La Crosse Encephalitis: A Persistent Arboviral Threat in North Carolina

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Mosquito-borne diseases remain a significant cause of economic, social, and health burdens in North Carolina. Although recently overshadowed by emerging threats such as chikungunya virus and Zika virus, La Crosse virus and other endemic arboviruses remain persistent environmental health hazards. Indeed, La Crosse virus, West Nile virus, and Eastern equine encephalitis virus accounted for more than 98% of the reported human arboviral diseases acquired in North Carolina in the past decade. Arbovirus infection is increasingly prevalent in Western North Carolina, with La Crosse encephalitis being endemic in this area. While infections are often asymptomatic and seldom fatal, the long-term neurologic sequelae of La Crosse encephalitis represent a significant burden.

The introduction of the Zika virus and the subsequent epidemics of Zika infection within the Americas represent the latest in a series of emerging infectious diseases that defy geopolitical boundaries and result in substantial economic, social, and health burdens [1]. However, endemic and epizootic arthropod-borne viruses (arboviruses) remain persistent and significant public health problems. The most commonly reported human arboviral diseases acquired in North Carolina result from neuroinvasive infections caused by La Crosse virus (LACv), West Nile virus, and Eastern equine encephalitis virus (see Figure 1) [2].

Each of these zoonotic arboviruses has a complex transmission cycle involving an animal reservoir or amplifying host and a variety of mosquito vectors, which presents inherent challenges for surveillance, prevention, and control measures. During the past decade (2006–2015), these 3 arboviruses accounted for more than 98% of the reported mosquito-borne diseases acquired by humans in North Carolina. Strikingly, the majority (84%) of these cases were attributable to La Crosse encephalitis (LACE) caused by LACv infections.

La Crosse Encephalitis

LACE is the most commonly reported pediatric arboviral encephalitis in North America [3]. Clinically apparent LACE is generally characterized by frank encephalitis or altered mental status that may progress to seizures and coma; in rare cases, LACE can cause death [4, 5]. However, serological evidence suggests that most LACv infections are asymptomatic or subclinical, indicating that LACv exposures are grossly underreported [6, 7]. Highly seasonal, the majority of LACE cases have an onset of illness during the months of July through September [3]. Although most LACE cases are reported in children younger than 15 years of age, adult cases are also occasionally recognized [8].

Historically, LACE was primarily reported in the midwestern region of the United States [9]. However, the disease geography appears to have shifted toward the Appalachian region; during the period 2003–2012, 81% of the reported pediatric LACE cases occurred in Ohio, North Carolina, West Virginia, and Tennessee [3]. The western region of North Carolina has long been recognized as an area where LACv and associated diseases are endemic, although reports as early as 1964 described presumptive LACE cases as “California virus encephalitis” [10].

Although the LACE case fatality rate is low (< 1%), long-term neurological sequelae may develop and result...
in chronic seizures, poor academic performance, impaired mental function, and/or behavioral problems [4, 5, 11]. Thus, LACE is associated with significant social and economic costs. In a study based on interviews with case patients from Western North Carolina (n = 25), Utz and colleagues estimated the direct and indirect medical costs and societal burdens imposed by LACE [11]. Case patients with lifelong neurological sequelae carried the greatest burdens of economic and social impacts of LACE. Notably, the projected costs of long-term medical expenses for these case patients ranged from $48,775 to $3,090,798. Severely affected LACE patients lost 17.5% to 92% of their productive life years to LACE. LACE patients were impaired during 54.8% of the timespan from convalescence until the interview completion date based on calculated disability-adjusted life-year metrics.

**La Crosse Virus Transmission Cycle**

LACv is maintained in an enzootic focus by transovarial, transstadial, and venereal transmission mechanisms within mosquitoes, and horizontal transmission can occur via small daytime-active mammals (eg, chipmunks and squirrels) that act as amplifying hosts for blood-feeding mosquitoes [12-15]. The eastern tree hole mosquito (*Aedes triseriatus*) is the primary maintenance vector of LACv. However, 2 invasive species of mosquitoes (*Aedes albopictus* and *Aedes japonicus*) are also competent LACv vectors and may play an emerging role in the transmission or maintenance of the virus in some areas where the virus is endemic [16]. These mosquitoes seek hosts during both daylight and twilight periods and will readily obtain blood-meals from humans. All 3 mosquito species lay their eggs in water-filled vessels, including both natural crevices (eg, tree holes and rock pools) and artificial containers (eg, clogged gutters, discarded tires, buckets, and pots). The immature mosquitoes develop as larvae and pupae in these aquatic environments. Thus, the presence of artificial containers within the peridomestic environment may serve to increase mosquito-human biting rates and thus increase disease risk.
La Crosse Encephalitis Risk Factors

Several environmental and behavioral factors are associated with elevated risk of LACE. Known environmental risk factors include the abundance of LACv transmission competent mosquitoes in immature or adult stages, the presence of tree holes or artificial containers, and residence in a rural forested habitat [17-19]. Behavioral risk factors include increased time spent outdoors, failure to use insect repellent or protective clothing, poor residence maintenance (eg, lack of screened windows, lack of air conditioning, or presence of discarded refuse), and lower socioeconomic and educational level. Older house age, deteriorating house condition, and degree of house isolation are also associated with increased risk of LACE. In addition, demographic factors such as male sex and age less than 15 years are historically associated with higher disease incidence, although seroprevalence increases with age [7].

Control and Prevention of La Crosse Encephalitis

Currently, no effective therapies or vaccinations are available to treat or prevent LACv infection. Similarly, evidence is lacking to support the use of mosquito-control measures such as residual barrier sprays, autocidal gravid ovitraps, or lethal ovitraps. Thus, the only currently viable strategy for alleviating morbidity and mortality from LACE is to prevent or reduce human contact with the mosquito vectors. In the context of LACE, disease prevention presently relies on personal protection efforts to prevent mosquito bites. Specifically, at-risk individuals should use insect repellents recommended by the Centers for Disease Control and Prevention (eg, DEET, picaridin, oil of lemon eucalyptus, and IR3535 per the manufacturers’ labeled instructions), wear long-sleeve shirts and pants, and take great care to avoid mosquito contact during peak transmission periods.

Sustained efforts to reduce the abundance of water-filled
vessels containing immature mosquitoes (ie, source reduction efforts) often require the assistance of a knowledgeable professional in order to identify cryptic habitats such as tree holes. However, there appears to be a lack of public knowledge of LACE in areas of Western North Carolina where the disease is endemic. Utz and colleagues reported that 20 (80%) of 25 case patient families were not previously aware of the illness [11]. Consequently, there is likely a widespread lack of concern for the public health consequences of this disease, resulting in the underutilization of personal protection or source reduction measures to reduce the risk of LACV infection.

Conclusion

Although most of the current public health response to mosquito-borne diseases in North Carolina remains appropriately focused on the emergence of the Zika virus in the Americas, endemic arboviral diseases such as LACE continue to be important environmental health hazards. Public health policy should thus prioritize sustainable and integrated mosquito-control programs at the local or regional level to address endemic disease while also preparing for emerging threats. Additional research and development efforts to address the paucity of mosquito-control tools for the control and prevention of LACE are urgently needed.

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