Date: 1 APR 2015
To: NC Medical Providers
From: Dr. Megan Davies, State Epidemiologist
Subject: Annual Update on Diagnosis and Surveillance for Arboviral disease (2 pages)

Arboviral Diseases:
Per North Carolina law, neuroinvasive arboviral diseases are reportable by health care providers to their local health department. These infections are transmitted by the bite of an infected mosquito and the spectrum of illness ranges from asymptomatic to fever, altered mental status, and acute signs of central or peripheral neurologic dysfunction and, rarely, death. La Crosse encephalitis (LACE) is the most commonly reported arboviral disease in North Carolina (figures 1, 2) and during 2014 LACE cases represented all of the domestically acquired arboviral disease cases. Although LAC infection has been reported across the state, historical data demonstrates that several southwestern counties report over 75% of all LACE cases. While LaCrosse virus infection was first characterized in and named after LaCrosse, Wisconsin, most cases are now reported from focal regions of the eastern US, specifically in Appalachia. [1] West Nile virus infection (WNV) and Eastern Equine encephalitis (EEE) are neuro-invasive diseases also reported in North Carolina, but are much less common than LAC. Over the past five years, fewer than 10 cases total have been reported annually.

Chikungunya, Dengue, and Yellow Fever are also reportable diseases. These infections are associated with travel to endemic areas and there is no transmission occurring within North Carolina. In 2014 there were 48 cases of Chikungunya and 7 cases of Dengue reported to the Division of Public Health; all were travel associated. These conditions should be considered in a person with a clinically compatible illness and appropriate travel history. Patients with these conditions should be advised to wear insect repellent as they may serve as a source of infection for local mosquito populations for up to one week post symptom onset. Aedes albopictus, a competent vector for both Chikungunya and Dengue, can be found throughout NC. There have been no cases of Yellow Fever reported in NC in the past 10 years.

Diagnosis:
Serologic testing for arboviral diseases is offered at no charge from the State Laboratory of Public Health (NCSLPH). The submission form, DHHS 3445, is available at http://slph.state.nc.us/virology-serology/special-serology.asp. Early diagnosis of La Crosse encephalitis is critical to adapting therapy and eliminating unnecessary treatment; and also important for surveillance of the disease. The sensitivity and rapidity of diagnosis of the MAC ELISA test provide a powerful tool for the clinically relevant serodiagnosis of LAC virus infections in humans. [2] MAC ELISA testing is performed by the NCSLPH. Additionally serologic testing by the IFA methodology is available at the NCSLPH. We encourage providers to collect acute AND convalescent (e.g., after two-three weeks) specimens to confirm diagnosis using this methodology.

Education of patients, prevention of disease:
We encourage all providers to educate their patients about personal protective measures that can be used to minimize their risk of acquiring these conditions. The Centers for Disease Control (CDC) has excellent resources on these and emerging arboviral diseases available at http://www.cdc.gov/ncidod/dvybid/arbor/index.htm. There also is updated information on the Division of Public Health’s Communicable Diseases website at http://epi.publichealth.nc.gov/cd/diseases/arbo.html. If you have any questions or concerns, please call Carl Williams or Jodi Reber at 919-733-3419.
References:

Figures 1, 2

LACE, Average Incidence by County, NC, 2010-2014, n=108
Cases are Reported by County of Residence
Introduction:
Chikungunya is a mosquito-borne disease caused by an alphavirus, chikungunya virus. The virus is transmitted predominantly by *Aedes aegypti* and *Ae. albopictus*, aggressive daytime biting mosquitoes. Chikungunya virus was first identified in Tanzania in 1952 and has periodically caused outbreaks in Africa for decades. Starting in February 2005, several large outbreaks of chikungunya occurred in India and islands of the Indian Ocean. During 2005-2006 over 1.7 million cases were reported, primarily from India and Reunion Island.

The first local transmission of chikungunya virus in the western hemisphere was reported on the island of St. Martin on December 6, 2013. Since then, it has spread throughout the Caribbean and the Americas and over 1.2 million cases have been reported (http://www.paho.org/chikungunya). Imported cases have been identified in residents from North Carolina and other states returning from endemic areas. Although transmission in the United States has only been documented in Florida to date, local transmission within North Carolina is possible, as a competent mosquito vector (*Ae. albopictus*) is found throughout North Carolina.

