*Epidemiology and Infection*

**La Crosse virus: A Scoping Review of the Global Evidence**

S. Harding, J. Greig, M. Mascarenhas, I. Young, L. Waddell

**Supplementary Material**

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# S1: Scoping Review Protocol

**TITLE**

What are the characteristics of the global evidence on La Crosse encephalitis virus?

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**RATIONALE**

This research aligns with PHRSD priorities, which include enhancing and guiding public health decision-making and policies by providing the authoritative analyses, recommendations and scientific collaborative services (using methods such as epidemiological studies and knowledge synthesis) to address the occurrence, trend and determinants of infectious disease in Canada with expert focus on the prevention of public health risks arising from the food chain, animals and the environment (LFZ, 2013).

This project has been prioritized via stakeholder consultation as an important vector-borne disease (VBD) that is likely to expand its range in Canada due to climate change. Funding for this project has been provided by the Public Health Agency of Canada’s VBD climate change and adaptation funding 2016-2021).

**BACKGROUND**

La Crosse encephalitis virus (LACV) is a rare viral disease that was first identified in La Crosse, Wisconsin, USA in 1963. The organism responsible for causing this disease is La Crosse virus, an arbovirus from the family Bunyaviridae. La Cross virus is the most pathogenic agent of the California encephalitis group and is the most common mosquito-borne disease that is native to North America. While LACV was originally confined to the Midwest US, in the past 20 years the virus has emerged in the mid-Atlantic which now has the highest reported risk for children less than 16 years old. Despite its recent emergence in the Mid-Atlantic USA, LACV has not received much attention in the literature.

The primary vector transmitting LACV is *Aedes triseriatus*, the tree-hole mosquito. *Aedes triseriatus* circulates LACV among small mammals including eastern chipmunks (*Tamias striatus*), gray squirrels *(Sciurus carolinensius*), and red foxes (*Vulpes fulva*). Transmission to humans occurs after the bite of an infected mosquito. It has been shown that humans rarely achieve high enough concentrations of LACV from one mosquito bite to develop a LACV infection or disease. Humans are considered an incidental and a dead end host in this transmission cycle.

Two other mosquito species have emerged to compete with *Aedes triseriatus* as vectors of LACV, *Aedes albopictus* and *Aedes japonicas;* although vertical transmission for *A. japonicas* has yet to be tested. The recent emergence of these two species in the Mid-Atlantic USA coincides with the increase in LACV cases reported in that region. Competition between the mosquito vectors and the geographic variation of abiotic and biotic environmental factors will make it difficult to predict the impacts of climate change and land use on LACV transmission.

According to CDC, there is an average of 80-100 LACV cases per year in the USA. Cases typically occur in late spring and early fall and most cases occur in children under 16 years old. There is very little literature that reports clinical illness from LACV infection in adults. A diagnosis can be made based on clinical features, travel and recent activities. Serological IgM tests are also used to diagnose LACV, these tests are usually available from state health department laboratories and/or the CDC in the USA. Isolation of the virus is difficult and usually attempted from brain tissue and CSF samples.

The time from the bite of an infected mosquito to the onset of illness ranges from 5 to 15 days. Infected people can be asymptomatic or have mild symptoms including fever, headache, myalgia, malaise and occasional prostration. As such, mild infections are often misdiagnosed as a cold or flu. Severe cases can lead to encephalitis with significant neurological sequelae or death (0.5% of cases). Long-term sequelae include lifelong neurological symptoms that represent a substantial economic burden (> $3 million/ patient). At this time there are no licensed therapeutics or vaccines for LACV.

Sources:

Rey, J. R. (2008). La Crosse Encephalitis. In *Encyclopedia of Entomology* (pp. 2117-2119). Springer Netherlands.

Teleron, A. L. A., Rose, B. K., Williams, D. M., Kemper, S. E., & McJunkin, J. E. (2016). La Crosse Encephalitis: An Adult Case Series. *The American journal of medicine*.

Leisnham, P. T., & Juliano, S. A. (2012). Impacts of climate, land use, and biological invasion on the ecology of immature Aedes mosquitoes: implications for La Crosse emergence. *Ecohealth*, *9*(2), 217-228.

Taylor, K. G., & Peterson, K. E. (2014). Innate immune response to La Crosse virus infection. *Journal of neurovirology*, *20*(2), 150-156.

La Crosse encephalitis. Accessed Nov 24, 2016: https://www.cdc.gov/lac/

**STUDY QUESTION**

What are the characteristics of the global evidence on La Crosse encephalitis virus?

Planned Study Outputs

1. A scoping review of the global evidence.
2. A repository and dataset of all relevant literature captured in this study.

**METHODS**

**Review Team Expertise and Responsibilities:**

|  |  |  |
| --- | --- | --- |
| **Member** | **Organization** | **Project Role** |
| Lisa Waddell | PHRS /NML | Synthesis expertise |
| Judy Greig | PHRS /NML | Synthesis expertise/TBD |
| Mariola Mascarenhas | PHRS /NML | Synthesis expertise |
| Shannon Harding | PHRS/NML | Project lead; Synthesis expertise/ TBD |
| Ian Young | Ryerson University | Synthesis expertise |

**Search Strategy:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Library/Database** | **Date of Search** | **Search String** | **# Hits** |
| PubMed | November 30, 2016 | (“La Crosse” OR “LaCrosse”) AND (encephalitis OR virus) | **494** |
| Scopus | November 30, 2016 | (“La Crosse” OR “LaCrosse”) AND (encephalitis OR virus) | **547** |
| Agricola 1970-/CAB 1973- /EMBASE 1974-, searched together as they are provided by OVID via the PHAC library. | November 30, 2016 | Article Title, Abstract, Keywords (“La Crosse” OR “LaCrosse”) AND (encephalitis OR virus) | **994** |
| Cochrane Central Register of Controlled Trials | November 30, 2016 | (“La Crosse” OR “LaCrosse”) AND (encephalitis OR virus) | **1** |
| ProQuest Dissertations & Theses | November 30, 2016 | (“La Crosse” OR “LaCrosse”) AND (encephalitis OR virus) | **43** |

Total # of citations prior to de-duplication (from above databases): **2079**

Total # of citations after 1st round of de-duplication in RefWorks: **846**

Total # of citations after 2nd round of de-duplication in DistillerSR: **743**

Total # citations added from search verification = **5**

Total # citations added from the grey literature search = **120**

**Grey Literature Sources and Procedures:**

The Centers for Disease Control and Prevention (CDC) website was first searched to identify which states had previously reported LACV cases (confirmed and probable). The CDC reported cases from 21 states (data available 2004-2013). The state health department websites were then searched for published/unpublished primary reports, news bulletins, and annual or semi-annual surveillance reports that reported LACV cases and that were not captured by the original electronic search.

**Search Verification:**

Reference lists were screened for potentially relevant citations that were missed by the electronic search. Literature reviews that focused on LACV were first identified at the relevance screening level. Of the reviews identified, 11 included La Crosse in the title. We were able to procure 6 of the 11 reviews and requested an additional 2 reviews from the library in order to reach a point of saturation where no new references were identified.

The 8 papers evaluated were:

Goddard, J. (2000). Viruses transmitted by mosquitoes: La Crosse encephalitis. Infections in Medicine, 17(6), 407-410.

Kalfayan, B. (1983). Pathology of La Crosse virus infection in humans. Progress in clinical and biological research, 123, 179.

Borucki, M. K., Kempf, B. J., Blitvich, B. J., Blair, C. D., & Beaty, B. J. (2002). La Crosse virus: replication in vertebrate and invertebrate hosts. Microbes and Infection, 4(3), 341-350.

Byrd, B. D. (2016). La Crosse Encephalitis A Persistent Arboviral Threat in North Carolina. North Carolina Medical Journal, 77(5), 330-333.

Leisnham, P. T., & Juliano, S. A. (2012). Impacts of climate, land use, and biological invasion on the ecology of immature Aedes mosquitoes: implications for La Crosse emergence. Ecohealth, 9(2), 217-228.

McJunkin, J. E., Khan, R. R., & Tsai, T. F. (1998). California–La Crosse encephalitis. Infectious disease clinics of North America, 12(1), 83-93.

Rust, R. S., Thompson, W. H., Matthews, C. G., Beaty, B. J., & Chun, R. W. (1999). Topical review: La Crosse and other forms of California encephalitis. Journal of Child Neurology, 14(1), 1-14.

Taylor, K. G., & Peterson, K. E. (2014). Innate immune response to La Crosse virus infection. Journal of neurovirology, 20(2), 150-156.

**Relevance Screening (RS):**

The relevance screening level will be done on the title, abstract, and keywords where available. There is 1 question that encompasses the inclusion / exclusion criteria, this tool can be found in the appendix.

**Inclusion / Exclusion criteria:**

1. Time frame – no time frame
2. Country – All
3. Language – English, French. All other languages will be identified and parked until resources and time is available. e.g. Spanish or Portuguese
4. Document Type: All - any peer-review primary articles, PhD/MSc Theses, reports.

5) Agent/Disease: La Crosse encephalitis virus (LACV)

6) Study design: all

7) Primary research: all articles describing primary research on the virus, or infection in any reservoir, vector or incidental host will be included. Relevant secondary research e.g. literature reviews and predictive models will be identified as such for search verification unless they are predictive models evaluating the impact of climate change on this virus, in which case it will be included for summarization. All other citations will be excluded.

**Study Characterization:**

The study characterization form will aim to classify and characterize the research on La Cross encephalitis virus (LACV) so we can understand where there are areas of knowledge saturation and gaps. The form will first confirm the relevance of the publication prior to extracting the characteristics of the study. This will include; study design, population, setting, outcomes, whether there is extractable data, and if the study addresses the impacts of climate change on this virus.

**Review Management:**

The search strategy will be compiled and de-duplicated in Refworks. This database will then be exported to Distiller SR, a web-based systematic review software designed to manage all stages of conducting scoping reviews and systematic reviews. All stages of the scoping study from relevance screening to data extraction will be conducted within this software. The final dataset will be exported into MS Excel, cleaned and tabulated for use in the publication and reports.

**Data Analysis:**

Descriptive tabulation of all pertinent information that aids in the characterisation and illustration of the available knowledge on LACV will be conducted mainly in MS excel unless further statistical analysis is required. Findings and recommendations, methods incorporated and their usefulness, and study limitations will also be captured.

**RELEVANCE SCREENING TOOL**

**What are the characteristics of the global evidence on La Cross encephalitis virus?**

**Relevance Screening Tool for Abstracts:**

|  |  |  |
| --- | --- | --- |
| **Question** | **Options** | **Definitions/additional notes** |
| Does this citation describe primary research on **La Crosse encephalitis virus** or a predictive model examining the impacts of climate change on **La Crosse encephalitis virus**? |  Yes – relevant primary research   Yes- relevant predictive CC model  No – relevant review   No – conference proceeding book   No – book, not primary lit.   No – other relevant non-primary source   No, not relevant (excluded, submit form) | **La Crosse encephalitis virus:** a rare arbovirus that predominately infects children under the age of 16. This virus is known to cause illness in humans in the USA. The epizootic cycle mainly includes small mammals. Include ALL research on this virus.  **Primary research** represents a study where the authors collected and analyzed their own data – may use quantitative or qualitative methods or both to investigate the research question and report original results.  **Predictive Model:** Any citation describing the use of published information to model the issue and make predictions. **Climate change:** any predictive model looking at the effects of a changing climate e.g. temperature, rainfall etc. should be included in this review.  **Review/commentary** is acomprehensive or brief narrative review or commentary (from peer-reviewed articles journals) summarising knowledge on an issue (include systematic reviews in here.)  **Other non-primary** will encompass lay magazine or newspaper articles etc.  Exclude:  Primary research not on the virus of interest. |

2 reviewers independently will evaluate each citation.

**DATA CHARACTERIZATION AND UTILITY (DCU) FORM**

**Broad topic:**

**What are the characteristics of the global evidence on La Crosse encephalitis virus?**

**Note:** Remember to only extract information for the applicable question – **not all questions apply.** Be very specific about the data you extract AND only **extract primary information** (information collected by the author in the course of a study).

