Tickborne Diseases: Challenges and Controversies

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Disclosures

- I have been on Advisory Boards for Cempra, Astellas, Gilead
- I will not be discussing any medications/products produced by any of these companies

Objectives

- The participant will be able to describe the symptoms of tickborne diseases in Ohio.
- The participant will be able to summarize testing and interpretation of tests for Lyme disease.
- The participant will be able to list recommended treatment for tickborne diseases.

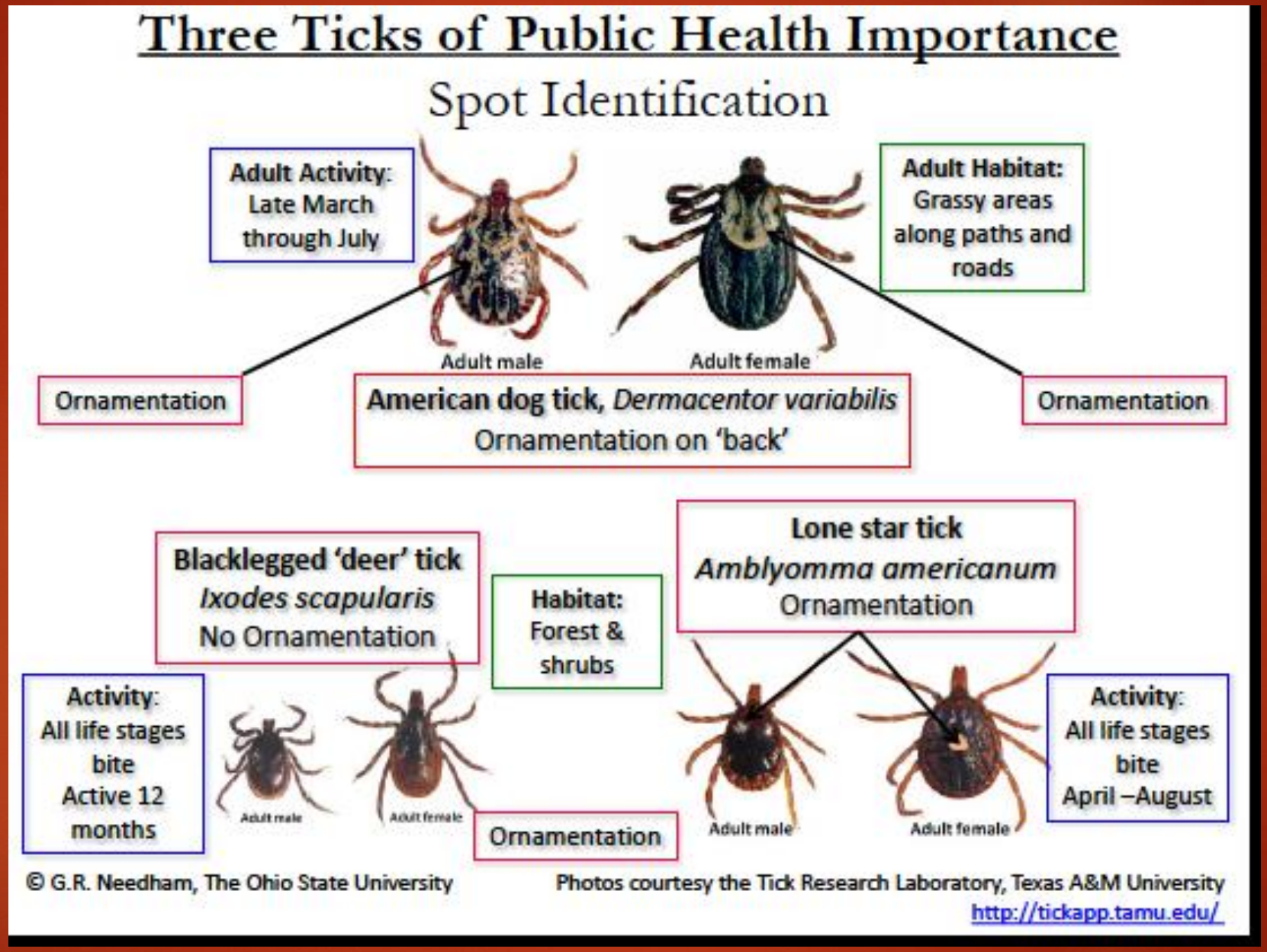
In the United States, some ticks carry pathogens that can cause human disease, including:

- **Anaplasmosis** is transmitted to humans by tick bites primarily from the blacklegged tick (*Ixodes scapularis*) in the northeastern and upper midwestern U.S. and the western blacklegged tick (*Ixodes pacificus*) along the Pacific coast.
- **Babesiosis** is caused by microscopic parasites that infect red blood cells. Most human cases of babesiosis in the U.S. are caused by *Babesia microti*. *Babesia microti* is transmitted by the blacklegged tick (*Ixodes scapularis*) and is found primarily in the northeast and upper midwest.
- ***Borrelia mayonii*** infection has recently been described as a cause of illness in the upper midwestern United States. It has been found in blacklegged ticks (*Ixodes scapularis*) in Minnesota and Wisconsin. *Borrelia mayonii* is a new species and is the only species besides *B. burgdorferi* known to cause Lyme disease in North America.
- ***Borrelia miyamotoi*** infection has recently been described as a cause of illness in the U.S. It is transmitted by the blacklegged tick (*Ixodes scapularis*) and has a range similar to that of Lyme disease.
- **Bourbon virus** infection has been identified in a limited number patients in the Midwest and southern United States. At this time, we do not know if the virus might be found in other areas of the United States.
- **Colorado tick fever** is caused by a virus transmitted by the Rocky Mountain wood tick (Dermacentor andersoni). It occurs in the the Rocky Mountain states at elevations of 4,000 to 10,500 feet.
- **Ehrlichiosis** is transmitted to humans by the lone star tick (*Ambylomma americanum*), found primarily in the southcentral and eastern U.S.
- **Heartland virus** cases have been identified in the Midwestern and southern United States. Studies suggest that Lone Star ticks can transmit the virus. It is unknown if the virus may be found in other areas of the U.S.
- **Lyme disease** is transmitted by the blacklegged tick (*Ixodes scapularis*) in the northeastern U.S. and upper midwestern U.S. and the western blacklegged tick (*Ixodes pacificus*) along the Pacific coast.
- **Powassan disease** is transmitted by the blacklegged tick (*Ixodes scapularis*) and the groundhog tick (*Ixodes cookei*). Cases have been reported primarily from northeastern states and the Great Lakes region.
- ***Rickettsia parkeri* rickettsiosis** is transmitted to humans by the Gulf Coast tick (*Amblyomma maculatum*).
- **Rocky Mountain spotted fever (RMSF)** is transmitted by the American dog tick (*Dermacentor variabilis*), Rocky Mountain wood tick (*Dermacentor andersoni*), and the brown dog tick (*Rhipicephalus sanguineus*) in the U.S. The brown dog tick and other tick species are associated with RMSF in Central and South America.
- **STARI (Southern tick-associated rash illness)** is transmitted via bites from the lone star tick (*Ambylomma americanum*), found in the southeastern and eastern U.S.
- **Tickborne relapsing fever (TBRF)** is transmitted to humans through the bite of infected soft ticks. TBRF has been reported in 15 states: Arizona, California, Colorado, Idaho, Kansas, Montana, Nevada, New Mexico, Ohio, Oklahoma, Oregon, Texas, Utah, Washington, and Wyoming and is associated with sleeping in rustic cabins and vacation homes.
- **Tularemia** is transmitted to humans by the dog tick (*Dermacentor variabilis*), the wood tick (*Dermacentor andersoni*), and the lone star tick (*Amblyomma americanum*). Tularemia occurs throughout the U.S.
- **364D rickettsiosis** (*Rickettsia phillipi*, proposed) is transmitted to humans by the Pacific Coast tick (*Dermacentor occidentalis* ticks). This is a new disease that has been found in California.

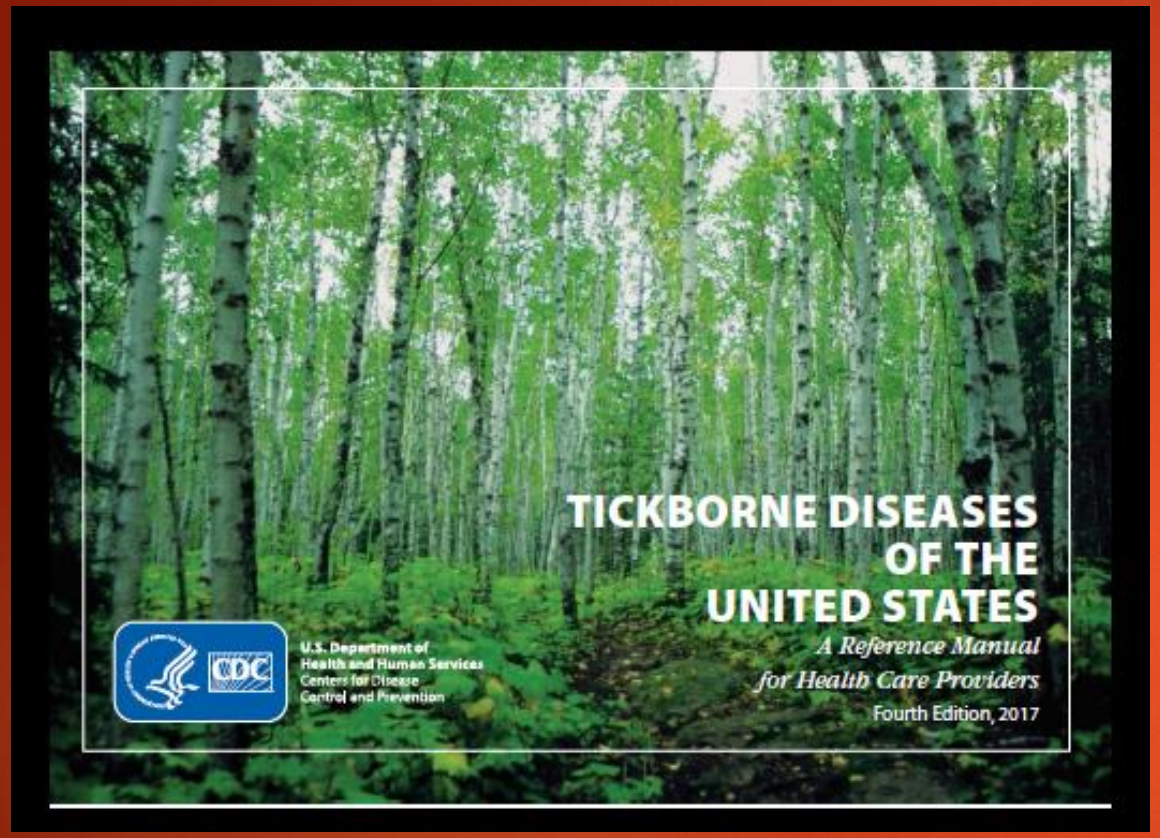
https://www.cdc.gov/ticks/diseases/index.html