Disease Transmission:
During epidemics, transiently infected humans are the reservoir for chikungunya. The incubation period following the bite of an infectious mosquito is typically 3-7 days (range, 1-12 days). Persons become viremic approximately two days prior to symptom onset and remain viremic for up to seven days. During the viremic phase, the patient can transmit the virus to mosquitoes biting them, which could then potentially infect another person. The disease is not directly transmitted from person-to-person.

Clinical Presentation:
Most people infected with chikungunya virus become symptomatic. The most common clinical findings are acute onset of fever and polyarthralgia, primarily affecting the hands, wrists, ankles and feet. Joint pains are often severe and debilitating. Chikungunya should be considered in patients who develop acute onset of fever and polyarthralgia within two weeks of returning from the Caribbean or from other endemic areas. Other symptoms may include headache, myalgia, arthritis, or rash. Persons at risk for more severe disease include neonates exposed intrapartum, adults ≥ 65 years of age, and persons with underlying medical conditions (e.g., hypertension, diabetes, or cardiovascular disease).

Case Management:
No specific antiviral treatment is available for chikungunya. The differential diagnosis of chikungunya virus infection is broad, as fever with or without arthralgia is a common manifestation of many diseases. Preliminary diagnosis is based on the patient’s clinical features, places and dates of travel, and activities. Treatment is focused...
on symptoms and includes rest, fluids, and use of analgesics and antipyretics. Dengue fever should be considered in the differential diagnosis for these patients because of the similarities in geographic distribution and symptoms.

People infected with chikungunya or dengue virus should be protected from further mosquito exposure during the first few days of illness to reduce the risk of local transmission. For more detailed case management information and keys to differentiating chikungunya infection from dengue infection, visit http://www.cdc.gov/chikungunya/hc/index.html.

**Diagnosis:**
Serologic and molecular testing for chikungunya are now available at the North Carolina State Laboratory of Public Health (NCSLPH). Please report suspected cases to your local health department if you plan to submit specimens for testing. (See Surveillance and Reporting below.) Specimens submitted to the NCSLPH for chikungunya testing must be accompanied by the NCSLPH submission form DHHS 3445, which is available at http://slph.state.nc.us/virology-serology/special-serology.asp. Please include all clinical and travel information, including date of onset.

NCSLPH will follow CDC testing guidelines for chikungunya. Patient samples collected ≤8 days post-illness onset will be tested by RT-PCR. If ≥4 days post-onset, the sample will also be tested for the presence of IgM antibody by ELISA. Samples >8 days post-onset will receive IgM ELISA testing only. All samples with “Presumptive Positive” IgM ELISA results will be referred to CDC for confirmatory plaque reduction neutralization testing. Testing for chikungunya will also be included with requests for arboviral panel testing on patients with a history of travel to an endemic area.

**Surveillance and Reporting:**
Chikungunya is reportable immediately in North Carolina. Due to the threat of introduction of this illness into North Carolina, this disease is required to be immediately reported by physicians to the local health department as soon as clinically suspected. Laboratory confirmed cases are also reportable. Laboratories are also required to report positive results to the Division of Public Health.

A suspected case is defined as a clinically compatible illness:
- Fever or chills as reported by the patient or a health-care provider, AND
- Arthralgia or arthritis involving two or more joints, AND
- Absence of a more likely clinical explanation

**Education of Patients, Prevention of Disease:**
We encourage all providers to educate their patients about personal protective measures that can be used to minimize the risk of acquiring this disease. Patients should be advised to consult their physician if they develop a compatible illness following travel to endemic areas. If chikungunya is suspected, patients should be encouraged to stay indoors or use mosquito repellant consistently during the first 5 days of illness when they might be viremic, in order to minimize the risk that they transmit the virus to local mosquitoes.

**Resources and Contact Information:**
- CDC website: http://www.cdc.gov/chikungunya/
- CDC Health Advisory: http://emergency.cdc.gov/HAN/han00358.asp
- NC DPH Communicable Disease Branch Epidemiologist On-Call: 919-733-3419 (24/7)
Lyme disease (LD) is caused by infection with the bacterium *Borrelia burgdorferi* sensu stricto transmitted by the bite of an infected *Ixodes scapularis* tick. The North Carolina Division of Public Health (DPH) would like to ensure that health care providers consider the possibility of LD when appropriate. The diagnosis of LD should be based on a combination of symptoms, physical findings, the possibility of exposure to infected ticks, and laboratory results.