|  |  |  |
| --- | --- | --- |
| **Question** | **Options** | **Definitions/Additional notes** |
| **Relevance Verification**  The first three questions are designed for verification of the relevance of the article. Please answer all 3 questions prior to submitting the form; we would like to characterize the foreign language papers by focus of the paper. If the foreign language papers are likely not relevant, please indicate this in the focus question so we are not over inflating the number of relevant studies we excluded due to language. | | |
| What language is the article published in? | * English * French * Other, please specify: \_\_\_\_ (Exclude) |  |
| What type of document is this article? | * Primary research in peer-reviewed journal * Predictive model on LACV * Thesis * Grey literature with primary data (government or research reports) * Conference proceeding with sufficient detail * Literature review (Exclude) * Systematic review/meta-analyses (Exclude) * Grey literature; may report previously reported research (newspaper or magazine articles; exclude) * Conference proceeding with insufficient detail | **Primary research:** original research/investigation/study carried out by the researcher (incl. surveys, interviews, outbreak reports, observations, etc.)  **Thesis:** a long paper/essay or dissertation involving personal research (usually written for a university degree)  **Conference proceeding abstract/short paper:** a collection of published academic papers  **Literature review:** examination of published literature  **Systematic review/meta-analyses:** analysis and interpretation of primary research  **Grey literature:** research that is unpublished or published in a non-commercial form |
| Verify the relevance and focus of the paper, this paper describes research on LACV or LACV infection in humans, vectors, hosts or other animal species or describes a climate change model for LACV?  (Check all that apply; When answering this question, only check off the topics for which there are study outcomes and do not check if a category was just “mentioned” in the paper.) | * **Pathogenesis** of LACV in human and animal hosts * LACV infection, clinical characteristics and complications including affected organs and systems in any species * Infection mechanism (cellular level) in the host * Immune response in the host (proteins, genes and receptors) * Animal pathogenesis model * **Treatment** of LACV infection * Evaluation of **diagnostic tests** for LACV * **Epidemiology** of LACV (prevalence, incidence, risk factors of exposure/disease) * **Transmission** of LACV or necessary conditions for transmission of LACV between vector and animal host or human (include vector characteristics/behaviour for LACV transmission). * **Surveillance** to determine the extent of LACV infections * La Crosse encephalitis **Virus study** (examines virus attributes such as pathogenesis, transmission characteristics and/or molecular characterisation) * Efficacy of **mitigation** strategies to prevent and/or control LACV infection in humans, hosts or vectors. * **Societal knowledge, attitudes and/or risk perceptions** towards LACV and potential mitigation strategies * **Economic burden or cost-benefit** analysis of LACV infection and/or mitigation strategies * **Predictive climate change model** for LACV * **Other** LACV topic (Use if absolutely necessary) * Not relevant to the review including research on predictive models for the vector and research on vectors of LACV but not the virus itself (e.g. mitigation, abundance, density, general survival attributes and characteristics of the vector unrelated to its LACV status.) | ***Pathogenesis:*** biological processes/mechanisms/pathways that lead to LACV in human or animal hosts. This includes the following:   * Pathology of disease (chronic or acute signs and symptoms and organs /systems e.g. CNS affected) * Infection mechanisms (at cellular level, stages of infection) including LACV entry/exit or inhibitors of LACV entry/exit in the host * Immune response (Proteins/genes/receptors involved; in host and vector) * Animal models studying pathogenesis   ***Diagnostic tests*** refer to tests detecting the presence of LACV in humans, non-human hosts or vectors.  ***Epidemiology:*** Please include articles describing outbreak and sporadic cases, incidence/ prevalence for LACV, and/or risk factors for developing LACV infection or risk factors/conditions (environmental and climatic mostly) for LACV survival in vectors.  *Risk factors* are environmental, behavioural, or biologic factors usually in longitudinal, cross-sectional, cohort or case control studies where exposures and outcomes are studied. A risk factor indicates an association with an increase or decrease in disease in the population with the risk factor compared to that without.  ***LACV transmission*** passing of virus from an infected host to another vector/host; e.g. tick transmission, mother to child and/or through blood transfusion and adaptability, the ability to adapt to new host/environment or become resistant to drug. This could also be climatic conditions required for virus transmission.  ***Vector suitability studies for LACV transmission*** include:   * Characteristics of competent LACV vector (genes, adaptations, etc.; ability to transmit disease) * Range and density of LACV infected vector and/or environmental/climatic conditions to sustain LACV infected vector population * Vector activity (biting rate, Fecundity/fertility rate, reproductive rate etc.) * Extrinsic incubation period (Interval between the uptake of LACV by vector and vector’s ability to transmit LACV to other susceptible hosts) * Transmission/rate of infectivity (ie: how many people could be exposed by one infected vector and how many vectors are likely to become infected by one viremic human or animal/host)   ***Surveillance***is the ongoing and systematic collection, analysis, and interpretation of outcome-specific data for use in the planning, implementation, and evaluation of public health practice. Include studies evaluating surveillance methods/programs.  Examples :   * Surveillance of human cases * Sylvatic host surveillance (Sylvatic cycling is when pathogen transmission occurs between animal i.e., sylvatic hosts and vectors) * Mosquito/vector surveillance   ***La Crosse encephalitis Virus studies*** included are typically studies that focus only on the virus, thus experiments are in vitro or analysis is focused on genetic analysis to characterize LACV:   * Molecular characterization of LACV (e.g. mutations, phylogenetic analysis) * LACV pathogenic attributes (Describes how viruses cause disease e.g. virulence factors, viral entry/exit/cycle (includes latency period), viral replication)   ***Mitigation strategies = interventions***  *Note: Relevant mitigation studies need to have an outcome that measures a change in the burden of LACV in humans, hosts or vectors. Measuring only abundance of mosquitos (or other vector) is outside the scope of this review and will be captured in the vector mitigation reviews.*   * Studies looking at intervention efficacy include control or challenge trials and quasi experiments (before and after). * Program evaluations can fall in here. * Risk factors looking at presence/absence of an intervention should also be checked here. * Examples include (but are not limited to) land management, vector management and control, personal protection, and public education campaigns   ***Risk perceptions***are the subjective judgements that people make about the characteristics and severity of a risk. Do individuals feel they are at risk? Do they have knowledge that they can implement to decrease their risk? What are their feelings concerning using sprays or treating vectors to decrease the risk of disease transmission?  ***Economic burden*** will include an actual dollar amount or discussion of implied cost associated with mitigation strategies.  ***Cost benefit analysis*** is a systematic process for calculating and comparing benefits and costs of a project, decision or government policy.  ***Predictive models*** are mathematical or statistical models used to forecast outcomes, spread of LACV and/or trends. Examples include (but are not limited to) using climate to predict outbreaks and/or models predicting high-risk populations. In the provided text box, please describe model in one line. If possible, copy and paste text from the abstract/objectives section. |
| **If exclusion criteria were selected above, submit the form before proceeding** | | |
| **General Information** | | |
| From what continent(s) were the samples obtained? (if not specified, resort to author affiliations)  Specify the country(ies)  Specify the state or province if an observational study: | * North America * Europe * Australasia * Central America/South America/Caribbean * Asia * Africa * Other   \_\_\_TXT\_\_\_  \_\_\_TXT\_\_\_ | **North America:** includes Canada, USA and Mexico  **Europe:** includes, Belarus, Latvia, Ukraine, Estonia, Cyprus & west (incl. Iceland and Greenland)  **Australasia:** limited to Australia, New Guinea, New Zealand, New Caledonia, and neighbouring islands, including the Indonesian islands from Lombok and Sulawesi eastward  **Central America/South America/ Caribbean:** includes Caribbean, and all of south and central America.  **Asia:** Russia, Turkey, middle eastern countries and east  **Please specify country in the text box and the province /state if relevant in the textboxes using the full name (exception: USA))** |
| When was the article published? Specify year XXXX | \_\_\_TXT\_\_\_ | **Year** e.g. 1979 |
| When were samples collected or the study conducted? Specify year XXXX  (This will allow aggregation of results according to timeframe) | \_\_\_TXT\_\_\_ | **Dates**: year/month (if available) e.g. 1984/05 – 1989/12  Note “NA” for experiments unless actually specified. |
| What is the study design? | * Observational study * Case series/ case report * Population-based case series * Cohort * Case control * Cross-sectional * Prevalence survey * Surveillance or monitoring program * Outbreak investigation * Longitudinal study * Other OBS: \_\_\_ * Experimental study * Controlled Trial * Challenge trial * Quasi-experiment * Other EXP:\_\_\_ * Evaluation of a diagnostic tests * Molecular epidemiology * Molecular characterization * Qualitative research * Predictive model * Economic model * Risk assessment * Other: specify \_\_\_\_ | **Observational study:** Assignment of subjects into treated group versus a control group is outside the control of the investigator.  **Case series/report:**  an in depth evaluation of one or more cases and their clinical history/ risk factors.  **Population-based case series**: Often the findings of a disease surveillance program where the results represent disease in a geographical area.  **Cohort:** prospectively follow a group of exposed and non-exposed individuals to evaluate whether they develop an outcome or retrospectively evaluate exposure / disease when the exposure was likely to be a point source such as a foodborne outbreak at a wedding.  **Case control:** usually retrospective, identified cases are matched with controls and their risk factors are evaluated for an association with disease.  **Cross-sectional:** Examines the relationship of a risk factors and outcome (disease) at a point in time on a representative sample of the target population.  **Prevalence survey:** A measurement of the outcome (disease)at a point in time on a representative sample of the target population.  **Longitudinal study:** Multiple measurements taken on the same individuals over specific period of time  **Surveillance/Monitoring program results**: on-going sampling from a defined representative sample of the target population to evaluate changes over time.  **Controlled Trial**: experiments where the investigator has control over the experiment, they ideally randomize subjects into treated and non-treated groups and apply uniform measurements of the outcome.  **Challenge trial** is a controlled trial that includes exposure to the agent  **Molecular epidemiology** is a branch of **epidemiology** and medical science that focuses on the contribution of potential genetic and environmental risk factors, identified at the **molecular** level, to the etiology, distribution and prevention of disease within families and across populations  **Molecular characterisation of LACV** studies are examining genetic make-up of the virus and identifying key areas of conservation or mutation. This may lead to a description of how changes in phenotype are related to genotype. |
| **Sample Population** | | |
| What vector or host species were studied in this article? (Including the number and type of samples for humans)  *(Check all that apply)* | ** Humans**  **Samples taken to test for LACV**:   * + Blood   + Semen   + Urine   + Saliva   + CSF   + Other, please specify\_\_\_\_\_   + Questionnaire/focus group   **Characterize the human population (or case report) sampled for LACV, specify details as described in the paper.**   * General population: \_\_\_ * Hospital patient(s): \_\_\_ * Other human population:\_\_\_\_   **LACV Co-infection specify: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**  **LACV Co-morbidity specify: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**  ** Other non-human host (reservoir) species \_\_\_\_\_**   * Species identified to be part of the sylvatic cycle. \_\_\_ * Species identified to be a dead end host. \_\_\_ * Species identified to suffer clinical disease from LACV infection.\_\_\_\_ * **Animal model experimental species**: \_\_\_\_\_\_\_\_ * **Mosquitos, specify** * *Aedes triseriatus* * *Aedes albopictus* * *Aedes japonicus* * *Aedes Canadensis* * *Aedes communis* * *Aedes trivittatus* * *Culex pipiens* * Other mosquito: \_\_\_\_\_ * **Other arthropod vector: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** * **Virus only studies using cell-cultures, in-vitro models** | Population sampled for LACV refers to the human population, **number sampled**, age range and any other important classifying characteristics such as identifying immunocompromised groups, co-infections & co-morbidities as specified by the author.  **General**: Most populations will fall under this category including confirmed and probable LACV cases  **Hospital:** Medical records, patients, most case reports (while the cases from case reports/series are not always hospitalized at the outset, the reports usually describe very severe cases that are eventually hospitalized)  **Other**: This is only for high risk groups or populations that are clearly not general (e.g. pregnant women, children, HIV+ etc.)  Indicate details on sylvatic hosts, dead end hosts and clinical disease in host as presented by the author. |
| **Pathogenesis- humans** | | |
| Reported signs and symptoms of human LACV infection.  (Format: +ve/N  /time units and comments)  *(Check all that apply/ can add new options to this question)* | * Fever, specify: \_\_\_\_\_\_\_\_ * Joint pain, specify: \_\_\_\_\_\_\_\_ * Headache, specify: \_\_\_\_\_\_\_\_ * Neurological symptoms, specify: \_\_\_\_\_ * Encephalopathy: \_\_\_\_\_\_\_\_ * Seizure: \_\_\_\_\_\_\_\_\_\_ * Vomiting: \_\_\_\_\_\_\_\_\_\_\_ * Confusion: \_\_\_\_\_\_\_\_\_\_ * Other, please specify: \_\_\_\_\_\_\_\_ | When specifying, state the number of cases with symptom(s), number of total cases, and duration of time with units and further comments. Order should be (#/#/time + units/comments)  If duration of illness in many patients is provided, state the range and mention that “individual patient data is available”. |
| Indicate the results of post-mortem or other pathology examination*. For the scoping review only capture high level information e.g. what systems or organs were affected.* | \_\_\_TXT\_\_\_ |  |
| How was LACV diagnosed in humans included in this study?  *(check all that apply/ can add new options to this question)* |  Based on clinical symptoms  Virus isolation  RT-PCR (reverse transcription PCR)   Serology   * IgG * IgM * Plaque reduction neutralization tests * Other, specify; \_\_\_\_    Molecular characterization   Other, specify: \_\_\_\_\_\_ | Note test name if a commercial test was used OR if there is an important detail about diagnosis that should be noted. |
| Are sequelae reported following LACV infection in humans?  (Format: symptom, #/#, duration + time units,  comments)  Were risk factors for experiencing the above mentioned conditions reported by the author, please specify details?  (format: description of the risk factor, # +ve/N and/or measure of association.) | \_\_\_\_\_TXT \_\_\_\_\_\_  \_\_\_\_\_TXT\_\_\_\_\_ | When specifying, state the symptom, number of cases with symptom(s)/ number of total cases, duration of symptom with time units and further comments. Order should be (symptom, #/#, duration + time units,  comments)  Risk factors may be descriptively described or quantitatively tested (e.g. odds ratios may be provided) Please extract both the description of the risk factor, # +ve/N and/or measure of association. |
| Characteristics of LACV infection in humans studied in this paper:  (Only answer if primary data is available) | * Time between exposure and viraemic period, please specify in days \_\_\_\_\_\_ * Viremic period, please specify in days: \_\_\_ * Intrinsic incubation period (IIP), please specify in days: \_\_\_ * Other \_\_\_\_ | **The intrinsic incubation period (IIP)** is the time between a human being becoming infected and the onset of symptoms due to the infection.  **Viraemic period** is the time period in which humans are infectious with LACV. |
| **Pathogenesis – all animals** | | |
| Describe the reported signs, symptoms and long term sequelae by animal species reported in the paper.  (Format: species; symptom, #/#, duration + time units,  comments) | \_\_TXT\_\_\_ | When specifying, state the number of positive LACV animals with symptom(s), number of total cases, and duration of time with units and further comments.  Also note long term sequelae.  If duration of illness in many cases is provided, state the range and mention that “individual case data is available”. |
| Indicate the results of post-mortem or other pathology examination*. For the scoping review only capture high level information e.g. what systems or organs were affected.* | \_\_\_TXT\_\_\_ |  |
| How was LACV diagnosed in animals included in this study?  *(check all that apply)* |  Based on clinical symptoms  Virus isolation  RT-PCR (reverse transcription PCR)   Serology   * IgG * IgM * Plaque reduction neutralization tests * Other, specify; \_\_\_\_    Molecular characterization   Other, specify: \_\_\_\_\_\_ | Note test name if a commercial test was used OR if there is an important detail about diagnosis that should be noted. |
| Characteristics of LACV infection in animal hosts studied in this paper:  (Only answer if primary data is available) | * Time between exposure and viremic period, please specify in days \_\_\_\_\_\_ * Viremic period, please specify in days: \_\_\_ * Intrinsic incubation period (IIP), please specify in days: \_\_\_ * Other \_\_\_\_ | **The intrinsic incubation period (IIP)** is the time between a host being becoming infected and the onset of symptoms due to the infection.  **Viraemic period** is the time period in which a host is infectious with LACV. |
| **Infection mechanism** | | |
| List the host studied and briefly describe the objective/findings of the study relevant to the cellular level infection mechanism studied in this paper | \_\_TXT\_\_\_ |  |
| **Immune Response** | | |
| List the host studied and briefly describe the objective/findings of the study relevant to immune response (e.g. proteins, genes, receptors involved). | \_\_TXT\_\_\_ |  |
| **Treatment of LACV** | | |
| What treatment options were used to treat LACV infections?  Briefly specify the type of treatment/ name of drug/ dose and duration if reported in the paper. | * Human treatments: \_\_\_\_ * Animal treatments: \_\_\_\_\_ * In vitro antiviral experiment: \_\_\_\_\_\_ | e.g. Plant-based inhibitors, non-steriodal anti-inflammatory drugs, corticosteroids, analgesics /anti-pyretic, anti-viral drugs, physical therapy or acupuncture, traditional medicine, etc. |
| Was the above noted treatment(s) evaluated for efficacy?  (If there were more than one treatment and they were not all evaluated for efficacy, state which treatments were evaluated.) | * Yes: \_\_\_\_ * No |  |
| **Accuracy of Diagnostic Tests** | | |
| What tests were examined for their accuracy in the diagnosis of human cases and/or detection of LACV in non-human hosts?  *(Please check all that apply)* | * Clinical diagnosis (by signs and symptoms) * Virus culture and identification * Serological Tests   + IgG   + IgM   + Plaque reduction neutralization tests   + Other serological test, specify: \_\_\_ * Molecular Tests   + RT-PCR (reverse transcription PCR)   + Other molecular tests, specify: \_\_ * Other, specify:\_\_\_ | **Plaque reduction neutralization tests** measure neutralizing antibodies for LACV  **RT-PCR:** Used to qualitatively detect gene expression through creation of complementary DNA transcripts from RNA |
| Is information about sensitivity, specificity and/or raw data provided? | * Yes, specify the test(s): \_\_\_\_\_   **What data is available?**   * Specificity is provided * Sensitivity is provided * Raw data is provided (for 2 by 2 table) * Detection limits of test, * When should this test be used? (e.g. X days after symptoms appear) Specify: \_\_\_\_   **Is this a commercial test?**   * Yes * No, it an in house or experimental test * No, insufficient data provided | **Sensitivity** (also called the **true positive rate**) measures the proportion of positives that are correctly identified as such.  **Specificity** (also called the **true negative rate**) measures the proportion of negatives that are correctly identified as such. E.g., if 100 people known to have a disease were tested and 43 tested positive, the test has 43% sensitivity. If 100 people with no disease are tested and 96 return a negative result, then the test has **96%** specificity.  **Detection limits** – examples are cut off values for detecting positive or negative results for each test  If information about SN/SP/raw data/limitations of test, etc. is provided for more than one test, select “Yes, for multiple tests” and more questions will become available. |
| **Epidemiology Section** | | |
| What is the **burden** of LACV in the sample population in this study?  (Only answer if the data is a population sample.) | * The sample represents [ date/ region/ population] = \_\_\_\_\_\_\_\_\_\_\_\_ * Sero-Prevalence= \_\_\_\_ * Case (disease) Prevalence = \_\_\_\_\_\_\_\_\_\_ * Incidence = \_\_\_ * Prevalence of Long-term sequelae = \_\_\_\_ * Case-fatality rate = \_\_\_\_ * Proportion hospitalized= \_\_\_ * Other measure \_\_\_\_ | **Sample:** describe what the sample represents – date, region, population sampled.  **Sero-prevalence:** Where a representative group of the target population is screened for sero-reactivity to LACV.  **Case Prevalence:** It is the number of cases of LACV in a defined population at a specific point in time. Record both numerator and denominator if provided [# of total LACV cases at a point in time, # of exposed individuals).  **Incidence:** It is the number of new cases of LACV arising within a given time period in a specified population. Record both numerator and denominator if provided [# of new LACV cases in a given time period, # of exposed individuals)  **Long-term sequalae:** Proportion of cases that develop chronic symptoms  **Case-fatality rate:** Proportion of cases that die from all LACV cases.  **Proportion** of cases that are **hospitalized**  **Other measures** e.g. prevalence of various co-infections or co-morbidities. |
| If this is a LACV **outbreak**, describe its characteristics  (Only answer if this is an outbreak report) |  Outbreak cases; total number reported:\_\_\_\_   * Outbreak start date (yyyy/mm/dd): \_\_\_\_ * Outbreak finish date (yyyy/mm/dd): \_\_\_\_ * Number of confirmed cases:\_\_\_\_ * Number of probable cases:\_\_\_\_ * Number of hospitalizations: \_\_\_ * Number of fatalities: \_\_\_\_ * Other measures, \_\_\_ | **Confirmed cases** include all LACV cases that are laboratory confirmed.  **Probable cases** are cases that are clinically diagnosed without laboratory confirmation |
| If this report describes one or more **sporadic cases** of LACV, describe their characteristics.  (Only answer if this is a sporadic cases report OR a case report/case series etc.) | * Describe the cases [e.g. date/ region etc.] = \_\_\_\_\_\_\_\_\_\_\_\_ * Sporadic cases; total number reported:\_\_\_\_ * Number of confirmed cases:\_\_\_\_ * Number of probable cases:\_\_\_\_ * Other measures to note: \_\_\_ | **Sporadic cases** = When you see cases here and there. There is nothing linking one case to another. |
| What significant **risk factors** for exposure to LACV or acquiring LACV infection were identified?  State species: list significant risk factors by positive association and negative association with LACV infection.  (Only applies to epidemiology studies: surveys, cross sectional, case control, cohort. Not outbreak investigations) | \_\_\_TXT\_\_\_ | The sample represents [ date/ region/ population] = \_\_\_\_\_\_\_\_\_\_\_\_ |
| **Transmission of LACV** | | |
| What aspect of transmission is examined in this paper?  (List relevant outcomes in the textboxes and note species if several species are examined in the paper). | * Vector to human * Human to vector * Vector to host * Host to vector * Suitability of the vector * Vector competence \_\_\_ * Vector behaviour \_\_\_ * Other vector attribute: * Other: \_\_\_\_\_ | e.g. Time to transmission of virus. Vector life stage that transmission occurs, climatic factors (temp etc.) that impact transmission, etc.  **Vector competence** outcomes may include: lifespan/ life cycle, density, range of habitats, reproduction rages, time required from vector infection until the virus reaches their salivary glands.  Vector behaviour: includes feeding behaviour, biting conditions, biting rate, etc. |
| **Surveillance** | | |
| 33. What is the goal of the surveillance system/program? | Text box | Please copy and paste the goal of the surveillance system. For example, to identify the emergence of LACV in a host population |
| 34. Describe region under surveillance | Textbox | Describe area (i.e. urban/rural) and comment on scale of it (i.e. size of area sampled) |
| 35. When was the surveillance program initiated/finished? | Start date: (yyyy/mm/dd)  End date: (yyyy/mm/dd) | State NA if not provided. If it’s still on-going, write “on-going” in the end date section |
| 36. What surveillance methods are described?  *(Check all that apply)* |  Active   Monitoring program   Passive   Physician reporting\_\_\_   Laboratory-based \_\_\_   Event-based \_\_\_   Other, specify: \_\_\_\_\_ | **Active surveillance**, in contrast to passive surveillance, requires that public health staff take direct action to collect disease information. For example, they may contact physicians, hospitals, laboratories, or other health entities to actively search for disease cases. Active surveillance may also occur through direct review of clinical or hospital charts, laboratory records, or emergency room patient logs. Active surveillance provides the most complete picture of disease incidence, i.e., cases are found in a timely manner, a greater number of cases are found, and more thorough information is obtained compared to passive surveillance methods. Active surveillance is an on-going activity and contains thresholds.  **Monitoring program:** Systematic purposeful program without active action plan. Simply counts numbers.  With **passive surveillance**, a member of the reporting community initiates a disease report that is communicated to a health department. For example, a physician may telephone a health department to discuss a case immediately upon seeing a patient with a suspected or confirmed case of a disease or an infection control practitioner may contact a health department upon receipt of positive laboratory results for a more common disease.  **Laboratory surveillance** differs from population-wide surveillance in that it can only monitor patients who are already receiving medical treatment and having lab tests done - does not identify patients who have never been tested.  **Event based surveillance** refers to the aggregation of data resulting from the monitoring of internet sources such as ProMed and GPHIN |
| **La Crosse encephalitis Virus Study** | | |
| This study examines LACV with the following goal:  Select the sub-category that the study best fits into and describe the objective/outcome of the study. | * Pathogenesis of LACV * LACV transmission characteristics * Molecular characterization of LACV | Please indicate the objective/outcomes of the study under the appropriate category.  **Pathogenesis**: A virus study on pathogenesis will look at virus factors that can up or down regulate / manage virus replication etc. to successfully cause infection/disease in the host.  **Transmission characteristics** are receptors etc. on the virus that are necessary for LACV to move from one host to another.  **Molecular characterisation of LACV** studies are examining genetic make-up of the virus and identifying key areas of conservation or mutation. This may lead to a description of how changes in phenotype are related to genotype. |
| Is this a molecular epidemiology study?  (*Appears here and under the epidemiology section)* | * Yes, provide details of findings \_\_\_\_\_\_\_\_\_\_ * No | **Molecular epidemiology** is a branch of **epidemiology** and medical science that focuses on the contribution of potential genetic and environmental risk factors, identified at the **molecular** level, to the etiology, distribution and prevention of disease within families and across populations |
| **Mitigation Strategies** | | |
| What prevention/control strategies were investigated?  (Please check all that apply)  Please provide details on the mitigation strategy and include the name of any included chemicals | * Human behavioural protective measures: * Wearing long pants and/or lightly-coloured clothing * Tucking pants into socks * Using repellents; please specify \_\_\_ * Wearing clothing treated with permethrin insecticide * Using bed nets * Having window/door screens * Emptying standing water from containers such as flowerpots or buckets and cleaning them * Removing/destroying vector habitats (e.g. containers/tires) * Other behavioural measure, \_\_\_\_\_ * Intervention for blood supply: \_\_\_\_ * Vaccination * Landscape modification: \_\_\_\_\_\_ * Chemical control measures: * Insecticides\_\_\_\_\_ * Other chemical control measures: \_\_\_\_\_ * Biologic control of vector: \_\_\_\_\_ * Public education: \_\_\_\_\_ * Other mitigation: \_\_\_\_\_ | **PPMs**  Are behaviours that may reduce the risk of contact with a tick or exposure to LACV or development of disease from LACV. This may include protective clothing, repellents, barriers between the home and outside, destruction of tick habitat close to home.  Other interventions may include:   * Protection of the blood supply * Vaccination (none are known) * Landscape modification (frequent mowing, branch trimming, leaf litter clearing, removal of bird feeders, fencing to keep deer out, and use of mulch or gravel as a dry barrier between lawn and woods. * biological control (exposing ticks to *H. hookeri*, fungi, nematodes and viruses)   Public education to decrease the risk of tick contact for humans and companion animals. |
| Did the authors describe the impact of the mitigation strategy? | * Successes/positive impact: \_\_\_\_\_\_ * Limitation/negative impact: \_\_\_\_\_\_ * Not discussed | Briefly highlight the findings of the evaluation under successes and limitations. |
| **Social Impact** | | |
| Did the paper investigate knowledge and attitudes and/or risk perceptions towards LACV and potential prevention and control strategies?  (please check all that apply) | * Yes, **concerns** about toxic or environmental effects of control measures (e.g. DEET) * Yes, **perceptions** about the severity of LACV or vulnerabilities * Yes, **perceived** efficacy of protective measures * Yes, **knowledge** on behavioural mitigation practices * Yes, **knowledge** on LACV disease * Yes, **knowledge** on LACV harbouring vectors * Yes, **public attitudes** towards paying for protection from LACV (willingness to pay) * Yes, other: \_\_\_\_\_\_\_\_\_\_ |  |
| This paper is focused on LACV. | * Yes, the data in this paper is specific to LACV * No, this paper more broadly refers to tick-borne (or other vector-borne) diseases |  |
| What specific populations were investigated for contextual information?  *(please check all that apply)* | * General public * Physicians * Other medical or public health professionals, please specify:\_\_\_\_\_\_\_\_ * Government personnel, please specify \_\_\_\_ * NGO personnel, please specify \_\_\_ * Other, please specify \_\_\_\_\_ | What populations did the researchers speak to? Gather information from? |
| **Economic Burden** | | |
| Does the article report on the economic burden of LACV disease or cost-benefit of control measures?  *Specify description of outcomes available in the paper under the appropriate category.*  (Check all that apply) | * Yes, economic burden * Yes, cost-benefit of control measures * Yes, Other economic measure * No data is reported in the paper although economics is discussed |  |
| **Predictive Model for LACV** | | |
| Does this predictive model include Canada or at least the USA? | * Yes, Canada * Yes, USA but not Canada * No |  |
| Does the model include predictions under different climate change scenarios, to explore the impact of spread or emergence of LACV in the future? | * Yes, climate change scenarios are explored * No, the model is built upon current climate parameters * No, other. Explain \_\_\_\_\_\_\_\_\_ |  |
| **Other LACV topics** | | |
| Describe the LACV topic discussed in the research article that doesn't fit into the previous categories. | \_\_\_TXT\_\_ |  |
| **Final Section** | | |
| Indicate the type of LACV isolated or used in this study as described by the author. | * LACV description \_\_\_\_\_\_\_ * LACV not typed (e.g. serology) * LACV not isolated and serology not conducted * Other, explain \_\_\_\_\_ | In option 1 indicate the name of the virus isolate as reported.  Option 2 is where serology classified samples as positive or negative only. |
| Does the article investigate or discuss the potential impacts of climate change on LACV? | * Yes * No | If the impacts of climate change are investigated as part of the study or are discussed in the discussion based upon the research findings, check yes to this question. |
| Is there sufficient extractable data in this paper to proceed to quality assessment and further data extraction? | * Yes * No | Quick QA on whether study is worth progressing to QA/DE levels and more in depth analysis. |
| Additional comments: Are there any important details that you believe were not extracted? | \_\_TXT\_\_\_ |  |