RMSF

Lyme
Anaplasmosis
Babesiosis



Ehrlichiosis



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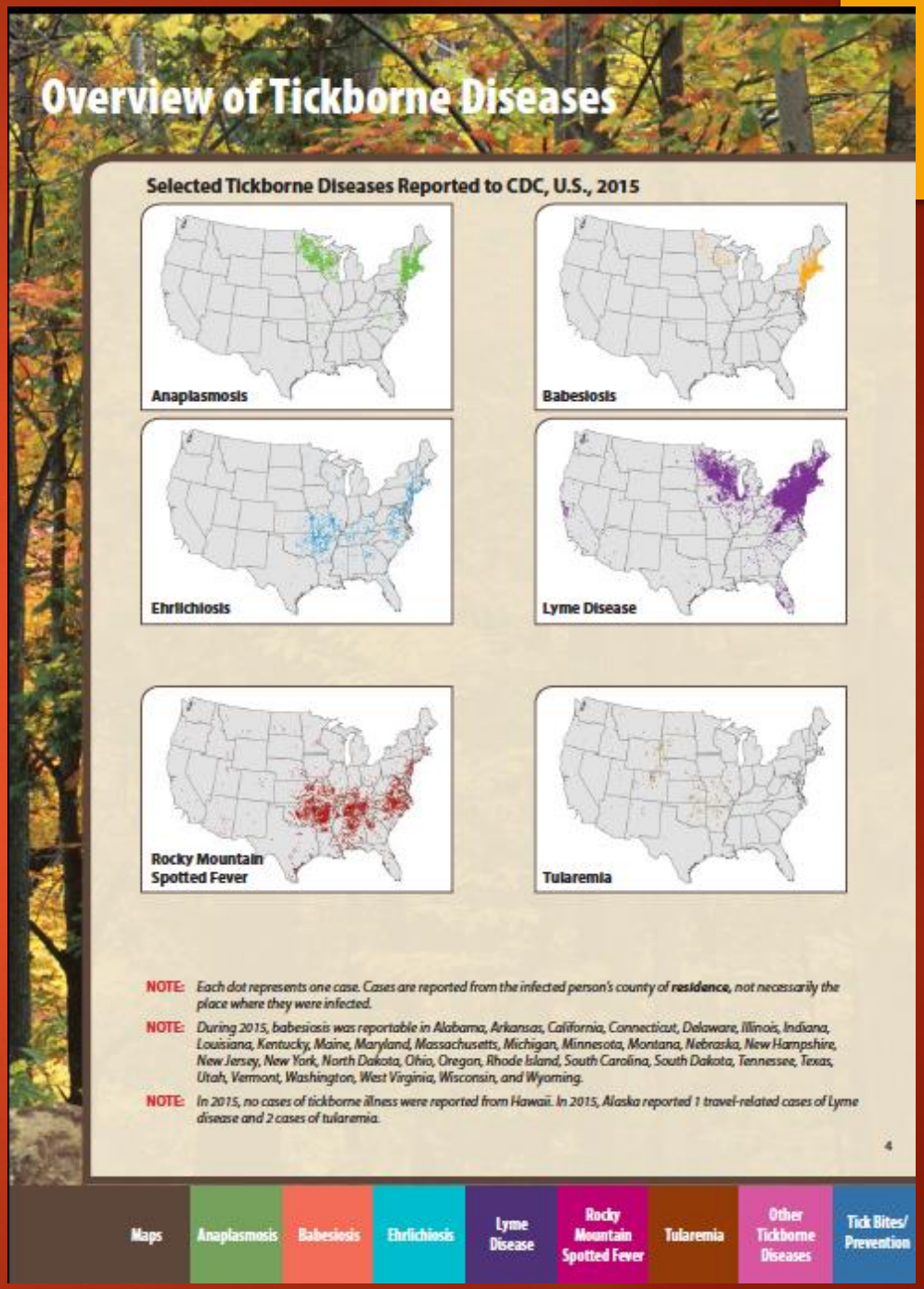
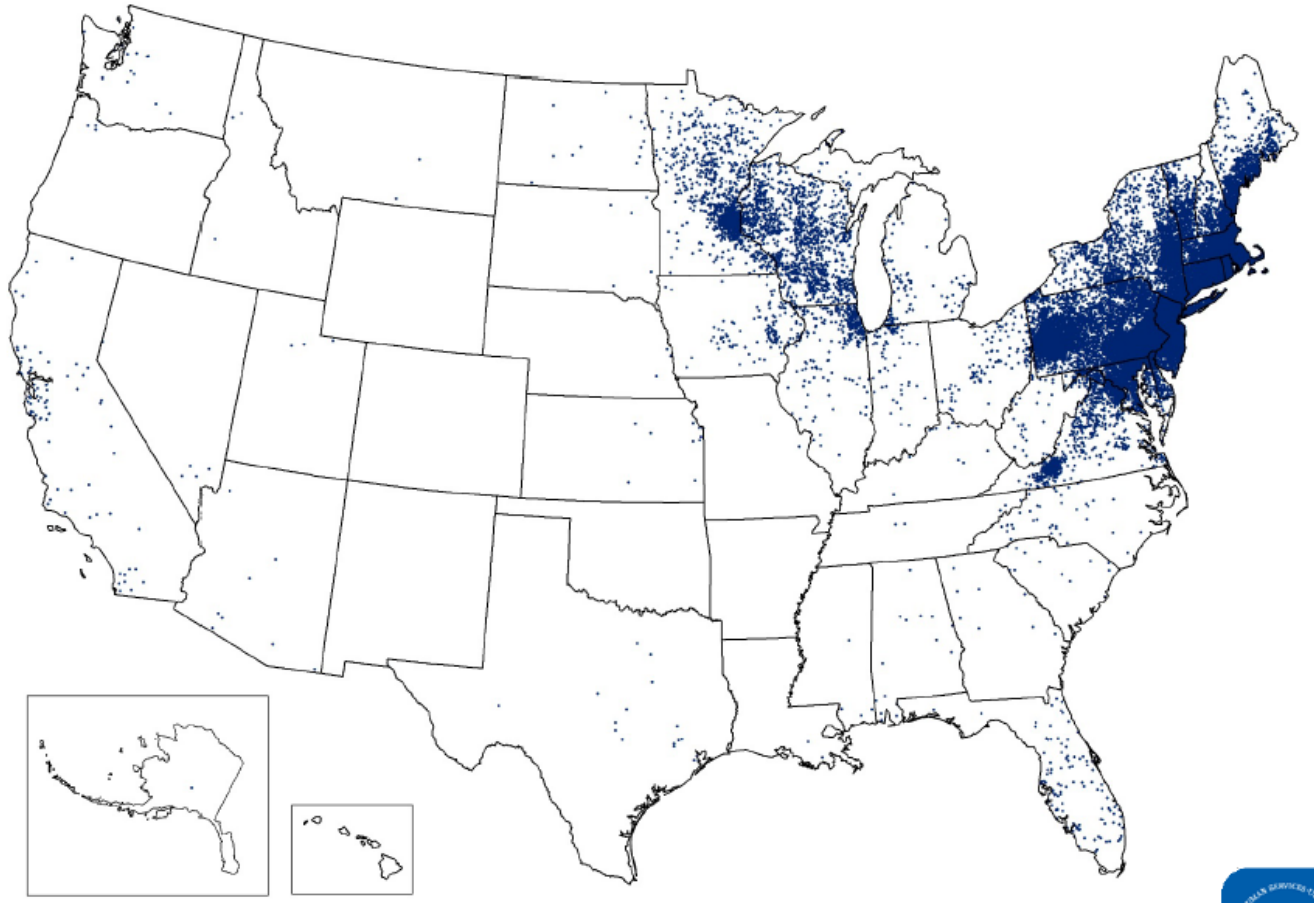


Lyme Disease

Reported Cases of Lyme Disease—United States, 2015

Each dot represents one case of Lyme disease and is placed randomly in the patient's county of residence. The presence of a dot in a state does not necessarily mean that Lyme disease was acquired in that state. People travel between states, and the place of residence is sometimes different from the place where the patient became infected.