**Surveillance for Lyme disease**

Per North Carolina law, LD is reportable by health care providers to their local health department. Laboratory diagnostic tests demonstrating isolation or identification of *B. burgdorferi* are also reportable by laboratories to the Division of Public Health. Surveillance for LD is based on the national case definition, which establishes uniform criteria for disease reporting in order to monitor trends, take action to reduce disease, and improve public health. During 2014, a total of 172 (28 confirmed, 144 probable; provisional data) cases of LD were reported in NC. Since 2008, when the probable case classification was introduced, the number of reported confirmed cases of LD has remained relatively constant with an average of 24 cases per year. In contrast the number of reported probable cases has increased over four times from 31 to 144. (Figures 1 & 2)

**Endemic County**

As of March 2015, five counties (Alleghany, Guilford, Haywood, Wake and Wilkes) are designated, for surveillance purposes, as endemic. Counties are designated as endemic if at least two laboratory confirmed cases of early LD (characterized by erythema migrans, EM) are identified in persons who did not travel outside of their county of residence during the incubation period, 30 days. In these situations, it is assumed that LD was acquired in the county of residence. A designation of endemic is not meant to imply a greater risk of transmission of *B. burgdorferi*, but is used to assist in classification of cases for surveillance. In counties classified as endemic, cases of EM alone, with no exposure to tick habitat outside of the endemic county of residence, are classified as confirmed. (Table 1)

**Serologic Testing for Lyme disease**

If LD is suspected in a patient, DPH requests that appropriate laboratory tests be ordered to support a surveillance diagnosis. Serologic testing is insensitive in the acute phase (the first two weeks) of infection and may be falsely negative, so should not be used for clinical decision-making in the acute phase. If laboratory testing is not supportive of a surveillance diagnosis, please consider reordering convalescent testing two weeks later. All late manifestations of LD (musculoskeletal, cardiac, and nervous) and early LD with exposure in a non-endemic county must also be accompanied by appropriate laboratory testing to fulfill the surveillance case definition requirements. Although testing for LD serology is not currently available at the NC State Laboratory of Public Health, samples submitted to the laboratory will be forwarded to CDC for testing. When ordering serologic tests be sure to request a total EIA (screening) test with an automatic reflex to IgG and IgM western blot if the EIA is positive or equivocal. (Figure 3)
Erythema Migrans rash in NC
There are multiple differential diagnosis for EM, including STARI (southern tick associated rash illness), ringworm, cellulitis and others. [4] STARI can occur after the bite of the lone star tick (*Amblyomma americanum*), the most common tick in North Carolina, which is not a known vector for *B. burgdorferi*. [5] The etiologic agent for STARI is unknown and there is no diagnostic test. STARI is an EM like skin lesion and a confounder for LD surveillance and the primary reason why all cases of EM should be accompanied by laboratory evidence of infection, to confirm diagnosis, particularly in areas where LD and STARI may coexist. In the southern United States, it has been recommended that EM rashes be treated presumptively as early LD, regardless of what the true cause of the rash may be. [6] However, where the incidence rate of LD is low, and the probability that an EM rash due to infection with *B. burgdorferi* is low, it has also been recommended that patients be observed, as opposed to receiving empiric treatment, to avoid complications of treatment. [7] Treatment for (potential) LD should be initiated on the best judgment of the attending clinician.

Education of patients, prevention of disease:
We encourage all providers to educate their patients about personal protective measures to minimize their risk of acquiring tick borne illness. Lyme disease prevention materials are available from the CDC. Please visit our website (http://epi.publichealth.nc.gov/cd/diseases/ticks.html) or contact Carl Williams or Jodi Reber at 919-733-3419 with any questions or concerns that you have regarding surveillance of Lyme disease. Your time and consideration on this topic are greatly appreciated.