Articles will be double extracted in Distiller SR.

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# S3. General characteristics of the 481 primary research articles on La Crosse virus (LACV) included in the scoping review.

|  |  |  |
| --- | --- | --- |
| **Category** | **N** | **%** |
| **Type of document** |  |  |
| Primary peer-reviewed | 376 | 78.2% |
| Grey literature with primary data | 90 | 18.7% |
| Conference abstract (sufficient data) | 8 | 1.7% |
| Thesis | 7 | 1.5% |
| **Continent** |  |  |
| North America | 437 | 90.9% |
| Europe | 43 | 8.9% |
| Central America | 1 | 0.2% |
| **Date of Publication** |  |  |
| Before 1979 | 70 | 14.6% |
| 1980-1989 | 125 | 26.0% |
| 1990-1999 | 78 | 16.2% |
| 2000-2009 | 106 | 22.0% |
| 2010-2016 | 102 | 21.2% |
| **LACV study focus\*** |  |  |
| Epidemiology | 216 | 44.9% |
| Describes surveillance activities | 114 | 23.7% |
| *In vitro* virus research1 | 124 | 25.8% |
| Transmission of LACV and vector competence | 90 | 18.7% |
| Pathogenesis in humans or animal hosts | 88 | 18.3% |
| Disease pathology | 82 | 17.0% |
| Infection mechanism | 5 | 1.0% |
| Immune response | 15 | 3.1% |
| Animal pathogenesis model | 34 | 7.1% |
| Accuracy of diagnostic tests | 42 | 8.7% |
| Treatment efficacy | 17 | 3.5% |
| Prevention and control strategies/ Interventions | 15 | 3.1% |
| Social impacts: knowledge and perception of LACV | 1 | 0.2% |
| Economic analysis | 3 | 0.6% |
| **Population Studied\*** |  |  |
| Humans | 174 | 36.2% |
| Animal hosts | 107 | 22.2% |
| Natural infection | 31 | 6.4% |
| Experimental infection | 78 | 16.2% |
| Vectors | 154 | 32.0% |
| Mosquito vector | 153 | 31.8% |
| Non-mosquito vector | 2 | 0.4% |
| Virus only | 146 | 30.4% |
| **Study Design\*** |  |  |
| Observational | 220 | 45.7% |
| Surveillance programme/monitoring | 117 | 24.3% |
| Prevalence survey | 46 | 9.6% |
| Case series/case report | 29 | 6.0% |
| Population based case series | 4 | 0.8% |
| Longitudinal | 8 | 1.7% |
| Cross sectional | 20 | 4.2% |
| Cohort | 4 | 0.8% |
| Case control | 6 | 1.2% |
| Sentinel animals | 6 | 1.2% |
| Experimental | 242 | 50.3% |
| Challenge trial | 161 | 33.5% |
| Controlled trial | 10 | 2.1% |
| Molecular characterisation | 90 | 18.7% |
| Molecular epidemiology | 8 | 1.7% |
| Evaluation of diagnostic tests | 42 | 8.7% |
| Economic model | 1 | 0.2% |
| Qualitative | 2 | 0.4% |

\*Total may not add to 100% as studies can be classified in more than one category

1*In vitro* LACV research included studies that only examined the virus itself. This could include pathogenesis, transmission, and diagnostic test accuracy studies using only virus cell cultures.

# S4. Supplementary table of references associated with key research categories described in the results section and tables of the scoping review.

|  |  |  |
| --- | --- | --- |
| Topic Category | Number of studies | References1 |
| La Crosse Virus Studies |  |  |
| Molecular Epidemiology outcomes | 8 | Klimas 1981, Huang 1995, Huang 1997, Armstrong 2006, Lambert 2015, Bennett 2007, Reese, 2008, Reese, 2010, |
| Three lineages | 3 | Lambert 2015, Klimas 1981, Armstrong 2011 |
| Lineage 1 associated with fatal human disease | 4 | Bennett 2008, Huang 1995, Huang 1997, Lambert 2015 |
| Phylogeny and viral mutations | 8 | Lambert 2015, Baldridge 1989, Bennett 2007, Reese 2008, Reese 2010, El Said 1979, Borucki 1998, Forrester 2012 |
| LACV vectors |  |  |
| Significant risk factors (Table 2) |  |  |
| Geography: High risk clusters in north central/eastern USA | 2 | Reese 2010, Trout Fryxell 2015 |
| Increased chipmunk density and Increased ground cover density | 1 | Lisitza 1977 |
| Increased risk in August vs. July | 3 | Scheidler 2006 |
| Vector behaviour association with LACV infection |  |  |
| probing | 4 | Patrican 1985a, Paulson 1987, Paulson 1992, Grimstad 1980 |
| feeding success or size | 5 | Grimstad 1985, Bevins 2008, Jackson 2012, Westby 2016, Grimstad 1980 |
| blood meal preferences | 2 | Lancaster 2005, Westby 2015 |
| diapause (period of arrested development in response to environmental conditions) | 2 | McGaw 1998, Woodring 1998 |
| grooming | 1 | Paulson, 1987 |
| time of feeding | 1 | Watts et al, 1974 |
| Impact of dual infection with LACV and other pathogens | 4 | Kramer 1983, Beaty 1985, Chandler 1991, Beaty 1983a, Patrican 1985 |
| Diagnostic test accuracy studies for vectors with extractable outcomes | 8 | Grimstad1983, Hildreth 1983, Hildreth 1982, Kempf 2006, Kuno 1996, Lambert 2005, Landry 1988, Vodkin1994, Wasieloski 1994 |
| LACV hosts |  |  |
| Significant risk factors (Table 2) |  |  |
| Increased risk in high quality habitats | 1 | Gauld 1974 |
| Increased risk for chipmunks vs. squirrels | 1 | Lancaster 2005 |
| LACV Seropositive Host (Table 3) |  |  |
| White-tailed deer  (*Odocoileus virginianus*)1 | 2 | Boromisa 1987, Hoff 1973, Issel 1972, Murphy 1989, Nagayama 2001, Neitzel 1991, Walker 1993 |
| Mule deer (O*docoileus hemionus*) | 2 | Hoff 1973, Campbell 1989) |
| Red fox (V*ulpes fulva*)1 | 1 | Amundson 1980 |
| Grey fox (*Urocyon cinereoargenteus*) | 1 | Amundson 1980 |
| *Procyon lotor* | 3 | Amundson 1980, Clark 1986, Papadopoulos 1970 |
| Eastern cottontail rabbits *(Sylvilagus floridanus)* | 1 | Dressler 1988 |
| Rabbits (species not reported | 1 | Papadopoulos 1970 |
| Gray squirrels (*Sciuris carolinensis*)1 | 4 | Balfour 1976, Lancaster 2005, Walker 1993, Lobo 2001 |
| Fox squirrel (*S. niger*)1 | 1 | Lancaster 2005 |
| Species not reported | 1 | Westby 2015 |
| Eastern chipmunks  (*Tamias striatus*)1 | 9 | Berry 1975, Landry 1988, Lancaster 2005, Gauld 1974, Walker 1993, Cully 1991, Gauld 1975, Kitron 1998 |
| Species not reported | 1 | Balfour 1976 |
| *Marmota monax1* | 1 | Berry 1975 |
| *Canis familiaris3* | 3 | Godsey 1988, Black 1994, Tatum 1999 |
| *Sus domesticus3* | 1 | Godsey 1988 |
| *Equus caballus3* | 2 | Godsey 1988, Berry 1975 |
| *Bos taurus3* | 1 | Godsey 1988 |
| Isolation of LACV in hosts (Table 3) |  |  |
| gray squirrels (*S. carolinensis*) | 2 | Ksiazek 1977b, Ksiazek 1977a |
| eastern chipmunks (*T. striatus*) | 3 | Ksiazek 1977b, Ksiazek 1977a, Landry 1988 |
| Successful host to vector transmission |  |  |
| Chipmunk | 5 | Berry 1986, Amundson 1980, Cully 1992, Patrican 1985b, Thompson 1983 |
| Hamster | 1 | Sardelis 2002 |
| Mouse | 3 | Watts 1975, Pantuwatana 1972, Berry 1986 |
| Dogs | 1 | Godsey 1988 |
| Fox | 1 | Amundson, 1980 |
| Unsuccessful host to vector transmission in deer | 1 | Osorio 1996 |
| Host to Host transmission: chipmunk to fox | 1 | Amundson 1980 |
| Diagnostic test accuracy studies in hosts with extractable outcomes | 2 | Beaty 1982b, Karabatsos 1980 |
| Human LACV |  |  |
| Significant risk factors (Table 2) |  |  |
| Demographics |  |  |
| Prevalence of LACV antibodies increases with age | 3 | Grimstad 1984, Szumlas 1996, Monath 1970 |
| Increased risk for males vs. females | 1 | Monath 1970 |
| Increased risk if less than high school degree | 1 | Haddow 2011b |
| Geography: Increased risk identified in certain counties from Illinois and Minnesota | 2 | Balfour 1976, Kitron 1997 |
| Geography: Southern states at greater risk vs. northern states in USA | 1 | Haddow 2009 |
| Increased risk in rural areas vs. urban | 1 | Monath 1970 |
| Increased risk on reservation vs. off reservation | 1 | Szumlas 1996 |
| Increased risk if area with lower housing density | 1 | Haddow 2011b |
| Children at increased risk if spent >1 hour in woods during the day | 1 | Woodruff 1992 |
| Increased risk with more hours spent outdoors | 1 | Erwin 2002 |
| Slight increased risk if child never wore repellent | 1 | Woodruff 1992 |
| Increased risk in children living in homes with no air conditioning | 1 | Woodruff 1992 |
| Increased risk if tree holes near residence | 2 | Woodruff 1992, Erwin 2002 |
| Increased risk the closer residence is to forest edge | 1 | Woodruff 1992 |
| Increased risk if artificial containers near residence | 2 | Woodruff 1992, Hedberg 1985 |
| Children were at increased risk if >10 tires near residence | 1 | Woodruff 1992 |
| Season: Increased risk in June-August and October vs. March-May, September and November | 1 | Haddow 2009 |
| Season: Increased risk in July to Sept compared to all other months | 1 | Kitron 1997 |
| Increased disease progression if patient presented with vomiting, seizure, coma, fever, and low sodium | 1 | McJunkin 2001 |
| Case fatalities from LACV | 29 | Berry 1984, Bice 2013, Chun 1983, Copps 1969, Gundersen 1983, Lambert 2015, McJunkin 2001, Miller 2012, Sotir 2007, Robinson 2003, Cooper 2006, West Virginia Department of Health 2014, CDC 2013, CDC 2012, Lindsey 2015, Lindsey 2014, Gaensbauer 2014, Balfour 1974, Balfour 1973, Robinson 2002, Cooper 2005, Cooper 2008, Levine 2015, CDC 1988, Haddow 2011a, Beaty 1982a, Andre 1985, Haddow 2009, Kentucky Department for Public Health 2002 |
| Proportion of hospitalizations of LACV cases | 29 | Bice 2013, CDC 2013, CDC 2012, Lindsey 2014, Lindsey 2015, Gaensbauer 2014, Balfour 1974, Balfour 1973, Jones 2000, CDC 1988, Teleron 2016, West Virginia Department of Health 2014, Boyce 1998, CDC 2010, Lambert 2015, McJunkin 1997, McJunkin 2001, Miller 2012, Monath 1970, Sokol 2001, Sotir 2007, Utz 2005, Utz 2003, Woodruff 1992, Wurtz 2000, West Virginia Department of Health 2010, Wisconsin Division of Public Health 2009, Sikes 1984 |
| Proportion of hospitalized LACV cases in intensive care | 2 | Miller 2012, McJunkin 1997 |
| Pathogenesis of LACV in humans | 18 | de los Reyes 2008, Erwin 2002, Gundersen 1983, Haddow 2011a, Jones 1999, Kobayashi 2011, McJunkin 1997, McJunkin 2001, Miller 2012, Sokol 2001, Teleron 2016, Thompson 1983, Wurtz 2000, Kelsey 1978 |
| Diagnostic test accuracy for humans |  |  |
| immunodiffusion | 2 | Papadopoulos 1970, Balfour 1974 |
| counter immunoelectrophoresis | 4 | Balfour 1974, Lindsey 1978, Beaty 1983b, Lindsey 1977 |
| serum dilution neutralisation | 1 | Lindsey 1978 |
| in-direct fluorescent antibody | 1 | Chandler 1998 |
| reverse transcription polymerase chain reaction | 2 | Chandler 1998, Lambert 2005 |
| nucleic acid sequence based amplification | 1 | Lambert 2005 |
| Treatment |  |  |
| ribavirin | 4 | Cassidy 1989, Gowen 2007, Toltzis 1988, McJunkin 2011 |
| cycloheximide | 3 | Raju 1988, Raju 1987, Raju 1986 |
| WP1130 | 2 | Gonzalez-Hernandez 2014, Perry 2012 |
| puromycin | 2 | Raju 1987, Raju 1986 |
| pactamycin | 2 | Raju 1987, Raju 1986 |
| iposomes, IFN-ß and Poly (I·C) | 1 | Taylor 2013 |
| Interventions |  |  |
| Vaccine candidates | 8 | Powers 1994, Keil 2015, Joyce 2011, Bennett 2012, Operschall 1999, Pavlovic 2000, Pekosz 1995, Schuh 1999 |
| Control of LACV in vectors | 3 | Glaser 2010, Eastep 2012, Powers 1996 |
| Personal protective measures (humans) | 4 | Thompson 1983, Sotir 2007, Wisconsin Division of Public Health 2006, Maryland Department of Health and Mental Hygiene 2001 |
| Social and Economic Burden | 4 | Utz 2003, Clark 1983, Lee 2002, Utz 2005 |