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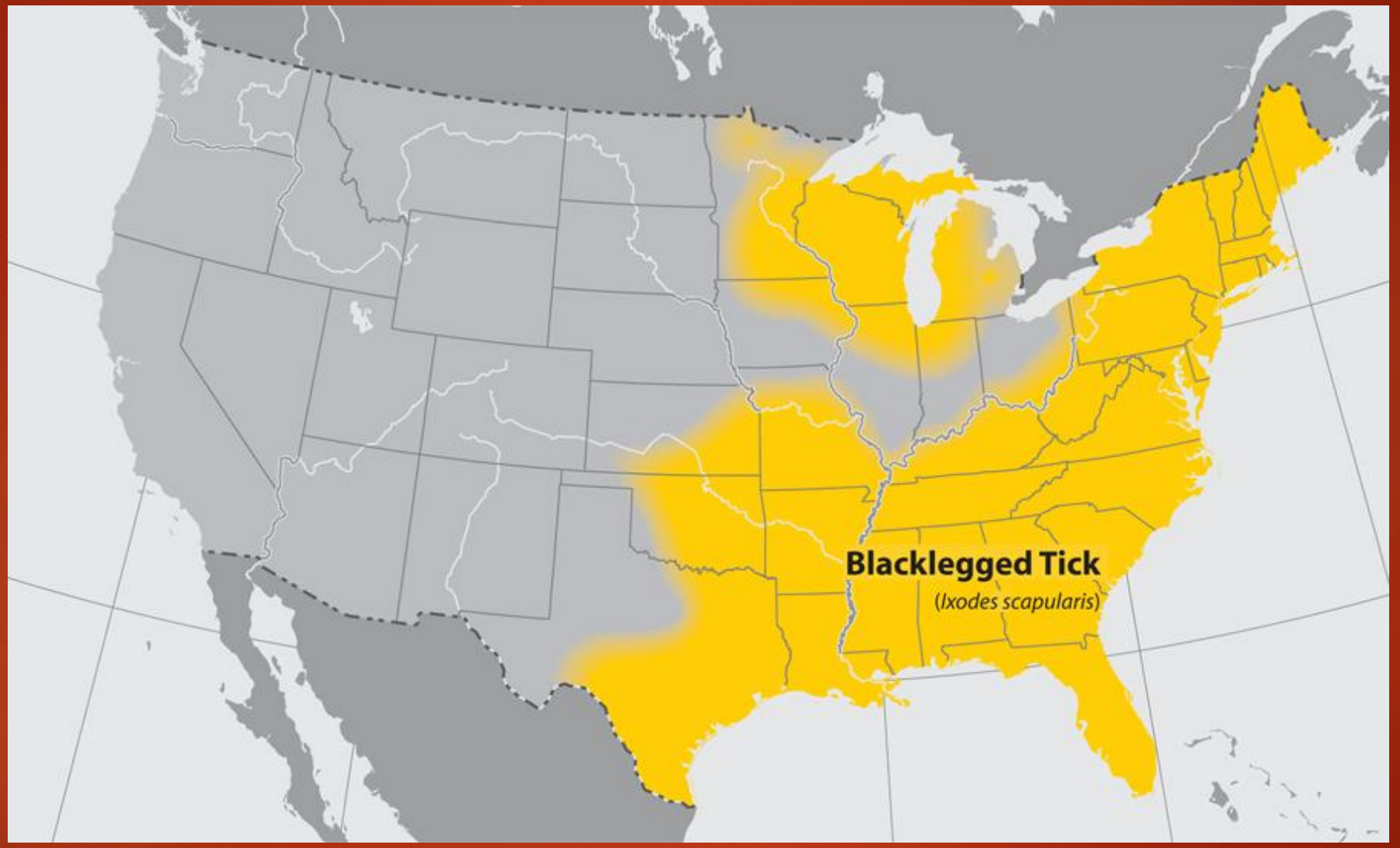
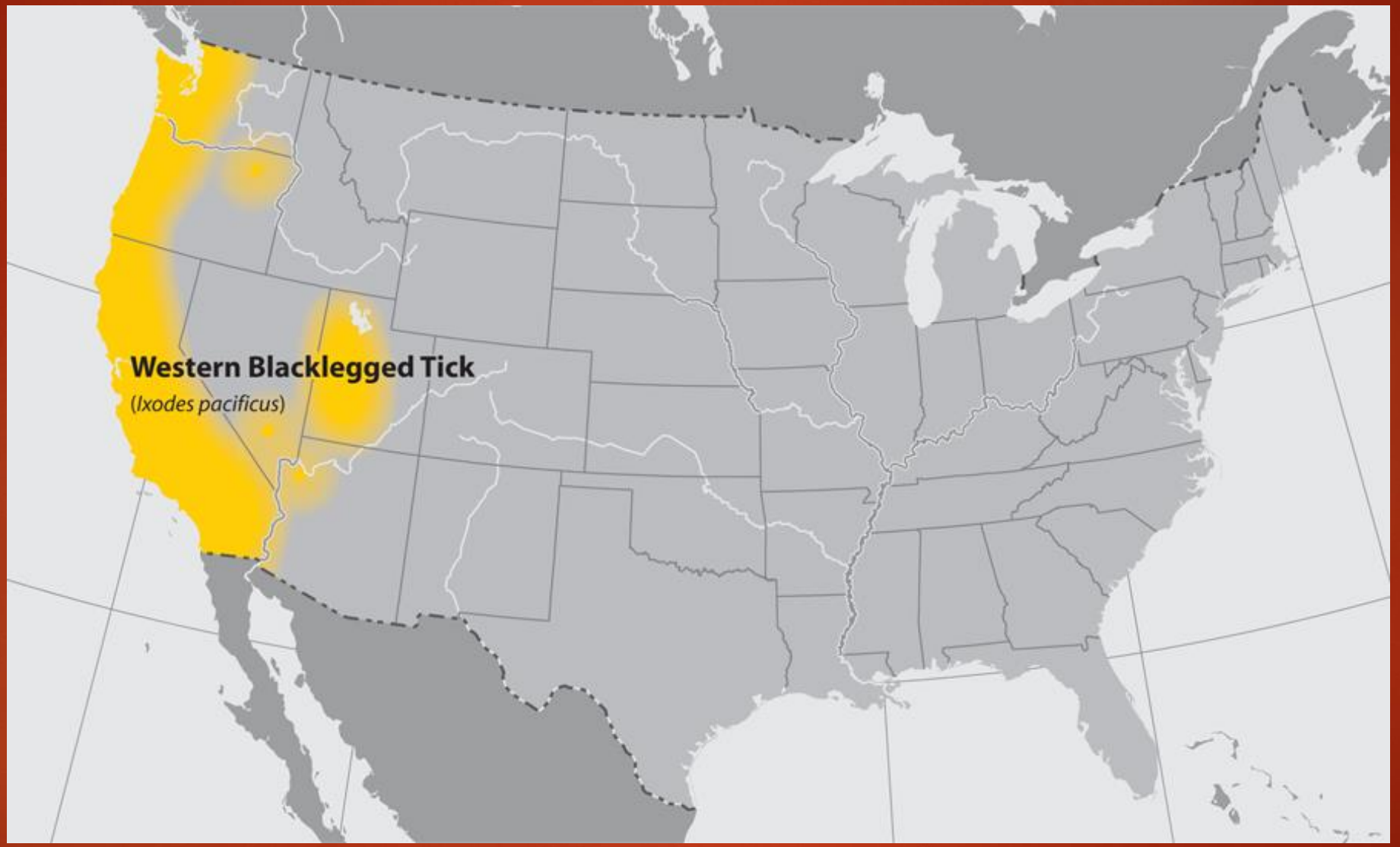
CDC

