school-aged dengue patients in Puerto Rico (4.0 days). Impacts of the illness on siblings of LACE case patients were also discussed during interviews. Participants explained that other than work and school, all other familial activities and extracurricular activities of siblings of case patients stopped completely until the case patient recovered or a new routine could be established to address the case patient’s needs.

La Crosse encephalitis is a disease that has a significant impact at individual, family, and community levels. In particular, LS and IS case patients experienced greater impairment than NS class case patients. However, due to passive surveillance and inconsistent reporting of cases, the true number of people impacted by the illness is currently unknown. From 1997 to 2001, an annual average of approximately eight cases of LACE were reported in North Carolina (Communicable Disease Morbidity Statistic, NC Department of Health and Human Services, Epidemiology Division). Using this average as an annual incidence of LACE in North Carolina, the annual mean DALYs due to LACE would be 1.10 DALYs (0, 0, 0) or 1.01 DALYs (0.03, 1, 0.04). Meaningful comparisons of DALY estimates for LACE in North Carolina to DALY estimates for other diseases cannot be made for several reasons. First, there are no other DALY estimates for LACE or encephalitis resulting from other California serogroup viruses in the United States available for comparison. Second, due to the lack of disease-specific disability tables, our DALY estimates are less specific than DALYs calculated for illnesses with disease-specific disability tables. Finally, the incidence of LACE in North Carolina is not currently defined for several reasons. Since the illness is under-recognized and under-reported, the true number of encephalitis cases is not known. Along with insufficient disease surveillance and case reporting, the at-risk population is not defined. In our study, 4 (16%) of 25 case patients resided outside the mountains where LAC virus is endemic. The remaining case patients resided in the mountains of North Carolina. In West Virginia, another state affected by LACE, an annual incidence of approximately four LACE cases per 100,000 people has been reported (Centers for Disease Control and Prevention, 1998). If this estimate is extrapolated to 40 cases per 1,000,000 people and used as a national average incidence for LACE in endemic areas, DALY estimates would range between 5.04 DALYs (0.03, 1, 0.04) and 5.48 DALYs (0, 0, 0) per 1,000,000 people. In Puerto Rico, the estimated mean ± SE number of annual DALYs for dengue over the period of 1984–1994 was 658 ± 114 DALYs per million population, which is much greater than our estimated average annual DALYs for LACE. Differences in estimated DALYs for the two illnesses may be accounted for in part by the passive surveillance used for an endemic disease such as LACE versus the active case surveillance used for the impact of epidemic dengue in Puerto Rico.

The mean total ILCES scores decreased in relationship to increasing severity of sequelae, indicating that there is an increase in the overall disease burden associated with a case of LACE with lifelong neurologic sequelae. The NS class of case patients had a positive ILCES score, indicating their quality of family life had not been detrimentally affected by LACE. The lack of an effect was due primarily to the increased number of positive interactions among family members resulting from what was perceived to be a life threatening illness. For LACE cases with sequelae, the negative effects of the illness on the life of the patient overshadowed any positive effects of the illness on family relationships as a whole.

When the ILCES scores are examined by major categories, it is evident that LACE impacts the social life of case patients in the NS and IS classes significantly less than for LS class case patients. Because of the small sample size of case patients for the NS class (n = 2), there was insufficient power in the Wilcoxon rank sum test to detect a significant difference between mean scores for the NS and LS classes for the “school” category. However, in view of lower scores in the “social life” and “self esteem” categories, it is likely that LS case patients would experience greater difficulty in school than NS case patients.

There is a discrepancy between the measures of the public health impact of LACE and QOL ratings for the IS class. The overall mean QOL scores for IS and NS class case patients were not significantly different, suggesting that LACE had not substantially affected the quality of life of these case patients. However, case patients in IS and LS classes experienced a significantly larger percent impaired life years during the period from the onset of illness to the date of interviews compared with NS class case patients. The IS and LS classes also experienced significantly greater percent burden by DALY type than the NS class. At the dates of the interviews, 13 (52%) of 25 case patients were reported to experience some form of sequelae, and of these case patients, 8 (62%) of 13 were in the IS class, indicating that LACE had deleteriously affected the lives of these case patients. We believe that parents of IS class case patients viewed the QOL rating as a measure of the effectiveness of their parenting and care giving rather than a measure of the effect of LACE on the quality of life of these case patients.