1 Please refer to supplementary material S2 for the citation list of included articles.

# S5. Fifty-six mosquito and seven non-mosquito vector species from 153 experimental and observational studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Vector** | All Study Designs | Observational Study Design (n=62) | | |
| **Total studies**  **N** | **Total studies**  **N (%)** | **N studies reporting LACV positive** | **Reference1**  **(LACV positive)** |
| **Mosquitos** | **153** |  |  |  |
| **Aedes species** |  |  |  |  |
| *Ae. triseriatus* | 131 | 53 (85.5) | 38 | Ref2 |
| *Ae. albopictus* | 33 | 20 (32.3) | 5 | Barker 2003, Erwin 2002, Lambert 2010, W. Virginia 2014, Gerhardt 2001 |
| *Ae. japonicus* | 14 | 10 (16.1) | 1 | Harris 2015 |
| *Ae. hendersoni* | 13 | 6 (9.7) | 1 | Mitchell 1998 |
| *Ae. vexans* | 13 | 11 (17.7) | 0 |  |
| *Ae. trivittatus* | 11 | 10 (16.1) | 1 | Thompson 1972 |
| *Ae. canadensis* | 9 | 8 (12.9) | 2 | Berry 1986, Nasci 2000 |
| *Ae. cinereus* | 6 | 5 (8.1) | 0 |  |
| *Ae. communis* | 5 | 4 (6.5) | 1 | Thompson 1972 |
| *Ae. aegypti* | 5 | 0 (0.0) | N/A |  |
| *Ae. stimulans* | 5 | 4 (6.5) | 0 |  |
| *Ae. zoosophus* | 2 | 0 (0.0) | N/A |  |
| *Ae. atropalpus* | 2 | 1 (1.6) | 0 |  |
| *Ae. brelandi* | 2 | 0 (0.0) | N/A |  |
| *Ae. punctor* | 2 | 2 (3.2) | 0 |  |
| *Ae. dianteus* | 2 | 2 (3.2) | 0 |  |
| *Ae. informatus* | 1 | 1 (1.6) | 1 | Boyd 1978 |
| *Ae. sticticus* | 1 | 1 (1.6) | 0 |  |
| *Ae. nigromaculis* | 1 | 1 (1.6) | 0 |  |
| *Ae. barberi* | 1 | 1 (1.6) | 0 |  |
| *Ae. taeniorhynchus* | 1 | 0 (0.0) | N/A |  |
| *Ae. dorsalis* | 1 | 1 (1.6) | 0 |  |
| *Ae. flavescens* | 1 | 1 (1.6) | 0 |  |
| *Ae. aurifer* | 1 | 1 (1.6) | 0 |  |
| *Ae. intrudens* | 1 | 1 (1.6) | 0 |  |
| *Ae. implicatus* | 1 | 1 (1.6) | 0 |  |
| *Ae. provocans* | 1 | 1 (1.6) | 0 |  |
| *Ae. abserratus-punctor* | 1 | 1 (1.6) | 0 |  |
| *Ae. atlanticus* | 1 | 1 (1.6) | 0 |  |
| *Ae. tormentor* | 1 | 1 (1.6) | 0 |  |
| *Ae. excrucians* | 1 | 1 (1.6) | 0 |  |
| *Ae. nigromaculis* | 1 | 0 (0.0) | N/A |  |
| *Ae. hendersoni/triseriatus hybrid* | 1 | 0 (0.0) | N/A |  |
| **Culex species** |  |  |  |  |
| *Cx. pipiens/restuans* | 15 | 14 (22.6) | 4 | Camille Harris 2015, Erwin 2002, Thompson 1972, W. Virginia 2014 |
| *Cx. erraticus* | 7 | 7 (11.3) | 0 |  |
| *Cx. territans* | 3 | 3 (4.8) | 0 |  |
| *Cx. tarsalis* | 2 | 2 (3.2) | 0 |  |
| *Cx. salinarus* | 1 | 1 (1.6) | 0 |  |
| *Cx. fatigans* | 1 | 0 (0.0) | N/A |  |
| *Cx. quinquefasciatus* | 1 | 1 (1.6) | 0 |  |
| **Anopheles species** |  |  |  |  |
| *An. punctipennis* | 11 | 10 (16.1) | 0 |  |
| *An. quadrimaculatus* | 6 | 6 (9.7) | 0 |  |
| *An. walkeri* | 3 | 3 (4.8) | 0 |  |
| *An. crucians* | 1 | 1 (1.6) | 0 |  |
| *An. earlei* | 1 | 1 (1.6) | 0 |  |
| **Phosphora species** |  |  |  |  |
| *Ps. ferox* | 2 | 2 (3.2) | 0 |  |
| *Ps. columbiae* | 2 | 2 (3.2) | 0 |  |
| *Ps. signipennis* | 1 | 0 (0.0) | N/A |  |
| *Ps. ciliata horrida* | 1 | 1 (1.6) | 0 |  |
| **Culiseta species** |  |  |  |  |
| *Cs. morsitans* | 3 | 3 (4.8) | 0 |  |
| *Cs. inornata* | 5 | 3 (4.8) | 0 |  |
| *Cs. impatiens* | 1 | 1 (1.6) | 0 |  |
| **Other species** |  |  |  |  |
| *Uranotenia sapphirina* | 4 | 4 (6.5) | 0 |  |
| *Toxorhynchites rutilus* | 1 | 1 (1.6) | 0 |  |
| *Orthopodomyia signifera* | 4 | 4 (6.5) | 1 | Erwin 2002 |
| *Coquillettidia perturbans* | 7 | 7(11.3) | 0 |  |
| Not identified | 10 | 7 (11.3) | 5 | W. Virginia 2014, Nasci 1996, Gabel 2010, Texas 2014, Mark-Carew 2013 |
| **Non-mosquito** | **2** |  |  |  |
| **Horse fly species** |  |  |  |  |
| *Hybomitra lasiophthalma* | 1 | 1 (1.6) | 1 | Wright 1970 |
| *Hy. illota* | 1 | 1 (1.6) | 0 |  |
| *Hy. epistates* | 1 | 1 (1.6) | 0 |  |
| *Hy. typhus* | 1 | 1 (1.6) | 0 |  |
| *Hy. nuda* | 1 | 1 (1.6) | 0 |  |
| **Deer fly species** |  |  |  |  |
| *Chrysops excitans* | 1 | 1 (1.6) | 0 |  |
| **Fruit fly species** |  |  |  |  |
| *Drosophila melanogaster* | 1 | 0 (0.0) | N/A |  |

N/A = not applicable as the study did not test for natural LACV exposure or infection

\*Total may not add to 100% as a single study may contain results for more than one species

1 Please refer to supplementary material S2 for the citation list of included articles.

2 Reese 2008, Armstrong 2006, Lambert 2015, Andre 1985, Balfour 1975, Balfour 1976, Barker 2003, Beaty1975, Berry 1974, Berry 1975, Berry 1986, Clark 1983b, Clark 1982, Erwin 2002, Freyman 2013, Kappus 1982, Lambert 2010, Landry 1988, Lisitza 1977, Mitchell 1998, Nasci 2000, Pantuwatana 1974, Pinger 1983, Pinger 1980, Reese 2010, Rowley 1979, Rowley 1973, Scheidler 2006, Szumlas 1996b, Thomas 1982, Thompson 1972, Trout Fryxell 2015, Watts 1973, Watts 1974, Westby 2011, Wong 1978, W. Virginia 2011, W. Virginia 2014

3 Glaser, 2010

# S6. The number and percent of articles reporting competence outcomes for the transmission of La Crosse virus in mosquito vectors infected by various modes (N=80).

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Mode of Infection** | **N\*** | % |
| Minimum/midgut infection rate1 (n=63) | Blood meal | 55 | 68.8% |
| Vertical | 28 | 35.0% |
| Inoculated (intrathoracically)2 | 15 | 18.8% |
| Venereal | 6 | 7.5% |
| Dissemination rate3 (n=28) | Blood meal | 26 | 32.5% |
| Vertical | 8 | 10.0% |
| Inoculated (intrathoracically) | 3 | 3.8% |
| Venereal | 2 | 2.5% |
| Transmission rate4 (n=42) | Blood meal | 37 | 46.3% |
| Vertical | 16 | 20.0% |
| Inoculated (intrathoracically)2 | 11 | 13.8% |
| Venereal | 6 | 7.5% |
| Impact of genetics/genetic changes (n=14) | Blood meal | 13 | 16.3% |
| Vertical | 8 | 10.0% |
| Inoculated (intrathoracically) | 4 | 5.0% |
| Impact on mosquito reproduction (n=8) | Blood meal | 8 | 10.0% |
| Vertical | 4 | 5.0% |
| Inoculated (intrathoracically) | 3 | 3.8% |
| Venereal | 1 | 1.3% |
| Survival rate (n=6) | Blood meal | 5 | 6.3% |
| Vertical | 2 | 2.5% |
| Inoculated (intrathoracically) | 4 | 5.0% |
| Venereal | 1 | 1.3% |
| Impact of LACV infection on body size/wing length (n=6) | Blood meal | 5 | 6.3% |
| Vertical | 1 | 1.3% |
| Other5 (n=8) | Blood meal | 9 | 11.3% |
| Vertical | 5 | 6.3% |
| Inoculated (intrathoracically) | 4 | 5.0% |
| Venereal | 1 | 1.3% |

\*Total may not add to 100% as studies may have reported results for multiple outcomes

1 Infection rate defined as virus present only in midgut

2 Mosquitoes inoculated intrathoracically, except one study (Miller 1978) which submerged mosquitoes in a viral suspension

3 Dissemination rate defined as when the virus spreads from the midgut to the head, thorax, legs etc.

4 Transmission rate defined as virus present in saliva

5 Other outcomes include: nutritional stress (n=2) (Camille Harris 2015, Patrican 1985), sex/life stage (n=2) (Patrican 1985, Kramer 1983), salivation rate (n=2) (Paulson 1987, Thompson 1979), gut microbiota (n=1) (Muturi 2016), re-feeding rate (n=1) (Turell 1985), diapause rate (n=1) (Woodring 1998)

# S7. Incubation period and viremic period of experimental La Crosse virus (LACV) infection by animal host (N=20)

|  |  |  |  |
| --- | --- | --- | --- |
| **Category** | **HostCategory** | **Range of days** | **Reference3** |
| Incubation period1 | Mice | 0-4 | Beaty 1982b, Bennett 2008, Gonzalez-Scarano 1985, Janssen 1984, Johnson 1983, Lienenklaus 2009, Mukherjee 2013, Pekosz 1995 |
| Chipmunks | 1-6 | Watts 1975, Cully 1992, Pantuwatana 1972, Patrican 1985, Seymour 1983 |
| Deer | 2-5 | Issel 1972a, Osorio 1996a |
| Rabbits | 2 | Osorio 1996b |
| Squirrels | 2-4 | Pantuwatana 1972 |
| Pigs | 1-2 | Godsey 1988 |
| Dogs | 1-2 | Godsey 1988 |
| Fox | 1-2 | Amundson 1980 |
| Viremic period2 | Chipmunks | 1-7 | Pantuwatana 1972, Issel 1975, Seymour 1983, Patrican 1985, Osorio 1996a, Cully 1992 |
| Squirrels | 2-4 | Pantuwatana 1972, Issel 1975 |
| Mice | 1-3 | Pekosz 1995, Beaty 1982b |
| Deer | 1 | Issel 1972a |
| Rabbits | 2 | Seymour 1983 |
| Dogs | 1-3 | Godsey 1988 |
| Pigs | 1-3 | Godsey 1988 |
| Fox | 1-4 | Amundson 1980 |
| Gerbils | 2-6 | Cheng 1999 |

1Incubation period defined as the time between the experimental animal being exposed to infection and the onset of first symptoms

2Viremic period defined as the time the experimental animal is infectious

3 Please refer to supplementary material S2 for the citation list of included articles.

# S8: Clinical signs, symptoms and sequelae reported in LACV infected animal hosts (N=21)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Sign/Symptom/Sequelae** | **Animal** | **Type of Host** | **No. of Articles** | **Proportion (%) affected** | **Reference\*1** |
| **Neurological** |  |  | **18** |  |  |
| Paralysis | Mice | Experimental | 7 | 22/22 (100%), NR | Hefti 1999, |
| Gerbils | Experimental | 1 | 4/10 (40%) | Osorio 1996b |
| Ataxia (loss of body control) | Mice | Experimental | 1 | NR |  |
| Dogs | Natural | 1 | 1/1 (100%) | Tatum 1999 |
| Lethargy | Dogs | Experimental | 1 | 1/8 (12.5%) | Godsey 1988 |
| Mice | Experimental | 1 | NR |  |
| Chipmunks | Experimental | 1 | 4/4 (100%) | Seymour 1983 |
| Tremors | Dogs | Natural | 1 | 5/6 (83.3%) | Godsey 1988 |
| Mice | Experimental | 2 | NR |  |
| Slow movement | Mice | Experimental | 3 | NR |  |
| Seizure | Mice | Experimental | 4 | NR |  |
| Dogs | Natural | 2 | 4/5 (80%) | Tatum 1999 |
| Arched back | Mice | Experimental | 1 | NR |  |
| Dogs | Experimental | 1 | 4/4 (100%) | Godsey 1988 |
| Not coordinated | Dogs | Both | 2 | 4/4 (100%), 1/1 (100%) | Godsey 1988, Tatum 1999 |
| Depression | Dogs | Natural | 1 | 1/1 (100%) | Tatum 1999 |
| Body twisting | Dogs | Natural | 1 | 1/1 (100%) | Tatum 1999 |
| Head tilt | Dogs | Natural | 1 | 1/1 (100%) | Tatum 1999 |
| Meningoencephalitis | Gerbils | Experimental | 1 | NR |  |
| Circled | Mice | Experimental | 1 | NR |  |
| Unresponsive | Mice | Experimental | 1 | NR |  |
| Not specified | Mice | Experimental | 8 | 22/22 (100%), NR | Hefti 1999 |
| Dogs | Natural | 1 | 1/1 (100%) | Tatum 1999 |
| **Other** |  |  | **8** |  |  |
| Weight loss | Mice | Experimental | 1 | NR |  |
| Rabbits | Experimental | 1 | NR |  |
| Respiratory | Mice | Experimental | 1 | NR |  |
| Dogs | Natural | 1 | 1/7 (14.3%) | Black 1994 |
| Fever | Dogs | Natural | 1 | 1/1 (100%) | Tatum 1999 |
| Anorexia | Dogs | Natural | 1 | 1/1 (100%) | Tatum 1999 |
| Decreased foot length | Rabbits | Experimental | 1 | NR |  |
| Inflammation | Mice | Experimental | 1 | NR |  |
| Pale | Mice | Experimental | 1 | NR |  |
| Fracture | Deer | Experimental | 1 | 1/11 (9.1%) | Issel 1972a |