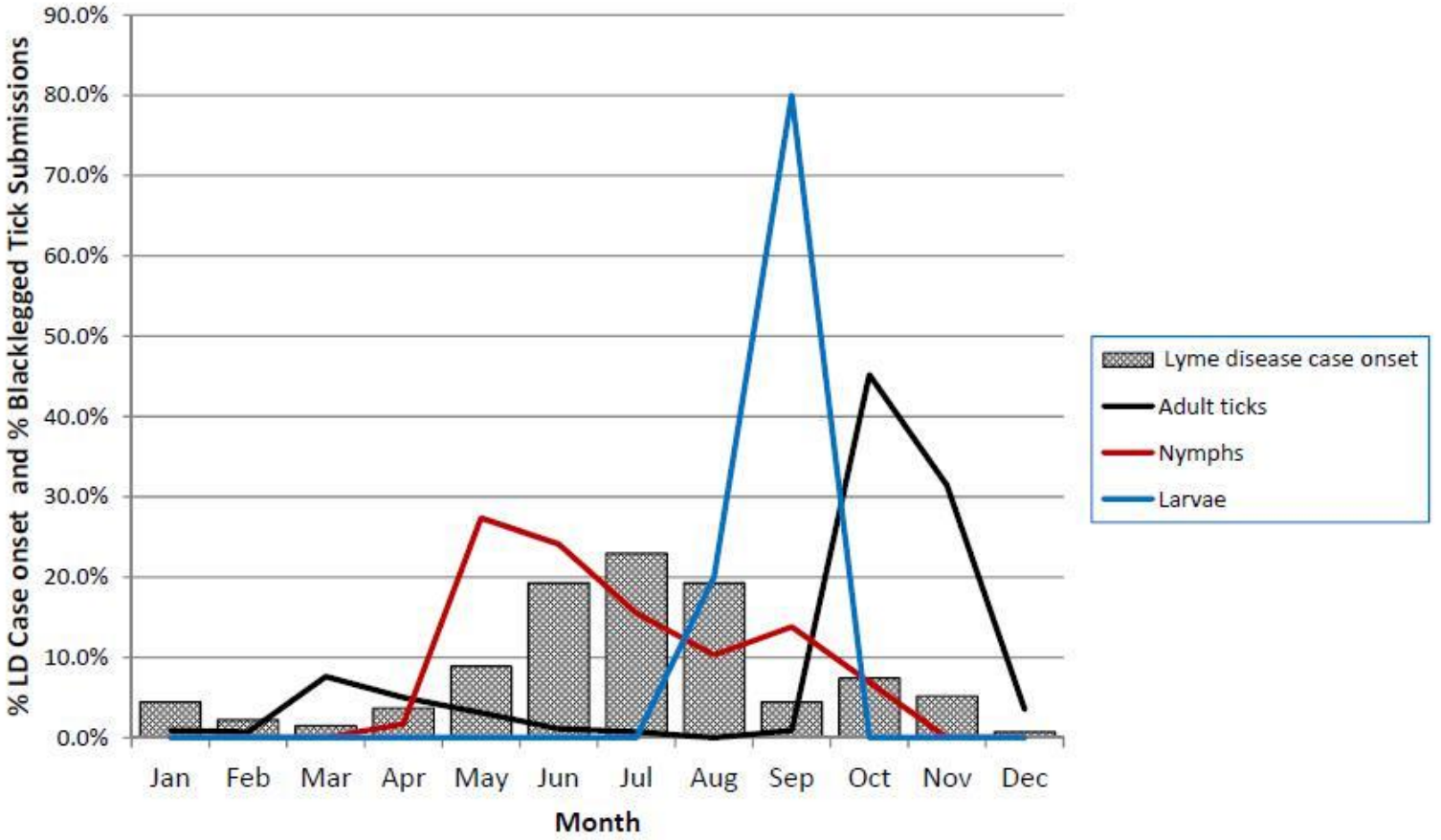

Blacklegged Tick
(Ixodes scapularis)


Western Blacklegged Tick
(Ixodes pacificus)

2000	61
2001	43
2002	89
2003	61
2004	50
2005	58
2006	43
2007	33
2008	44
2009	60
2010	44
2011	53
2012	67
2013	93
2014	119
2015	154
2016	160
2017	175
Total	**2,021**

- Lyme Cases in Ohio

Lyme disease case onset & activity of blacklegged ticks in Ohio



Blacklegged ticks are active throughout the year in Ohio. The adults are active in the spring, fall and winter. The nymphs are active in the spring and summer and the larvae are active late summer. The onset of human **Lyme disease** cases occurs year round in Ohio but peaks in summer following the emergence of nymphs. (Source: ODH, Zoonotic Disease Program)

ODH-ZDP

Revised 1/2015

Lyme Disease: Early Signs and Symptoms (3-30D after tick bite)

- Fever, chills, headache, fatigue, muscle and joint aches, and swollen lymph nodes
- Erythema migrans (EM) rash:
  - Occurs in approximately 70 to 80 percent of infected persons
  - Begins at the site of a tick bite after a delay of 3 to 30 days (average is about 7 days)
  - Expands gradually over a period of days reaching up to 12 inches or more (30 cm) across
  - May feel warm to the touch but is rarely itchy or painful
  - Sometimes clears as it enlarges, resulting in a target or "bull's-eye" appearance
  - May appear on any area of the body

Lyme Disease: Late Signs

- Severe headaches and neck stiffness
- Additional EM rashes on other areas of the body
- Arthritis with severe joint pain and swelling, particularly the knees and other large joints.
- Facial palsy (loss of muscle tone or droop on one or both sides of the face)
- Intermittent pain in tendons, muscles, joints, and bones
- Heart palpitations or an irregular heart beat (Lyme carditis)
- Episodes of dizziness or shortness of breath
- Meningitis or transverse myelitis
- Nerve pain
- Shooting pains, numbness, or tingling in the hands or feet
- Problems with short-term memory

Lyme Carditis