Lack of information was the primary stressor reported in interviews both during and after the acute phase of illness. Interestingly, lack of information was also the most frequently identified stressor for dengue case patients in Puerto Rico. In general, participants in our study were not informed of serologic confirmation of LACE for several days after admission to the hospital, and in a few cases, diagnoses were not established until weeks or even months after release from the hospital. Participants felt that the lack of a timely
diagnosis during hospitalization made the event more confusing and stressful. Even though there are no specific treatment protocols for managing most forms of acute arboviral encephalitis, accurate and early diagnoses of cases would reduce the impact of this stressor, and it could conceivably speed and improve recovery if coupled with appropriate supportive and rehabilitative care. After diagnosis, the lack of information regarding the course of recovery and possible long-term effects of the illness compounded the emotional burden. The lack of information available in an easily accessible, comprehensible format was a primary complaint of participants. Along with the “lack of information” stressor, participants also noted their frustration with the lack of convalescent medical and mental health follow-up for case patients. Participants questioned if current and/or future medical, and especially social and educational residual effects, could be linked to the lack of follow-up medical care. After identifying the most frustrating aspect of LACE during and after hospitalization and discussing the emotional impact of the illness, participants explained that a number of other stressors contributed to the overall anxiety from LACE. For example, logistical issues such as taking care of other children and trying to maintain a sense of normalcy in their lives, were a continual concern of parents during the course of hospitalization and recovery for the patient.

The frequency of severe sequelae (LS class case patients) in our study is similar to the frequency of severe sequelae in other studies of LACE in the southeastern United States.6 If the frequency of severe sequelae (20%) in our study were applied to the 47 officially reported cases of LACE in North Carolina from 1989 to 2001, there would be approximately 10 persons with lifetime residual sequelae resulting from LACE. Using the four similar LS cases of LACE as a basis for calculating costs for the estimated 10 LS cases, the average lifetime direct medical costs would be $723,510 and total DALYs accumulated would range between 141.4 (USDALY [0.03, 1, 0.04]) and 282.2 (USDALY [0, 0, 0]). By including the frequency of occurrence of the most severe case of LACE in the present study to the projected 10 LS cases, two of the 10 cases would experience profound neurologic sequelae. Lifetime costs would be amplified to $6,760,404 and total DALYs would increase to between 174.3 (USDALY [0.03, 1, 0.04]) and 362.1 (USDALY [0, 0, 0]) for the same 12-year period.

In our investigation, reported impaired life years, estimated DALYs, ILCES scores, and described stressors demonstrated that LACE is a life-altering event for both patients and families of patients. However, 21 (84%) of 25 case patients resided in the mountains of North Carolina, and 20 (80%) of 25 of families in our study were not familiar with LACE before a family member contracted the illness. This finding indicates that in endemic areas there may be widespread lack of public understanding of LACE and consequently a lack of concern for the health consequences of the illness. Entomologic surveys indicate that environmental risk factors associated with LAC virus transmission are under-appreciated as well.

Without question, there is a need for public education about LACE, the LAC virus transmission cycle, vector biology, and methods of disease prevention through personal protection and mosquito control. However, past experience with dengue prevention programs has shown that increasing public awareness and levels of disease-related knowledge did not result in a substantial reduction in peridomestic mosquito populations. Consequently, for LACE, disease prevention programs should involve community-based support for development of organized mosquito control programs, as well as public education.

We view the results of our study as providing a springboard for increasing awareness of the public health community about the significant disease burden imposed by LACE in endemic areas. Accordingly, an aggressive approach to prevention, surveillance, diagnosis, and reporting of LACE cases needs to be developed and implemented by local and state public health agencies, and actively supported by the medical community of North Carolina.

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