NR = not reported

\*References provided only if article reported the proportion affected

1 Please refer to supplementary material S2 for the citation list of included articles.

# S9. General characteristics of the articles (number and proportion) investigating human populations affected by La Crosse virus (N=174)

|  |  |  |
| --- | --- | --- |
| **Category** | **N\*** | **%** |
| **Sampling frame** |  |  |
| General population | 138 | 79.3% |
| Hospital/clinic patients | 25 | 14.4% |
| At risk population 1 | 16 | 9.2% |
| Sample library | 7 | 4.0% |
| **Health Status** |  |  |
| Co-infection2 | 3 | 1.7% |
| Co-morbidity3 | 8 | 4.6% |
| **Age** |  |  |
| Child (≤18 years old) | 63 | 36.2% |
| Adult (≥19 years old) | 6 | 3.4% |
| Both | 23 | 13.2% |
| Not reported | 82 | 47.1% |
| **Type of sample** |  |  |
| Blood | 71 | 40.8% |
| Cerebrospinal fluid (CSF) | 15 | 8.6% |
| Tissue4 | 10 | 5.7% |
| Not reported | 101 | 58.0% |
| **Diagnostic test** |  |  |
| Immunoassay | 85 | 48.9% |
| Molecular | 6 | 3.4% |
| Virus isolation/culture | 6 | 3.4% |
| Not reported | 87 | 50.0% |
| **Study Design** |  |  |
| Observational | 160 | 92.0% |
| Surveillance reports | 112 | 64.4% |
| Case series | 27 | 15.5% |
| Cross sectional | 14 | 8.0% |
| Case control | 6 | 3.4% |
| Population based case series | 4 | 2.3% |
| Prevalence survey | 5 | 2.9% |
| Longitudinal study | 2 | 1.1% |
| Cohort | 3 | 1.7% |
| Controlled trial | 2 | 1.1% |
| Diagnostic test evaluation | 21 | 12.1% |
| Qualitative study | 2 | 1.1% |
| Economic models | 1 | 0.6% |

\*Total may not add to 100% as studies can be categorized in more than one way

1At risk populations: occupation (n=3) (Boyd 1978, Adjemian 2012, Kosoy 2016), children (n=11) (Hinckley 2009, Fredia 2001, Kappus 1982, Balfour 1976, Boyce 1998, de los Reyes 2008, Hardin 2003, Jones 2000, McJunkin 2011, Miller 2012, Thompson 1983), developmental delay in children (Monath 1970, Gauld 1979) and adults (Gauld 1979) (n=2), pregnant (n=1) (Hinckley 2009)

2Co-infections: West Nile Virus (Levine 2015) and mixed viral infections including enteroviruses (Balfour 1974), adenovirus (type I) (Balfour 1974, Balfour 1973), echovirus (type 11, 25, 30)(Balfour 1973), mumps (Balfour 1974), and coxsackievirus B5 (Balfour 1973)

3Co-morbidities: endocrine disorder (Lindsey 2014, Hinckley 2009, Bice 2013, McJunkin 1997, Wurtz 2000), behavioral disorder (Balkhy 2000, Tatum 1999), seizure disorder (Balkhy 2000), neurological disorder (Kobayashi 2011), heart disease (Lindsey 2014), hypertension (Lindsey 2014), arthritis (Lindsey 2014)

4Tissues: brain (n=7) (McJunkin 2001, Lambert 2015, Fredia 2001, McJunkin 1997, Kobayashi 2011, Chandler 1998, Lambert 2005), nasopharyngeal (n=2) (Fredia 2001), umbilical cord and placenta (n=1) (Hinckley 2009), rectal (n=1) (Fredia 2001), not reported (n=1) (Minnesota 1998)

# S10. The number of cases and incidence rate of La Crosse virus (LACV) cases per 100000 person-years in the general human population captured through disease surveillance in the USA from 1963-2016 (N=130)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **State** | **Year Sampled** | **Number of cases of LACV reported** | **Incidence rate\* per 100000 person-years** | **Reference9** |
| USA | 1991 | 38 | 0.02 | CDC 1992 |
| 2003-20121 | 754 | 0.032 | Gaensbauer 2014 |
| 2003-20121 | 665 children | 0.09 | Gaensbauer 2014 |
| 2004 | 117 | 0.042 | CDC 2016 |
| 2005 | 80 | 0.032 | CDC 2016 |
| 2006 | 67 | 0.022 | CDC 2016 |
| 2007 | 53 | 0.022 | CDC 2016 |
| 2008 | 53 | 0.022 | CDC 2016 |
| 2009 | 49 | 0.022 | CDC 2016 |
| 2010 | 75 | 0.022 | CDC 2016 |
| 20111 | 116 | 0.04 | CDC 2012 |
| 2011 | 130 | 0.04 | CDC 2012 |
| 2011 | 123children | 0.17 | CDC 2012 |
| 20121 | 71 | 0.02 | CDC 2013 |
| 2012 | 78 | 0.032 | CDC 2016 |
| 2012 | 65 children | 0.09 | CDC 2013 |
| 20131 | 77 | 0.02 | Lindsey 2014 |
| 2013 | 85 | 0.03 | Lindsey 2014, CDC 2016 |
| 2013 | 76 children | 0.16 | Lindsey 2014 |
| 20141 | 76 | 0.02 | Lindsey 2015 |
| 2014 | 80 | 0.03 | Lindsey 2015 |
| 2014 | 72 children | 0.10 | Lindsey 2015 |
| Alabama3 | 2000 | 1 | 0.02 | Alabama 2000 |
| 2001 | 1 | 0.02 | Alabama 2001 |
| 2005 | 1 | 0.022 | CDC 2016, Alabama 2005 |
| 20111 | 1 | 0.02 | CDC 2012, CDC 2016 |
| 20131 | 1 | 0.02 | Lindsey 2014, CDC 2016 |
| Florida | 2004 | 2 | 0.012 | CDC 2016 |
| 2006 | 1 | 0.014 | Shultz 2006, CDC 2016 |
| 2007 | 1 | 0.014 | Shultz 2007 |
| 2008 | 1 | 0.014 | CDC 2016, Radke 2009 |
| 20111 | 1 | 0.01 | CDC 2012, CDC 2016 |
| 20141 | 1 | 0.01 | Lindsey 2015, Florida 2016 |
| 2015 | 1 | 0.014 | Florida 2016 |
| Georgia | 1982 | 8 | 0.14 | Sikes 1984 |
| 2004 | 5 | 0.062 | CDC 2016 |
| 2005 | 1 | 0.012 | CDC 2016 |
| 2006 | 1 | 0.012 | CDC 2016 |
| 2007 | 2 | 0.022 | CDC 2016 |
| 2008 | 2 | 0.022 | CDC 2016 |
| 2009 | 2 | 0.022 | CDC 2016 |
| 2010 | 2 | 0.022 | CDC 2016 |
| 20111 | 2† | 0.02 | CDC 2012, Gabel 2012 |
| 20131 | 1† | 0.01 | Lindsey 2014, CDC 2016, Gabel 2014 |
| 20141 | 1 | 0.01 | Lindsey 2015 |
| 2014 | 2 | 0.022 | CDC 2016 |
| Illinois3 | 1966-1995 | 175 | 0.052 | Kitron 1997 |
| 1966-1980 | 61 | 0.036 | Clark 1983a |
| 19841 | 2 | 0.02 | WHO 1989 |
| 2004 | 9 | 0.072 | CDC 2016 |
| 2005 | 1 | 0.012 | CDC 2016 |
| 2007 | 1 | 0.012 | CDC 2016 |
| 2009 | 1 | 0.012 | CDC 2016 |
| Indiana | 1963-19831 | NR | 0.085 | WHO 1989 |
| 1982 | 12 | 0.22 | WHO 1989 |
| 19841 | 15 | 0.28 | WHO 1989 |
| 2000 | 2 | 0.03 | Indiana 2000 |
| 2002 | 4 | 0.06 | Indiana 2002 |
| 2003 | 3 | 0.05 | Indiana 2003 |
| 2004 | 2 | 0.032 | CDC 2016 |
| 2004 | 1 | 0.02 | Indiana 2004 |
| 2005 | 1 | 0.022 | CDC 2016 |
| 2006 | 3 | 0.052 | CDC 2016 |
| 2009 | 1 | 0.02 | CDC 2016, Cierzniewski 2009 |
| 20111 | 2 | 0.03 | CDC 2012, CDC 2016 |
| 2011 | 3 | 0.05 | CDC 2012, La Netta 2014 |
| 20121 | 2 | 0.03 | CDC 2013 |
| 2012 | 3 | 0.05 | CDC 2013, LaNetta 2014 |
| 20131 | 1 | 0.02 | Lindsey 2014, La Netta 2015 |
| 2014 | 2 | 0.03 | LaNetta 2015 |
| Iowa | 1963-19831 | NR | 0.145 | WHO 1989 |
| 1972-1975 | 20† | 0.182 | Wong 1973 |
| 1975 | 12 | 0.42 | Rowley 1979 |
| 19781 | 18 | 0.62 | Andre 1985 |
| 19791 | 6 | 0.21 | Andre 1985 |
| 19801 | 8 | 0.28 | Andre 1985 |
| 19841 | 7 | 0.24 | WHO 1989 |
| 2004 | 2 | 0.072 | CDC 2016 |
| 2006 | 1 | 0.032 | CDC 2016 |
| 2007 | 1 | 0.032 | CDC 2016 |
| Kentucky | 2002 | 3† | 0.05 | Kentucky 2002 |
| 2008 | 1 | 0.022 | CDC 2016 |
| 20111 | 1 | 0.02 | Chandler 1998, CDC 2012 |
| Louisiana | 2001 | 1 | 0.02 | Louisiana 2015 |
| 2002 | 1 | 0.02 | Louisiana 2015 |
| 2003 | 3 | 0.07 | Louisiana 2015 |
| 2004 | 3 | 0.072 | CDC 2016 |
| 2005 | 1 | 0.02 | CDC 2016, Louisiana 2015 |
| 2006 | 3 | 0.07 | CDC 2016, Louisiana 2015 |
| 2008 | 1 | 0.02 | CDC 2016, Louisiana 2015 |
| 2015 | 1 | 0.02 | Louisiana 2015 |
| Maryland | 2001 | 1 | 0.02 | Maryland 2010, Maryland 2001 |
| 2010 | 2 | 0.03 | Maryland 2010 |
| Michigan3 | 2004 | 1 | 0.012 | CDC 2016 |
| 2006 | 2 | 0.022 | CDC 2016 |
| 2010 | 2 | 0.02 | CDC 2016, Stobierski 2013 |
| 20111 | 1 | 0.01 | CDC 2016, CDC 2012 |
| Minnesota | 1963-19831 | NR | 0.35 | WHO 1989 |
| 1978 | 24 | 0.60 | Sjogren 1979 |
| 1979 | 45 | 1.11 | Hedberg 1985 |
| 1997 | 5† | 0.11 | Minnesota 1998 |
| 1998 | 4† | 0.09 | Minnesota 1999 |
| 1999 | 6† | 0.13 | Minnesota 2000 |
| 2000 | 8† | 0.16 | Minnesota 2001 |
| 2001 | 12† | 0.24 | Minnesota 2002 |
| 2002 | 13 | 0.26 | Minnesota 2004 |
| 2003 | 3 | 0.06 | Minnesota 2004 |
| 2004 | 2 | 0.04 | CDC 2016, Minnesota 2005 |
| 2005 | 2 | 0.04 | CDC 2016, Minnesota 2006 |
| 2006 | 1 | 0.02 | Minnesota 2007 |
| 2007 | 1 | 0.02 | CDC 2016, Minnesota 2008 |
| 2008 | 1 | 0.02 | CDC 2016, Minnesota 2009 |
| 2010 | 1 | 0.02 | CDC 2016, Minnesota 2011 |
| 20111 | 1 | 0.02 | CDC 2016, Minnesota 2012, CDC 2012 |
| 20121 | 4 | 0.07 | Minnesota 2013, CDC 2013 |
| 20131 | 4 | 0.07 | Lindsey 2014 |
| 2013 | 5 | 0.09 | CDC 2016, Minnesota 2015b, Lindsey 2014 |
| 2014 | 4 | 0.07 | Minnesota 2015a, Lindsey 2015 |
| 2015 | 1 | 0.02 | Minnesota 2016 |
| Mississippi | 1968 | 4† | NR | Monath 1970 |
| 1998-2007 | 12 | 0.042 | Mississippi 2008 |
| 2005 | 1 | 0.032 | CDC 2016 |
| 2008 | 3 | 0.10 | Mississippi 2009, CDC 2016 |
| 20121 | 1 | 0.03 | CDC 2016, CDC 2013 |
| 20131 | 2 | 0.07 | Lindsey 2014 |
| 2013 | 3 | 0.07 | CDC 2016, Lindsey 2014 |
| Missouri | 2009 | 1 | 0.02 | CDC 2010 |
| 2010 | 1 | 0.022 | CDC 2016 |
| New York | 19841 | 2 | 0.01 | WHO 1989 |
| 2010 | 1 | 0.012 | CDC 2016 |
| North Carolina3 | 1977-1979 | 12children | 2.275,6 | Kappus 1982 |
| 1977 | 4 | NR | Kelsey 1978 |
| 1984 | 3 | 0.05 | WHO 1989 |
| 1989-2001 | 25 | 0.032 | Utz 2005, Utz 2003 |
| 2003 | 26 | 0.31 | N. Carolina 2004 |
| 2004 | 13 | 0.15 | CDC 2016, N. Carolina 2004 |
| 2007 | 10 | 0.112 | CDC 2016 |
| 2008 | 9 | 0.102 | CDC 2016 |
| 2009 | 16 | 0.172 | CDC 2016 |
| 2010 | 22 | 0.232 | CDC 2016 |
| 20111 | 26 | 0.27 | CDC 2012, CDC 2016 |
| 20121 | 26 | 0.27 | CDC 2016, CDC 2013 |
| 20131 | 13 | 0.13 | CDC 2016, Lindsey 2014 |
| 20141 | 23 | 0.23 | CDC 2016, Lindsey 2015 |
| Ohio | 1963-19831 | 558† | 0.25 | WHO 1989 |
| 1963-1969 | 207 | 0.302 | Ohio 20169 |
| 1970-1979 | 236 | 0.222 | Ohio 20169 |
| 1980-1989 | 284 | 0.262 | Ohio 20169 |
| 1984 | 26 | 0.24 | WHO 1989 |
| 1990-1999 | 140 | 0.132 | Ohio 20169 |
| 2000 | 18 | 0.162 | Ohio 2016 |
| 2001 | 14 | 0.122 | Ohio 2016 |
| 2002 | 32 | 0.282 | Ohio 2016 |
| 2003 | 20 | 0.172 | Ohio 2016 |
| 2004 | 26 | 0.232 | CDC 2016, Ohio 2016 |
| 2005 | 15 | 0.132 | CDC 2016, Ohio 2016 |
| 2006 | 11 | 0.102 | CDC 2016, Ohio 2016 |
| 2007 | 9 | 0.082 | CDC 2016, Ohio 2016 |
| 2008 | 9 | 0.082 | CDC 2016, Ohio 2016 |
| 2009 | 5 | 0.042 | CDC 2016, Ohio 2016 |
| 2010 | 24 | 0.212 | CDC 2016, Ohio 2016 |
| 2011 | 50 | 0.432 | CDC 2016, Ohio 2016 |
| 20111 | 44 | 0.38 | CDC 2012 |
| 2012 | 14 | 0.122 | CDC 2016, Ohio 2016 |
| 20121 | 12 | 0.10 | CDC 2013 |
| 2013 | 16 | 0.142 | Ohio 2016 |
| 20131 | 14 | 0.12 | Lindsey 2014 |
| 2014 | 31 | 0.272 | Ohio 2016 |
| 20141 | 30 | 0.26 | Lindsey 2015 |
| 2015 | 24 | 0.212 | Ohio 2016 |
| 2016 | 9 | 0.082 | Ohio 2016 |
| Oklahoma | 19841 | 1 | 0.03 | WHO 1989 |
| South Carolina | 19841 | 1 | 0.03 | WHO 1989 |
| 2006 | 1 | 0.02 | CDC 2016, S. Carolina 2006 |
| 20111 | 1 | 0.02 | CDC 2012, CDC 2016 |
| 20121 | 1 | 0.02 | CDC 2013, CDC 2016 |
| 20131 | 1 | 0.02 | Lindsey 2014, CDC 2016 |
| 2015 | 1 | 0.02 | S. Carolina 2016 |
| Tennessee | 1996 | 1 | 0.02 | Robinson 2002, Robinson 2003, Cooper 2005 |
| 1997-2006 | 118 | 0.212 | Haddow 2009 |
| 1997 | 8 | 0.15 | Robinson 2002, Robinson 2003, Cooper 2005, Cooper 2006 |
| 1998 | 9 | 0.16 | Robinson 2002, Robinson 2003, Cooper 2005, Cooper 2006, Cooper 2007 |
| 1999 | 6 | 0.10 | Robinson 2002, Robinson 2003, Cooper 2005, Cooper 2006, Cooper 2007, Cooper 2009 |
| 2000 | 19 | 0.33 | Robinson 2002, Robinson 2003, Cooper 2005, Cooper 2006, Cooper 2007 |
| 2000-2009 | NRmedical claims | 0.045 | Jones 2013 |
| 2000-2009 | NRhealth department records | 0.15 | Jones 2013 |
| 2001 | 17 | 0.30 | Robinson 2002, Robinson 2003 Cooper 2005, Cooper 2006, Cooper 2007 |
| 2002 | 15 | 0.26 | Robinson 2002, Robinson 2003 Cooper 2005, Cooper 2006, Cooper 2007 |
| 2003 | 14 | 0.24 | Robinson 2002, Robinson 2003 Cooper 2005, Cooper 2006, Cooper 2007, Dreyzehner 2012 |
| 2004 | 13 | 0.22 | Robinson 2002, Robinson 2003 Cooper 2005, Cooper 2006, Cooper 2007, Dreyzehner 2012 |
| 2005 | 2 | 0.03 | Robinson 2002, Robinson 2003 Cooper 2005, Cooper 2006, Cooper 2007, Dreyzehner 2012 |
| 2006 | 7 | 0.11 | Robinson 2002, Robinson 2003 Cooper 2005, Cooper 2006, Cooper 2007, Cooper 2009, Dreyzehner 2012 |
| 2007 | 14 | 0.23 | Cooper 2007, Dreyzehner 2012 |
| 2008 | 6 | 0.10 | Cooper 2009, Cooper 2008, Dreyzehner 2012 |
| 2009 | 9 | 0.15 | CDC 2016, Cooper 2008, Dreyzehner 2012 |
| 2010 | 11 | 0.172 | CDC 2016, Dreyzehner 2012 |
| 20111 | 12 | 0.19 | CDC 2016, CDC 2012, Dreyzehner 2012 |
| 20121 | 9 | 0.14 | CDC 2013, CDC 2016, Dreyzehner 2012 |
| 20131 | 23 | 0.35 | Lindsey 2014, CDC 2016 |
| 20141 | 11 | 0.17 | CDC 2016, Lindsey 2015 |
| Texas | 2010 | 1 | 0.0042 | CDC 2016 |
| 20121 | 3 | 0.01 | CDC 2013, Texas 2014, CDC 2016 |
| Virginia | 1994 | 1 | 0.022 | Virginia, 1994 |
| 1995 | 1 | 0.022 | Virginia, 1995 |
| 1996 | 2 | 0.032 | Virginia, 1996 |
| 1997 | 6 | 0.092 | Virginia, 1997 |
| 1998 | 3 | 0.042 | Virginia, 1998 |
| 2001 | 2 | 0.032 | Virginia, 2001 |
| 2002 | 2 | 0.032 | Virginia, 2002 |
| 2003 | 4 | 0.052 | Virginia, 2003 |
| 2004 | 2 | 0.032 | CDC 2016, Virginia 2004 |
| 2005 | 4 | 0.052 | CDC 2016, Virginia 2005 |
| 2008 | 2 | 0.032 | CDC 2016, Remley 2008 |
| 2009 | 1 | 0.012 | CDC 2016 |
| 2010 | 2 | 0.02 | Remley 2008 |
| 2011 | 1 | 0.012 | CDC 2016 |
| 20121 | 2 | 0.02 | CDC 2016, CDC 2013, Romero 2012 |
| 20131 | 2 | 0.02 | CDC 2016, Lindsey 2014 |
| 20141 | 2 | 0.02 | Lindsey 2015 |
| West Virginia3 | 1984 | 6 | 0.31 | Anon1988 |
| 1985 | 2 | 0.11 | Anon 1988 |
| 1987 | 19 | 1.022, 8 | Woodruff 1992, CDC 1988b, Anon 1988a |
| 1988 | 16 | 0.87 | Woodruff 1992 |
| 2004 | 30 | 1.652 | CDC 2016 |
| 2005 | 15 | 0.822 | CDC 2016 |
| 2003-2007 | 95 | 1.032 | Hinckley 2009 |
| 2007 | 11 | 0.602 | CDC 2016 |
| 2008 | 14 | 0.762 | CDC 2016 |
| 2009 | 14 | 0.762 | CDC 2016 |
| 2010 | 8† | 0.43 | W. Virginia 2010, W. Virginia 2011 |
| 2011 | 26† | 1.40 | W. Virginia 2011, W. Virginia 2014 |
| 20111 | 22 | 1.19 | CDC 2012 |
| 2012 | 14† | 0.75 | W. Virginia 2012, CDC 2016 |
| 20121 | 9 | 0.49 | CDC 2013 |
| 2013 | 11† | 0.59 | Lindsey 2014, CDC 2016 |
| 20131 | 10 | 0.54 | Lindsey 2014 |
| 2014 | 2† | 0.11 | W. Virginia 2014 |
| 20141 | 1 | 0.05 | Lindsey 2015, W. Virginia 2014 |
| 2015 | 3 | 0.16 | W. Virginia 2015 |
| Wisconsin | 1963-19831 | NR | 0.435 | WHO 1989 |
| 1965 | 14 | 0.332 | Copps & Elston 1969 |
| 19841 | 11 | 0.23 | WHO 1989 |
| 2002-2006 | 53 | 0.202 | Sotir 2007 |
| 2003 | 4 | 0.07 | Wisconsin 2005 |
| 2004 | 7 | 0.132 | CDC 2016 |
| 2005 | 4† | 0.072 | CDC 2016 |
| 2006 | 3 | 0.052 | CDC 2016, Wisconsin 2006 |
| 2007 | 7† | 0.122 | Wisconsin 2009, Wisconsin 2007 |
| 2008 | 4 | 0.072 | CDC 2016 |
| 2008 | 8† | 0.142 | Wisconsin 2009 |
| 2008-2015 | 25† | 0.06 | Wisconsin 2016 |
| 2009 | 1 | 0.022 | CDC 2016 |
| 2011 | 5 | 0.092 | CDC 2016 |
| 20111 | 2 | 0.04 | CDC 2012 |
| 20121 | 2 | 0.03 | CDC 2013, CDC 2016 |
| 2013 | 8 | 0.142 | CDC 2016 |
| 20131 | 5 | 0.09 | Lindsey 2014 |
| 20141 | 3 | 0.05 | Lindsey 2015 |