- Most often diagnosed due to conduction disturbances, usually AV block
- may have a-fib, bundle brach block, IVCD, SVT, VT
- Myocarditis and pericarditis are uncommon
- Acute heart failure, chronic cardiomyopathy, infective endocarditis and recurrent pericardial effusions are rare
- Treatment is usual treatment of Lyme disease, prognosis is very good

Lyme Arthritis

- Initial description of Lyme disease was an outbreak of arthritis in children in Lyme, Connecticut
- In early infection, borellia disseminate to joints- usually asymptomatic
- Arthritis is a late manifestation months after initial infection
- Most often affects one or both knees, and fever is not usually present
- PCR of synovial fluid may yield diagnosis (40-96%); Lyme IgG is positive, and WBC's are present, counts vary
- Treatment with antibiotic therapy and anti-inflammatory medications usually resolves problem
- Initial therapy is Doxycycline 30D, if persistent mild symptoms, another 30D of doxycycline or if severe symptoms, IV ceftriaxone
- Persistent arthritis after above treated with NSAID's, MTX, DMARDS

Neurological Manifestations of Lyme Disease

- early manifestations include radiculopathy, cranial neuropathy, mononeuropathy multiplex
- early lymphocytic meningitis may occur; transverse myelitis and encephalitis is rare
- late manifestations include encephalopathy, peripheral neuropathy,
- CSF shows lymphocytic pleocytosis, normal glucose and elevated protein

Erythema Migrans

Southern Tick Associated Rash Illness (STARI)

STARI vs. Lyme

- Patients with STARI were more likely to recall a tick bite
- Rash started within less time (6 D) for STARI
- less likely to be multi-focal and smaller in size than Lyme
- Rash is more circular in shape with more central clearing
- Patients with STARI were less likely to have other symptoms
- Patients with STARI recovered more quickly after antibiotic treatment in one study, but it is not clear whether antibiotics are indicated
- Cause of STARI is unknown


Lone Star Tick
(Amblyomma americanum)

“Chronic Lyme Disease”