Figures 1 & 2:

![Graph](image)

<table>
<thead>
<tr>
<th>EM Rash ≥ 5 cm</th>
<th>Objective Late Manifestation(s)</th>
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<tr>
<td>Confirmed if known exposure occurred in a county endemic for LD (DPH encourages laboratory evidence be obtained to support case classification)</td>
<td>Laboratory evidence required for confirmation</td>
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<td>Laboratory evidence required for confirmation</td>
<td>Laboratory evidence required for confirmation</td>
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References:
1. 10A NCAC 41A .0101 REPORTABLE DISEASES AND CONDITIONS

![Diagram](image)
To: NC Medical Providers

From: Dr. Megan Davies, State Epidemiologist

Subject: Annual Update on Diagnosis and Surveillance for Tickborne Rickettsial Disease (2 pages)

Spotted Fever Group Rickettsiosis, Ehrlichiosis and Anaplasmosis Diseases --Introduction:

Tick-borne rickettsial diseases (TBRD) share clinical similarities and include Rocky Mountain spotted fever as well as diseases caused by other *Rickettsia*, *Ehrlichia* and *Anaplasma* species. Rocky Mountain spotted fever and other spotted fever illnesses are not distinguished by the present level of testing and, for surveillance purposes, are reported as Spotted Fever Group Rickettsiosis (SFGR, *Rickettsia* spp.). SFGR predominate in NC and comprise 85% of all TBRD reported in 2014. Cases of Human Monocytic Ehrlichiosis (13%) and Anaplasmosis (2%) are caused by *Ehrlichia chaffensis* and *Anaplasma phagocytophilum* respectively.

Confirmation of Diagnosis and Surveillance:

Serologic testing of specimens by Immunofluorescent Assay (IFA) of IgG antibody is the most common means to confirm a diagnosis of TBRD for surveillance purposes. Although testing is available for RMSF specifically, the test is not species specific and will cross react with other species in the genus *Rickettsia*. Testing for spotted fever rickettsia is available at no charge from the State Laboratory of Public Health. See: [http://slph.state.nc.us/virology-serology/special-serology.asp](http://slph.state.nc.us/virology-serology/special-serology.asp). The CDC notes that ELISA (EIA) tests alone are not quantitative and IgM tests lack specificity. For these reasons, if testing is performed through a commercial laboratory, we strongly encourage the use of paired acute and convalescent (2-3 weeks later) sera submitted for IgG IFA testing for surveillance purposes.

Several commercial laboratories (LabCorp, Quest Diagnostics, ARUP, Mayo Medical Laboratories) also offer PCR testing for *Rickettsia rickettsii*, *Ehrlichia chaffensis* and *Anaplasma phagocytophilum* or some combination of them. DNA detection is a confirmatory test per the national case definitions for TBRD and may, from a surveillance standpoint, lead to higher proportion of confirmed cases, because a convalescent clinical specimen is not required.

In North Carolina, the number of reported cases of SFGR (including RMSF) has increased steadily since 2009. However, only about 5% of cases in any year are confirmed via paired acute and convalescent serology. The vast majority of cases are classified as probable, based on a single serologic result. While this is consistent with national reporting patterns, we request your support to improve surveillance by ordering both acute and convalescent serum samples (or consider PCR testing). (Figures 1 – 4)

Treatment:

Regardless of the ultimate cause of infection, if TBRD is suspected, patients of all ages, including children, should be treated promptly and appropriately with doxycycline. [1,3,4] Laboratory confirmation of infection with TBRD organism may take weeks and therapy should not be delayed pending diagnosis. TBRD are potentially fatal and treatment guidelines are available. In a recent survey of healthcare providers, 80% identified doxycycline as the appropriate treatment for Rocky Mountain spotted fever in patients greater than 8 years old, but only 35% correctly chose doxycycline in patients aged less than 8 years. These findings raise concerns about the higher pediatric case-fatality rate of Rocky Mountain spotted fever observed nationally. [2]
Recommendations of the CDC and American Academy of Pediatrics [3,4,5]

The use of doxycycline to treat suspected ehrlichiosis/RMSF in children is standard practice recommended by both CDC and the AAP Committee on Infectious Diseases. Unlike older generations of tetracyclines, the recommended dose and duration of medication needed to treat ehrlichiosis/RMSF has not been shown to cause staining of permanent teeth, even when five courses are given before the age of eight. Healthcare providers should use doxycycline as the first-line treatment for suspected ehrlichiosis/RMSF in patients of all ages.

If you have any questions about surveillance of tick borne rickettsial diseases please visit our website (http://epi.publichealth.nc.gov/cd/diseases/ticks.html) or contact Jodi Reber or Carl Williams at 919-733-3419.

References:
5. Todd, et. al. No Visible Dental Staining in Children Treated with Doxycycline for Suspected Rocky Mountain Spotted Fever. J Pediatr. 2015 Mar 14

Figures 1 – 4