NR = Not reported

† Denotes some cases were considered probable cases; otherwise cases were confirmed or not specified as confirmed or sporadic

\* Incidence rate was calculated as the number of new cases in a population during a specified time divided by the number of subjects at risk in the population at the beginning of the period. All population estimates (national or state) were obtained from USA Census Bureau data (<https://www.census.gov/programs-surveys/popest/data/tables.html>)

1 Reported by the author as neuroinvasive cases of LACV.

2 The incidence rate was calculated from case information.

3 Data not included in the table due to missing information (Date/represented population):

* Alabama: 1 probable case 1994 (Mancao 1996);
* Michigan: 2 confirmed cases (date not reported) (Abuhammour 2005);
* North Carolina: 1 confirmed case (date not reported) (Bice 2013); 2004-2009 47children (Miller, 2012)
* Tennessee: cluster of 10 cases 1997 (Jones 1999), 16 cases 2000 (Erwin 2002), 15 cases 2001 (population not defined) (Hardin 2003).
* West Virginia: 1 confirmed case (date not reported) (McJunkin 1997), 127 children 1987-1996 (McJunkin 2001); 1 confirmed case in a pregnant woman and a probable case for her newborn in 2006-2007 (2009);128 children 1987-1996 (McJunkin 2001, Kentucky 2002); 9 children 1992-1997 (McJunkin 1997), 10 cases 2001-2012 (Teleron 2016)
* Wisconsin: 29 cases 1960-1968 (Copps 1969); 1965-1982 178 children (Gundersen 1983); 33 cases 1979 (Beaty 1982a)
* Wisconsin/Minnesota/Iowa: 151 cases (Chun 1983) 178 cases 1965-1982 (Gundersen 1983);

4 All cases were reported as acquired from outside the state. Cases in Florida from 2006-2008 were acquired in North Carolina.

5 Median incidences per year as reported by the author.

6 The cases in this study were from a Cherokee Indian Reserve in Western North Carolina (Kappus 1982)

7 The cases in this study were diagnosed in La Crosse Wisconsin, however they came from the surrounding area that included Iowa and Minnesota (Gundersen 1983)

8 Incidence of 20/100000 in children <15 years old or 4.7/100000 for the whole population in the 5 county area (not whole state) where all the LACV cases occurred in 1987 (Woodruff 1992, Anon1988b, Anon 1988a)

9 Please refer to supplementary material S2 for the citation list of included articles.

# S11. The proportion of La Crosse virus (LACV) cases in patients with CNS or encephalitis studied in the USA from 1967-2008 (N=8).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **State** | **Year Sampled** | **Population Characteristics** | **Prevalence data (positive/N)** | **Reference2** |
| Minnesota | 19731 | CNS patients | 17/127 (13.4%) | Balfour & Edelman, 1974 |
| 1967-19721 | Encephalitis patients | 66/1617 (4.1%) | Balfour 1973, Balfour 1974 |
| New York | 1971-19821 | CNS patients | 18/327 (5.5%) | Srihongse 1984 |
| Tennessee | 2000-2002 | Encephalitis patients | 8/216 (3.7%) | Fredia 2001 |
| 2000-2007 | Encephalitis patients | 31/559 (5.5%) | Cooper 2007 |
| 2000- 2008 | Encephalitis patients | 31/598 (5.2%) | Cooper 2008 |
| Wisconsin | 19791 | Encephalitis patients | 26/67 (38.8%) | Beaty 1982a |
| 1 The denominator represents patients presenting with CNS infection or encephalitis during May/June through to October/November only.  2 Please refer to supplementary material S2 for the citation list of included articles. | | | | |

# S12. The seroprevalence of La Crosse virus (LACV) in humans from the USA from 1965-2010 (N=12).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **State** | **Year Sampled** | **Population Sampled\*** | **Seroprevalence (%)** | | **Reference4** |
| Indiana | 1978-1979 | General population | 370/10194 | (3.6) | Grimstad 1984 |
| Minnesota | 1971 | General population | 14/79 | (17.7) | Balfour 1976 |
| 1971 | Children (primary school) | 27/533 | (5.1) | Balfour 1976 |
| 1968 | General population1 | 136/1904 | (7.1) | Monath 1970 |
| 1968 | Developmental delay2 | 4/54 | (7.4) | Monath 1970 |
| New York | 1971-1982 | General population | 29/5013 | (5.8) | Srihongse 1984 |
| North Carolina | 1989-1990 | General population | 98/1016 | (9.7) | Szumlas 1996a |
| 1968 | Children (second grade) | 1/50 | (2.0) | Kappus 1982 |
| 1978 | Children (second grade) | 3/67 | (4.5) | Kappus 1982 |
| 1979 | General population | 6/53 | (11.3) | Kappus 1982 |
| Tennessee, North Carolina | 2008 | Park employees | 17/75 | (22.7) | Kosoy 2016, Adjemian 2012 |
| Tennessee | 1998-1999 | General population | 5/1000 | (0.5) | Balkhy 2000 |
| Texas | 1968-1970 | Outdoor workers | 6/49 | (12.3) | Boyd 1978 |
| Wisconsin | 1965-1976 | Developmental delay | 51/612 | (8.3) | Gauld 1979 |
| 1972-1973 | General population | 15/265 | (5.7) | Thompson 1983 |
| 1972-1973 | Children (<20 yrs of age) | 5/132 | (3.8) | Thompson 1983 |
| \*All samples were tested for neutralizing antibodies to La Crosse virus  1General population seroprevalence was also investigated using plaque reduction neutralization test that was shown to cross react with Trivittatus virus and resulted in a seroprevalence of 276/1360 (20.3%) (Monath 1970)  2Develpmental delay population also tested with the plaque reduction neutralization test that cross reacted with Trivittatus virus and resulted in a seroprevalence of 14/54 (25.9% ) (Monath, 1970)  3 24/29 of the positive samples were also plaque reduction neutralization tests (PRNT) positive for Jamestown Canyon virus (Srihongse, 1984).  4 Please refer to supplementary material S2 for the citation list of included articles. | | | | | |

# S13: Clinical signs and symptoms reported in LACV infected humans (N=46)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Symptom** | **State** | **Sample Year** | | **Study Design(s)** | | **Population** | | **Proportion affected** | | | | **Reference1** |
| **Neurological (n=46)** | | | | | | | | | | | | |
| Headache (n=27) | Alabama | 1994 | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | | Mancao 1996 |
| Georgia | 1982 | | Surveillance | | Clinical case, age 0-10 yr | | 8/8 | | 100% | | Sikes 1984 |
| Illinois | NR | | Case series | | Clinical case, age 39 yr | | 1/1 | | 100% | | Wurtz 2000 |
| 1966-1980 | | Surveillance | | Clinical cases, age 0-14 yr | | 48/59 | | 81% | | Clark 1983a |
| Michigan | NR | | Case series | | Clinical cases, age 5 and 12 yr | | 2/2 | | 100% | | Abuhammour 2005 |
| Minnesota | 1967-1973 | | Case series | | CNS patients, age 0-19 yr | | NR | | NR | | Balfour 1974 |
| 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 43/57 | | 75.40% | | Balfour 1973 |
| Missouri | 2009 | | Case series | | Clinical case, age 8 yr | | 1/1 | | 100% | | CDC 2010 |
| North Carolina | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 45/47 | | 95.70% | | Miller 2012 |
| 1977 | | Case series | | Clinical case, age 7 yr | | 1/4 | | 25% | | Kelsey 1978 |
| 1977-1979 | | Population based, prevalence | | Children, age 2-9 yr | | 2/12 | | 16.70% | | Kappus 1982 |
| 2008 | | Case series | | Clinical case, age 12 yr | | 1/1 | | 100% | | Kobayashi 2011 |
| Ohio, West Virginia | 1992-1997 | | Case series | | Hospital patients, age 6-11 yr | | NR | | NR | | de los Reyes 2008 |
| Tennessee | NR | | Case series | | Clinical cases, age 10 and 14 yr | | 2/2 | | 100% | | Boyce 1978 |
| 2000 | | Cohort | | Hospital patients, mean age 7.5 year | | 15/15 | | 100% | | Erwin 2002 |
| 2001 | | Case control | | Hospital patients, age <18 yr | | 15/15 | | 100% | | Hardin 2003 |
| 1997 | | Population based | | Hospital patients, age 3-14 yr | | 9/10 | | 90% | | Jones 1999 |
| 1998-1999 | | Case series, prevalence | | Hospital patients | | 15/15 | | 100% | | Jones 2000 |
| West Virginia | 2006-2007 | | Case series | | Pregnant woman, age 43 yr | | 1/1 | | 100% | | Anon 2009 |
| NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | | McJunkin 1997 |
| 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 105/126 | | 83.30% | | McJunkin 2001 |
| 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 7/10 | | 70% | | Teleron 2016 |
| Wisconsin | 1972-1973, 1977 | | Cohort, cross sectional | | General population, age 0-60+ | | 3/14 | | 21.40% | | Teleron 1983 |
| 1960-1968 | | Case series | | Clinical cases, age 1-11 yr | | 19/19 | | 100% | | Copps 1979 |
| 2002-2006 | | Surveillance | | Clinical case, age 1-83 yr | | 49/53 | | 92% | | Sotir 2007 |
| 2007 | | Surveillance | | Clinical case | | NR | | NR | | Wisconsin 2007 |
| 1965-1982 | | Case series | | Hospital patients, age 0-14 yr | | 114/178 | | 64% | | Gundersen 1983 |
| **Muscle and Mobility (n=27)** | | | | | | | | | | | | |
| Stiff neck (n=12) | Alabama | 1994 | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | | Mancao 1996 |
| Illinois | 1966-1980 | | Surveillance | | Clinical cases, age 0-14 yr | | 34/59 | | 57.60% | | Clark 1983a |
| Missouri | 2009 | | Case series | | Clinical case, age 8 yr | | 1/1 | | 100% | | CDC 2010 |
| North Carolina | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 9/47 | | 19.10% | | Miller 2012 |
| Tennessee | 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 9/15 | | 60% | | Erwin 2002 |
| 2001 | | Case control | | Hospital patients, age <18 yr | | 6/15 | | 40% | | Hardin 2003 |
| West Virginia | 2006-2007 | | Case series | | Pregnant, age 43 yr | | 1/1 | | 100% | | Anon 2009 |
| 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 31/120 | | 25.80% | | McJunkin 2001 |
| 2003-2007 | | Predictive, surveillance | | Clinical cases, age 0-15 yr | | 32/96 | | 33.30% | | Haddow 2011 |
| 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 3/10 | | 30% | | Teleron 2016 |
| Wisconsin | 2002-2006 | | Surveillance | | Clinical case, age 1-83 yr | | 32/33 | | 97% | | Sotir 2007 |
| 1965-1982 | | Case series | | Hospital patients, age 0-14 yr | | 80/178 | | 44.90% | | Gundersen 1983 |
| Paralysis/paresis (n=8) | USA | 2003-2012 | | Surveillance | | Clinical cases, age 0-18 yr | | 10/665 | | 1.50% | | Gaensbauer 2014 |
| 2013 | | Surveillance | | Clinical cases, age 4-11 yr | | 4/85 | | 4.71% | | Lindsey 2014 |
| Georgia | 1982 | | Surveillance | | Clinical case, age 0-10 yr | | 1/8 | | 12.50% | | Sikes 1984 |
| Illinois | 1966-1980 | | Surveillance | | Clinical cases, age 0-14 yr | | 5/59 | | 8.47% | | Clark 1983a |
| Minnesota | 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 1/57 | | 1.75% | | Balfour 1973 |
| Minnesota, Wisconsin, Ohio | NR | | Case series | | Clinical case, age 0-17 yr | | NR | | NR | | Chun 1983 |
| Wisconsin | 1960-1968 | | Case series | | Hospital patient, age 1-11 yr | | 3/19 | | 15.80% | | Copps 1979 |
| Reflexes (n=2) | Michigan | NR | | Case series | | Clinical case, age 5 and 12 yr | | 1/2 | | 50% | | Abuhammour 2005 |
| Wisconsin | 1960-1968 | | Case series | | Hospital patient, age 1-11 yr | | 4/19 | | 21.10% | | Copps 1979 |
| Weakness (n=8) | Alabama | 1994 | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | | Mancao 1996 |
| Illinois | NR | | Case series | | Clinical case, age 39 yr | | 1/1 | | 100% | | Wurtz 2000 |
| Michigan | NR | | Case series | | Clinical case, age 5 and 12 yr | | 1/2 | | 50% | | Abuhammour 2005 |
| North Carolina | 1977 | | Case series | | Clinical case, age 7 yr | | 1/4 | | 25% | | Kelsey 1978 |
| Ohio | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 2/6 | | 33.30% | | Balkhy 2000 |
| West Virginia | 2006-2007 | | Case series | | Pregnant, age 43 yr | | 1/1 | | 100% | | Anon 2009 |
| 2003-2007 | | Surveillance | | Clinical case, age 0-15 yr | | 40/96 | | 41.70% | | Haddow 2011 |
| 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 5/10 | | 50% | | Teleron 2016 |
| Involuntary movement (n=4) | Illinois | 1966-1980 | | Surveillance | | Clinical cases, age 0-14 yr | | 4/59 | | 6.78% | | Clark 1983a |
| Michigan | NR | | Case series | | Clinical case, age 5 and 12 yr | | 1/2 | | 50% | | Abuhammour 2005 |
| Tennessee | 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 1/15 | | 6.67% | | Erwin 2002 |
| West Virginia | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | | McJunkin 1997 |
| Balance (n=3) | North Carolina | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 27/47 | | 57.40% | | Miller 2012 |
| Ohio | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 3/6 | | 50% | | Balkhy 2000 |
| Tennessee | 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 1/15 | | 6.67% | | Erwin 2002 |
| Myalgia (n=4) | Michigan | NR | | Case series | | Clinical case, age 5 and 12 yr | | 1/2 | | 50% | | Abuhammour 2005 |
| Minnesota | 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 3/57 | | 5.26% | | Balfour 1973 |
| 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 1/57 | | 1.75% | | Balfour 1973 |
| Wisconsin | 2002-2006 | | Surveillance | | Clinical cases, age 1-83 yr | | 33/33 | | 100% | | Sotir 2007 |
| 2007 | | Surveillance | | Clinical case | | NR | | NR | | Wisconsin 2007 |
| Arthralgia (n=3) | West Virginia | 2003-2007 | | Surveillance | | Clinical case, age 0-15 yr | | 7/96 | | 7.29% | | Haddow 2011 |
| Wisconsin | 2002-2006 | | Surveillance | | Clinical cases, age 1-83 yr | | 32/33 | | 97% | | Sotir 2007 |
| 2007 | | Surveillance | | Clinical case | | NR | | NR | | Wisconsin 2007 |
| Dexterity/mobility (n=4) | Minnesota, Wisconsin, Ohio | NR | | Case series | | Clinical case, age 0-17 yr | | NR | | NR | | Chun 1983 |
| North Carolina | 2008 | | Case series | | Clinical case, age 12 yr | | 1/1 | | 100% | | Kobayashi 2011 |
| Tennessee | 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 1/15 | | 6.67% | | Erwin 2002 |
| 2012 | | Case series, prevalence | | Clinical case, age 6 yr | | 1/1 | | 100% | | Lambert 2015 |
| **Mental (n=25)** | | | | | | | | | | | | |
| Altered consciousness (n=4) | Minnesota | 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 27/57 | | 43.90% | | Balfour 1973 |
| Tennessee | 1997 | | Population based | | Hospital patients, age 3-14 yr | | 7/10 | | 70% | | Jones 1999 |
| 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 2/15 | | 13.30% | | Erwin 2002 |
| West Virginia | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | | McJunkin 1997 |
| Coma (n=5) | Minnesota | 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 7/57 | | 12.30% | | Balfour 1973 |
| Ohio | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 1/6 | | 16.70% | | Balkhy 2000 |
| Tennessee | 2012 | | Case series, prevalence | | Clinical case, age 6 yr | | 1/1 | | 100% | | Lambert 2015 |
| West Virginia | 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 42/127 | | 33.10% | | McJunkin 2001 |
| 2003-2007 | | Predictive, surveillance | | Clinical cases, age 0-15 yr | | 4/95 | | 4.21% | | Haddow 2011 |
| Irritable (n=2) | Ohio | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 1/6 | | 16.70% | | Balkhy 2000 |
| Tennessee | NR | | Case series | | Clinical cases, age 10 and 14 yr | | 1/2 | | 50% | | Boyce 1978 |
| Behaviour change (n=3) | Tennessee | 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 13/15 | | 86.70% | | Erwin 2002 |
| 2001 | | Case control | | Hospital patients, age <18 yr | | 8/15 | | 53.30% | | Hardin 2003 |
| 1997 | | Population based | | Hospital patients, age 3-14 yr | | 7/10 | | 70% | | Jones 1999 |
| Confused (n=13) | Illinois | NR | | Case series | | Clinical case, age 39 yr | | 1/1 | | 100% | | Wurtz 2000 |
| Michigan | NR | | Case series | | Clinical cases, age 5, 12 yr | | 2/2 | | 100% | | Abuhammour 2005 |
| North Carolina | 2008 | | Case series | | Clinical case, age 12 yr | | 1/1 | | 100% | | Kobayashi 2011 |
| Ohio and West Virginia | 1992-1997 | | Case series | | Hospital patients, age 6-11 yr | | 9/9 | | 100% | | de los Reyes 2008 |
| Tennessee | 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 9/15 | | 60% | | Erwin 2002 |
| 2001 | | Case control | | Hospital patients, age <18 yr | | 6/15 | | 40% | | Hardin 2003 |
| West Virginia | 2006-2007 | | Case series | | Pregnant, age 43 yr | | 1/1 | | 100% | | Anon 2009 |
| 2003-2007 | | Surveillance | | Clinical cases, age 0-15 yr | | 32/96 | | 33.30% | | Haddow 2011 |
| NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | | McJunkin 1997 |
| 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 50/119 | | 42% | | McJunkin 2001 |
| 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 5/10 | | 50% | | Teleron 2016 |
| Wisconsin | 1960-1968 | | Case series | | Hospital patients, age 1-11 yr | | 19/19 | | 100% | | Copps 1979 |
| 2002-2006 | | Surveillance | | Clinical cases, age 1-83 yr | | 33/33 | | 100% | | Sotir 2007 |
| Disoriented (n=3) | Indiana | 1996 | | Case series | | Clinical case, age 10 yr | | 1/1 | | 100% | | Sokol 2001 |
| North Carolina | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 27/47 | | 57.40% | | Miller 2012 |
| Ohio | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 2/6 | | 33.30% | | Balkhy 2000 |
| Trouble thinking (n=1) | Tennessee | 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 1/15 | | 6.67% | | Erwin 2002 |
| Delirious (n=1) | Wisconsin | 1960-1968 | | Case series | | Hospital patients, age 1-11 yr | | 5/19 | | 26.30% | | Copps 1979 |
| Hallucinations (n=3) | North Carolina | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 27/47 | | 57.40% | | Miller 2012 |
| 1977 | | Case series | | Clinical case, age 7 yr | | 1/4 | | 25% | | Kelsey 1978 |
| Tennessee | 2012 | | Case series, prevalence | | Clinical case, age 6 yr | | 1/1 | | 100% | | Lambert 2015 |
| Lethargic (n=7) | Illinois | 1966-1980 | | Surveillance | | Clinical cases, age 0-14 yr | | 5/59 | | 8.47% | | Clark 1983a |
| Minnesota | 1967-1973 | | Case series | | CNS patients, age 0-19 yr | | NR | | NR | | Balfour 1974 |
| Ohio | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 4/6 | | 66.70% | | Balkhy 2000 |
| Tennessee | NR | | Case series | | Clinical case, age 10, 14 yr | | 1/2 | | 50% | | Boyce 1978 |
| Wisconsin | 1960-1968 | | Case series | | Hospital patients, age 1-11 yr | | 19/19 | | 100% | | Copps 1979 |
| 1965-1982 | | Case series | | Hospital patients, age 0-14 yr | | 123/178 | | 69.10% | | Gundersen 1983 |
| West Virginia | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | | McJunkin 1997 |
| Memory loss (n=4) | Minnesota, Wisconsin, Ohio | NR | | Case series | | Clinical cases, age 0-17 yr | | NR | | NR | | Chun 1983 |
| North Carolina | NR | | Case series | | Clinical case, age 95 yr | | 1/1 | | 100% | | Bice 2013 |
| Ohio | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 1/6 | | 16.70% | | Balkhy 2000 |
| Wisconsin | 2002-2006 | | Surveillance | | Clinical cases, age 1-83 yr | | 33/33 | | 100% | | Sotir 2007 |
| Decreased arousal (n=2) | North Carolina | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 27/47 | | 57.40% | | Miller 2012 |
| Tennessee | 2012 | | Case series, prevalence | | Clinical case, age 6 yr | | 1/1 | | 100% | | Lambert 2015 |
| **Encephalopathy (n=27)** | | | | | | | | | | | | |
| Encephalitis (n=21) | USA | | 2003-2007 | | Surveillance | | Clinical cases, age 0-86 yr | | 78/377 | | 20.70% | Haddow 2009 |
| 2003-2012 | | Surveillance | | Clinical cases, age 0-18 yr | | 521/665 | | 78.30% | Gaensbauer 2014 |
| 2014 | | Case series, surveillance | | Clinical cases, age 6-11 yr | | 63/80 | | 78.80% | Lindsey 2015 |
| 2013 | | Surveillance | | Clinical cases, 4-11 yr | | 65/85 | | 76.50% | Lindsey 2014 |
| Georgia | | 2010 | | Surveillance | | Clinical cases | | 1/2 | | 50% | Gabel 2010 |
| 2011 | | Surveillance | | Clinical cases | | 2/2 | | 100% | Gabel 2011 |
| 2014 | | Surveillance | | Clinical case | | 1/1 | | 100% | Gabel 2014 |
| 1982 | | Surveillance | | Clinical cases, age 0-10 yr | | 5/5 | | 100% | Sikes 1984 |
| Minnesota | | 1967-1973 | | Case series | | CNS patients, age 0-19 yr | | 38/83 | | 45.80% | Balfour 1974 |
| 2014 | | Surveillance | | Clinical cases, age 6-11 yr | | 4/4 | | 100% | Minnesota 2015 |
| North Carolina | | 1977-1979 | | Population based, prevalence | | Children, age 2-9 yr | | 7/12 | | 58.30% | Kappus 1982 |
| 2008 | | Case series | | Clinical case, age 12 yr | | 1/1 | | 100% | Kobayashi 2011 |
| Tennessee | | 2012 | | Case series, prevalence | | Clinical case, age 6 yr | | 1/1 | | 100% | Lambert 2015 |
| West Virginia | | 1987 | | Surveillance | | Clinical cases, age 1-14 yr | | 11/19 | | 57.90% | CDC 1988b |
| 1987 | | Case series | | Hospital patients, age 1-14 yr | | 11/19 | | 57.90% | CDC 1988b |
| NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| 1987-1988 | | Case control | | Clinical cases, age 1-14 yr | | 20/35 | | 57.10% | Woodruff 1992 |
| 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 10/10 | | 100% | Teleron 2016 |
| 2003-2007 | | Surveillance | | Clinical cases, age 0-15 yr | | 38/94 | | 40.60% | Haddow 2011 |
| Wisconsin | | 1972-1973, 1977 | | Cohort, cross sectional | | General population, age 0-60+ | | NR | | NR | Teleron 1983 |
| Meningitis (n=11) | USA | | 2003-2007 | | Surveillance | | Clinical cases, age 0-86 yr | | 87/506 | | 17.20% | Haddow 2009 |
| 2003-2012 | | Surveillance | | Clinical cases, age 0-18 yr | | 134/665 | | 20.20% | Gaensbauer 2014 |
| 2014 | | Case series, surveillance | | Clinical cases, age 6-11 yr | | 12/80 | | 15% | Lindsey 2015 |
| 2013 | | Surveillance | | Clinical cases, 4-11 yr | | 8/85 | | 9.41% | Lindsey 2014 |
| Georgia | | 2010 | | Surveillance | | Clinical cases | | 1/2 | | 50% | Gabel 2010 |
| 1982 | | Surveillance | | Clinical cases, age 0-10 yr | | 3/3 | | 100% | Sikes 1984 |
| North Carolina | | 1977-1979 | | Population based, prevalence | | Children, age 2-9 yr | | 3/12 | | 25% | Kappus 1982 |
| West Virginia | | 1987 | | Surveillance | | Clinical cases, age 1-14 yr | | 4/19 | | 21.10% | CDC 1988b |
| 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 17/33 | | 51.50% | McJunkin 2001 |
| 1987-1988 | | Case control | | Clinical cases, age 1-14 yr | | 7/35 | | 20% | Woodruff 1992 |
| 2003-2007 | | Surveillance | | Clinical cases, age 0-15 yr | | 39/94 | | 41.60% | Haddow 2011 |
| Meningoencephalitis (n=7) | USA | | 2003-2007 | | Surveillance | | Clinical cases, age 0-86 yr | | 242/377 | | 56.30% | Haddow 2009 |
| Georgia | | 2011 | | Surveillance | | Clinical cases | | 2/2 | | 100% | Gabel 2011 |
| Minnesota | | 1967-1973 | | Case series | | CNS patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| North Carolina | | NR | | Case series | | Clinical case, age 95 yr | | 1/1 | | 100% | Bice 2013 |
| West Virginia | | 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 16/33 | | 48.50% | McJunkin 2001 |
| 1987-1988 | | Case control | | Clinical cases, age 1-14 yr | | 8/35 | | 22.90% | Woodruff 1992 |
| 1987 | | Surveillance | | Clinical cases, age 1-14 yr | | 4/19 | | 21.10% | CDC 1988b |
| 1987 | | Case series | | Hospital patients, age 1-14 yr | | 4/19 | | 21.10% | CDC 1988b |
| Meningeal irritation (n=3) | Michigan | | NR | | Case series | | Clinical cases, age 5 and 12 yr | | 2/2 | | 100% | Abuhammour 2005 |
| Minnesota | | 1967-1973 | | Case series | | CNS patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| 1967-1972 | | Longitudinal | | CNS patients, age 0-17 yr | | 30/57 | | 52.60% | Balfour 1973 |
| Meningismus (n=2) | Ohio | | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 1/6 | | 16.70% | Balkhy 2000 |
| Tennessee | | 1997 | | Surveillance, population based | | Hospital patients, age 3-14 yr | | 1/10 | | 10% | Jones 1999 |
| **Seizures (n=25)** | | | | | | | | | | | | |
| General seizure (n=5) | Alabama | | 1994 | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | Mancao 1996 |
| Michigan | | NR | | Case series | | Clinical cases, age 5 and 12 yr | | 1/2 | | 50% | Abuhammour 2005 |
| Ohio, West Virginia | | 1992-1997 | | Case series | | Hospital patients, age 6-11 yr | | 2/9 | | 22.20% | de los Reyes 2008 |
| Ohio | | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 3/6 | | 50% | Balkhy 2000 |
| Wisconsin | | 1960-1968 | | Case series | | Hospital patients, age 1-11 yr | | 5/19 | | 26.30% | Coppsn 1979 |
| Focal seizure (n=4) | Michigan | | NR | | Case series | | Clinical cases, age 5 and 12 yr | | 1/2 | | 50% | Abuhammour 2005 |
| Ohio | | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 1/6 | | 16.70% | Balkhy 2000 |
| Ohio, West Virginia | | 1992-1997 | | Case series | | Hospital patients, age 6-11 yr | | 7/9 | | 77.80% | de los Reyes 2008 |
| Wisconsin | | 1960-1968 | | Case series | | Hospital patients, age 1-11 yr | | 2/19 | | 10.50% | Copps 1979 |
| Partial seizure (n=2) | Florida | | NR | | Case series | | Clinical case | | 4/4 | | 100% | Tatum 1999 |
| Indiana | | 1996 | | Case series | | Clinical case, age 10 yr | | 1/1 | | 100% | Sokol 2001 |
| Convulsions (n=2) | Wisconsin | | 1960-1968 | | Case series | | Hospital patients, age 1-11 yr | | 7/19 | | 36.80% | Copps 1979 |
| 2002-2006 | | Surveillance | | Clinical cases, age 1-83 yr | | 31/33 | | 93.90% | Sotir 2007 |
| Seizure during acute infection (n=1) | Wisconsin | | 1965-1982 | | Case series | | Hospital patients, age 0-14 yr | | 58/178 | | 32.60% | Gundersen 1983 |
| After acute infection (n=1) | Wisconsin | | 1965-1982 | | Case series | | Hospital patients, age 0-14 yr | | 16/178 | | 8.99% | Gundersen 1983 |
| Unspecified seizure (n=16) | Georgia | | 1982 | | Surveillance | | Clinical cases, age 0-10 yr | | 5/8 | | 62.50% | Sikes 1984 |
| Minnesota | | 1967-1973 | | Case series | | CNS patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| 1967-1972 | | Longitudinal | | CNS patients, age 0-17 yr | | 28/57 | | 49.10% | Balfour 1973 |
| North Carolina | | 2008 | | Case series | | Clinical case, age 12 yr | | 1/1 | | 100% | Kobayashi 2011 |
| 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 9/47 | | 19.10% | Miller 2012 |
| 1977 | | Case series | | Clinical case, age 7 yr | | 1/4 | | 25% | Kelsey 1978 |
| Tennessee | | NR | | Case series | | Clinical cases, age 10, 14 yr | | 1/2 | | 50% | Boyce 1978 |
| 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 4/15 | | 26.70% | Erwin 2002 |
| 2001 | | Case control | | Hospital patients, age <18 yr | | 6/15 | | 40% | Hardin 2003 |
| 1997 | | Population based | | Hospital patients, age 3-14 yr | | 8/10 | | 80% | Jones 1999 |
| 1998-1999 | | Case series, prevalence | | Hospital patients, age 0-13 yr | | 4/15 | | 26.70% | Jones 2000 |
| 2012 | | Case series, prevalence | | Clinical case, age 6 yr | | 1/1 | | 100% | Lambert 2015 |
| West Virginia | | 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 2/10 | | 20% | Teleron 2016 |
| NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 58/127 | | 45.70% | McJunkin 2001 |
| 2003-2007 | | Surveillance | | Clinical cases, age 0-15 yr | | 23/96 | | 24% | Haddow 2011 |
| **Speech problems (n=10)** | | | | | | | | | | | | |
| Trouble understanding/articulating (n=6) | Indiana | | 1996 | | Case series | | Clinical case, age 10 yr | | 1/1 | | 100% | Sokol 2001 |
| Michigan | | NR | | Case series | | Clinical cases, age 5 and 12 yr | | 1/2 | | 50% | Abuhammour 2005 |
| Minnesota, Wisconsin, Ohio | | NR | | Case series | | Clinical case, age 0-17 yr | | NR | | NR | Chun 1983 |
| North Carolina | | 2008 | | Case series | | Clinical case, age 12 yr | | 1/1 | | 100% | Kobayashi 2011 |
| 1977 | | Case series | | Clinical case, age 7 yr | | 1/4 | | 25% | Kelsey 1978 |
| Tennessee | | 2001 | | Case control | | Hospital patients, age <18 yr | | 5/13 | | 38.50% | Hardin 2003 |
| Slurred speech (n=3) | North Carolina | | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 27/47 | | 57.40% | Miller 2012 |
| Ohio | | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 1/6 | | 16.70% | Balkhy 2000 |
| Wisconsin | | 2002-2006 | | Surveillance | | Clinical case, age 1-83 yr | | 31/33 | | 93.90% | Sotir 2007 |
| Non-verbal (n=1) | West Virginia | | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| Repetitive speech (n=1) | Indiana | | 1996 | | Case series | | Clinical case, age 10 yr | | 1/1 | | 100% | Sokol 2001 |
| **Eye problems (n=14)** | | | | | | | | | | | | |
| Photophobia (n=11) | Michigan | | NR | | Case series | | Clinical cases, age 5 and 12 yr | | 2/2 | | 100% | Abuhammour 2005 |
| Minnesota | | 1967-1972 | | Longitudinal | | CAN patients, age 0-17 yr | | 2/57 | | 3.51% | Balfour 1973 |
| Mississippi | | 1968 | | Cross sectional | | General population, age 0-40+ yr | | 1/4 | | 25% | Monath 1970 |
| Developmental delay, age 4-15 yr | |
| Missouri | | 2009 | | Case series | | Clinical case, age 8 yr | | 1/1 | | 100% | CDC 2010 |
| Tennessee | | 2001 | | Case control | | Hospital patients, age <18 yr | | 13/15 | | 86.70% | Hardin 2003 |
| 1997 | | Population based | | Hospital patients, age 3-14 yr | | 4/10 | | 40% | Jones 1999 |
| 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 11/15 | | 73.30% | Erwin 2002 |
| West Virginia | | 2006-2007 | | Case series | | Pregnant, age 43 | | 1/1 | | 100% | Anon 2009 |
| 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 3/10 | | 30% | Teleron 2016 |
| 2003-2007 | | Surveillance | | Clinical cases, age 0-15 yr | | 50/96 | | 52.10% | Haddow 2011 |
| Wisconsin | | 2002-2006 | | Surveillance | | Clinical cases, age 1-83 yr | | 33/33 | | 100% | Sotir 2007 |
| Eyes deviated (n=3) | Georgia | | 1982 | | Surveillance | | Clinical cases, age 0-10 yr | | 1/8 | | 12.50% | Sikes 1984 |
| Tennessee | | NR | | Case series | | Clinical cases, age 10, 14 yr | | 1/2 | | 50% | Boyce 1978 |
| West Virginia | | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| Excessive blinking (n=1) | West Virginia | | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| **Not specified (n=8)** | | | | | | | | | | | | |
| Not specified (n=8) | USA | | 2014 | | Case series, surveillance | | Clinical cases, age 6-11 yr | | 1/80 | | 1.25% | Lindsey 2015 |
| Georgia | | 2014 | | Surveillance | | Clinical case | | 1/1 | | 100% | Gabel 2014 |
| Minnesota | | 1967-1972 | | Longitudinal | | CNS patients, age 0-17 yr | | 9/57 | | 15.80% | Balfour 1973 |
| 2014 | | Surveillance | | Clinical cases, age 6-11 yr | | 4/4 | | 100% | Minnesota 2015 |
| North Carolina | | 2008 | | Case series | | Clinical case, age 12 yr | | 1/1 | | 100% | Kobayashi 2011 |
| Tennessee | | 1997 | | Population based | | Hospital patients, age 3-14 yr | | 1/10 | | 10% | Jones 1999 |
| 2012 | | Case series, prevalence | | Clinical case, age 6 yr | | 1/1 | | 100% | Lambert 2015 |
| West Virginia | | 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 23/126 | | 18.30% | McJunkin 2001 |
| **Other (n=35)** | | | | | | | | | | | | |
| Fever (n=30) | USA | | 2003-2007 | | Surveillance | | Clinical case, age 0-86 yr | | 18/437 | | 4.12% | Haddow 2009 |
| Alabama | | 1994 | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | Mancao 1996 |
| Georgia | | 1982 | | Surveillance | | Clinical case, age 0-10 yr | | 8/8 | | 100% | Sikes 1984 |
| Illinois | | 1966-1980 | | Surveillance | | Clinical cases, age 0-14 yr | | 55/59 | | 93% | Clark 1983a |
| NR | | Case series | | Clinical case, age 39 yr | | 1/1 | | 100% | Wurtz 2000 |
| Indiana | | 1996 | | Case series | | Clinical case, age 10 yr | | 1/1 | | 100% | Sokol 2001 |
| Michigan | | NR | | Case series | | Clinical cases, age 5 and 12 yr | | 2/2 | | 100% | Abuhammour 2005 |
| Minnesota | | 1967-1973 | | Case series | | CNS patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| 1967-1972 | | Longitudinal | | CNS patients, age 0-17 yr | | 57/57 | | 100% | Balfour 1973 |
| Mississippi | | 1968 | | Cross sectional | | General population, age 0-40 yr | | 1/4 | | 25% | Monath 1970 |
| Developmental delay, age 4-15 yr | |
| Missouri | | 2009 | | Case series | | Clinical case, age 8 yr | | 1/1 | | 100% | CDC 2010 |
| North Carolina | | NR | | Case series | | Clinical case, age 95 years | | 1/1 | | 100% | Bice 2013 |
| 2008 | | Clinical case, age 12 years | | 1/1 | | 100% | Kobayashi 2011 |
| 2004-2009 | | Hospital patients, age 1-17 years | | 20/47 | | 42.60% | Miller 2012 |
| 1977 | | Clinical case, age 7 years | | 1/4 | | 25% | Kelsey 1978 |
| Ohio | | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 6/6 | | 100% | Balkhy 2000 |
| Ohio, West Virginia | | 1992-1997 | | Case series | | Hospital patients, age 6-11 yr | | 9/9 | | 100% | de los Reyes 2008 |
| Tennessee | | NR | | Case series | | Clinical cases, age 10, 14 yr | | 2/2 | | 100% | Boyce 1978 |
| 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 15/15 | | 100% | Erwin 2002 |
| 2001 | | Case control | | Hospital patients, age 0-18 yr | | 15/15 | | 100% | Hardin 2003 |
| 1997 | | Population based | | Hospital patients, age 3-14 yr | | 10/10 | | 100% | Jones 1999 |
| 1998-1999 | | Case series, prevalence | | Hospital patients, age 0-13 yr | | 14/15 | | 93.30% | Jones 2000 |
| West Virginia | | 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 107/125 | | 85.60% | McJunkin 2001 |
| 2006-2007 | | Case series | | Pregnant woman, age 43 | | 1/1 | | 100% | Anon 2009 |
| 2003-2007 | | Surveillance | | Clinical case, age 0-15 yr | | 73/96 | | 76% | Haddow 2011 |
| 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 9/10 | | 90% | Teleron 2016 |
| Wisconsin | | 1960-1968 | | Case series | | Clinical cases, age 1-11 yr | | 19/19 | | 100% | Copps 1979 |
| 2002-2006 | | Surveillance | | Clinical case, age 1-83 yr | | 49/53 | | 92% | Sotir 2007 |
| 1972-1973, 1977 | | Cohort, Cross sectional | | General population, age 0-60+ | | 1/6 | | 16.70% | Teleron 1983 |
| 2007 | | Surveillance | | Clinical case | | NR | | NR | Wisconsin 2007 |
| Vomiting (n=22) | Georgia | | 1982 | | Surveillance | | Clinical cases, age 0-10 yr | | 3/8 | | 37.50% | Sikes 1984 |
| Indiana | | 1996 | | Case series | | Clinical case, 10 yr | | 1/1 | | 100% | Sokol 2001 |
| Michigan | | NR | | Case series | | Clinical case, age 5 and 12 yr | | 2/2 | | 100% | Abuhammour 2005 |
| Minnesota | | 1967-1973 | | Case series | | CNS patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| Mississippi | | 1968 | | Cross sectional | | General population, age 0-40+ | | 1/4 | | 25% | Monath 1970 |
| Missouri | | 2009 | | Case series | | Clinical case, age 8 yr | | 1/1 | | 100% | CDC 2010 |
| North Carolina | | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 36/46 | | 78.30% | Miller 2012 |
| Mississippi | | 1977 | | Case series | | Clinical case, age 7 yr | | 1/4 | | 25% | Kelsey 1978 |
| Ohio, West Virginia | | 1992-1997 | | Case series | | Hospital patients, age 6-11 yr | | NR | | NR | de los Reyes 2008 |
| Tennessee | | NR | | Case series | | Clinical cases, age 10, 14 yr | | 2/2 | | 100% | Boyce 1978 |
| 2000 | | Cohort | | Hospital patients, mean age 7.5 yr | | 14/15 | | 93.30% | Erwin 2002 |
| 2001 | | Case control | | Hospital patients, age <18 yr | | 12/15 | | 80% | Hardin 2003 |
| 1997 | | Population based | | Hospital patients, age 3-14 yr | | 7/10 | | 70% | Jones 1999 |
| 1998-1999 | | Case series, prevalence | | Hospital patients, age 0-13 yr | | 10/15 | | 66.75 | Jones 2000 |
| 2012 | | Case series, prevalence | | Clinical case, age 6 yr | | 1/1 | | 100% | Lambert 2015 |
| Wisconsin | | 1960-1968 | | Case series | | Hospital patients, age 1-11 yr | | 17/19 | | 89.50% | Copps 1979 |
| 1965-1982 | | Case series | | Hospital patients, age 0-14 yr | | 151/178 | | 84.80% | Gundersen 1983 |
| 2002-2006 | | Surveillance | | Clinical cases, age 1-83 yr | | 33/33 | | 100% | Sotir 2007 |
| West Virginia | | 2003-2007 | | Surveillance | | Clinical cases, age 0-15 yr | | 72/96 | | 75% | Haddow 2011 |
| NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| 1987-1996 | | Case series | | Hospital patients, age 0-15 yr | | 89/127 | | 70.10% | McJunkin 2001 |
| 2001-2012 | | Population based | | Hospital patients, age >18 yr | | 2/10 | | 20% | Teleron 2016 |
| Nausea (n=8) | Georgia | | 1982 | | Surveillance | | Clinical case, age 0-10 yr | | 3/8 | | 37.5% | Sikes 1984 |
| Mississippi | | 1968 | | Cross sectional | | Developmental delay, age 4-15 yr | | 1/4 | | 25% | Monath 1970 |
| Missouri | | 2009 | | Case series | | Clinical case, age 8 yr | | 1/1 | | 100% | CDC 2010 |
| North Carolina | | NR | | Case series | | Clinical case, age 95 yr | | 1/1 | | 100% | Bice 2013 |
| 1977 | | Case series | | Clinical case, age 7 yr | | 1/4 | | 25% | Kelsey 1978 |
| Wisconsin | | 2002-2006 | | Surveillance | | Clinical cases, age 1-83 yr | | 33/33 | | 100% | Sotir 2007 |
| 2007 | | Surveillance | | Clinical case | | NR | | NR | Wisconsin 2007 |
| West Virginia | | 2003-2007 | | Surveillance | | Clinical cases, age 0-15 yr | | 48/96 | | 50% | Haddow 2011 |
| Michigan | | NR | | Case series | | Clinical cases, age 5 and 12 yr | | 1/2 | | 50% | Abuhammour 2005 |
| Ohio | | 1996 | | Case series | | Hospital patients, age 0-2 yr | | 1/6 | | 16.70% | Balkhy 2000 |
| Minnesota | | 1967-1973 | | Case series | | CNS Patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| Incontinence (n=2) | North Carolina | | NR | | Case series | | Clinical case, age 95 yr | | 1/1 | | 100% | Bice 2013 |
| Minnesota | | 1967-1973 | | Case series | | CNS Patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| alaise (n=2) | Minnesota | | 1967-1973 | | Case series | | CNS Patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| Missouri | | 2009 | | Case series | | Clinical case, age 8 yr | | 1/1 | | 100% | CDC 2010 |
| Anorexia (n=1) | Indiana | | 1996 | | Case series | | Clinical case, age 10 yr | | 1/1 | | 100% | Sokol 2001 |
| Abdominal pain (n=2) | Minnesota | | 1967-1973 | | Case series | | CNS Patients, age 0-19 yr | | NR | | NR | Balfour 1974 |
| Diarrhea (n=5) | Wisconsin | | 1965-1982 | | Case series | | Hospital patients, age 0-14 yr | | 9/178 | | 5.06% | Gundersen 1983 |
| 2002-2006 | | Surveillance | | Clinical case, age 1-83 yr | | 33/33 | | 100% | Sotir 2007 |
| 2007 | | Surveillance | | Clinical case | | NR | | NR | Wisconsin 2007 |
| Minnesota | | 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 32/57 | | 56.10% | Balfour 1973 |
| North Carolina | | 1977 | | Case series | | Clinical case, age 7 yr | | 1/4 | | 25% | Kelsey 1978 |
| 1977-1979 | | Population based, prevalence | | Children, age 2-9 yr | | 2/12 | | 16.70% | Kappus 1982 |
| Gastrointestinal (n=2) | Tennessee | | 2001 | | Case control | | Hospital patients, age <18 yr | | 2/15 | | 13.30% | Hardin 2003 |
| Minnesota | | 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 10/57 | | 17.50% | Balfour 1973 |
| Respiratory problems (n=2) | Mississippi | | 1968 | | Cross sectional | | General population, age 0-40+ | | 1/4 | | 25% | Monath 1970 |
| Developmental delay, age 4-15 yr | | 2/15 | | 13.30% | Monath 1970 |
| Sore throat (n=2) | Minnesota | | 1967-1972 | | Longitudinal | | CNS Patients, age 0-17 yr | | 10/57 | | 17.5% | Balfour 1973 |
| West Virginia | | 2006-2007 | | Case series | | Pregnant, age 43 yr | | 1/1 | | 100% | Anon 2009 |
| Cough (n=1) | Wisconsin | | 2002-2006 | | Surveillance | | Clinical case, age 1-83 yr | | 33/33 | | 100% | Sotir 2007 |
| Rash (n=3) | Missouri | | 2009 | | Case series | | Clinical case, age 8 yr | | 1/1 | | 100% | CDC 2010 |
| Wisconsin | | 2002-2006 | | Surveillance | | Clinical case, age 1-83 yr | | 33/33 | | 100% | Sotir 2007 |
| 2007 | | Surveillance | | Clinical case | | NR | | NR | Wisconsin 2007 |
| Fatigue (n=3) | West Virginia | | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| Wisconsin | | 2007 | | Surveillance | | Clinical case | | NR | | NR | Wisconsin 2007 |
| West Virginia | | 1987 | | Case series, surveillance | | Hospital patients, age 1-14 yr | | 1/19 | | 5.26% | CDC 1988b |
| Chills (n=2) | West Virginia | | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| Edema (n=1) | North Carolina | | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 7/47 | | 14.90% | Miller 2012 |
| Cranial pressure (n=1) | USA | | 2003-2007 | | Predictive, surveillance | | Clinical cases, age 0-86 yr | | 3/43 | | 6.98% | Haddow 2009 |
| Bradycardia (n=1) | West Virginia | | NR | | Case series | | Clinical case, age 7 yr | | 1/1 | | 100% | McJunkin 1997 |
| Low sodium (n=1) | North Carolina | | 2004-2009 | | Case series | | Hospital patients, age 1-17 yr | | 7/47 | | 14.90% | Miller 2012 |
| Not specified (n=1) | USA | | 2003-2007 | | Predictive, surveillance | | Clinical cases, age 0-86 yr | | 3/43 | | 6.98% | Haddow 2009 |

1 Please refer to supplementary material S2 for the citation list of included articles.