- Term used by some healthcare providers and patients to describe a constellation of musculoskeletal and neuropsychiatric symptoms
- Patients often have other diseases that explain these symptoms, and are given long courses of antibiotics and alternative therapies without benefit
- Diagnosis may be made only on basis of symptoms, or lab testing through labs that have developed their own diagnostic criteria not in agreement with CDC
- Alternative treatment have included hyperbaric oxygen, IV hydrogen peroxide, IVIG, colloidal silver, stem cell transplants , long and repeated courses of IV antibiotics
- Labeling patient with “Chronic Lyme” may lead to unnecessary treatments and complications, and failure to diagnose underlying disease

Morbidity and Mortality Weekly Report

Serious Bacterial Infections Acquired During Treatment of Patients Given a Diagnosis of Chronic Lyme Disease — United States

Natalie S. Marzec, MD[1]; Christina Nelson, MD[2]; Paul Ravi Waldron, MD[3]; Brian G. Blackburn, MD[4]; Syed Hosain, MD[5]; Tara Greenhow, MD[6]; Gary M. Green, MD[6]; Catherine Lomen-Hoerth, MD, PhD[7]; Marjorie Golden, MD[8]; Paul S. Mead, MD[2]

The term "chronic Lyme disease" is used by some health care providers as a diagnosis for various constitutional, musculoskeletal, and neuropsychiatric symptoms (*1*,*2*). Patients with a diagnosis of chronic Lyme disease have been provided a wide range of medications as treatment, including long courses of intravenous (IV) antibiotics (*3*,*4*). Studies have not shown that such treatments lead to substantial long-term improvement for patients, and they can be harmful (*1*,*5*). This report describes cases of septic shock, osteomyelitis, *Clostridium difficile* colitis, and paraspinal abscess resulting from treatments for chronic Lyme disease. Patients, clinicians, and public health practitioners should be aware that treatments for chronic Lyme disease can carry serious risks.

Lyme disease is a well-known condition caused by infection with the spirochete *Borrelia burgdorferi* sensu lato. Features of early infection include erythema migrans (an erythematous skin lesion with a bull's-eye or homogeneous appearance), fever, headache, and fatigue. If left untreated, the spirochete can disseminate throughout the body to cause meningitis, carditis, neuropathy, or arthritis (*5*,*6*). The recommended treatment for Lyme disease is generally a 2–4-week course of antibiotics (*5*).

Chronic Lyme disease, on the other hand, is a diagnosis that some health care providers use to describe patients with a variety of conditions such as fatigue, generalized pain, and neurologic disorders. Many of these patients have experienced significant debilitation from their symptoms and have not found relief after consultation with conventional medical practitioners. As a result, some seek treatment from practitioners who might identify themselves as Lyme disease specialists ("Lyme literate" doctors) or from complementary and alternative medicine clinics, where they receive a diagnosis of chronic Lyme disease (*3*,*7*).

A diagnosis of chronic Lyme disease might be based solely on clinical judgment and without laboratory evidence of *B. burgdorferi* infection, objective signs of infection, or a history of possible tick exposure in an area with endemic Lyme disease (*1*,*7*). There is a belief among persons who support the diagnosis and treatment of chronic Lyme disease that *B. burgdorferi* can cause disabling symptoms even when standard testing is negative, despite evidence that the recommended two-tiered serologic testing is actually more sensitive the longer *B. burgdorferi* infection has been present (*6*). Some practitioners use tests or testing criteria that have not been validated for the diagnosis of Lyme disease (*1*). A significant concern is that after the diagnosis of chronic Lyme disease is made, the actual cause of a patient's symptoms might remain undiagnosed and untreated (*3*,*8*).

Patients given a diagnosis of chronic Lyme disease have been prescribed various treatments for which there is often no evidence of effectiveness, including extended courses of antibiotics (lasting months to years), IV infusions of hydrogen peroxide, immunoglobulin therapy, hyperbaric oxygen therapy, electromagnetic frequency treatments, garlic supplements, colloidal silver, and stem cell transplants (*1*,*3*). At least five randomized, placebo-controlled studies have shown that prolonged courses of IV antibiotics in particular do not substantially improve long-term outcome for patients with a diagnosis of chronic Lyme disease and can result in serious harm, including death (*1*,*5*,*9*).*

Clinicians and state health departments periodically contact CDC concerning patients who have acquired serious bacterial infections during treatments for chronic Lyme disease. Five illustrative cases described to CDC over the past several years are presented.

Patient A

A woman in her late 30s with fatigue and joint pain received a diagnosis of chronic Lyme disease, babesiosis, and *Bartonella* infection by a local physician. Despite multiple courses of oral antibiotics, her symptoms worsened, and a peripherally inserted central catheter (PICC) was placed for initiation of IV antibiotic treatment. After 3 weeks of treatment with IV ceftriaxone and cefotaxime, the patient's joint pain continued, and she developed fever and rash. She became hypotensive and tachycardic and was hospitalized in an intensive care unit, where she was treated with broad spectrum IV antibiotics and required mechanical ventilation and vasopressors. Despite maximal medical support, she continued to worsen and eventually died. The patient's death was attributed to septic shock related to central venous catheter–associated bacteremia.

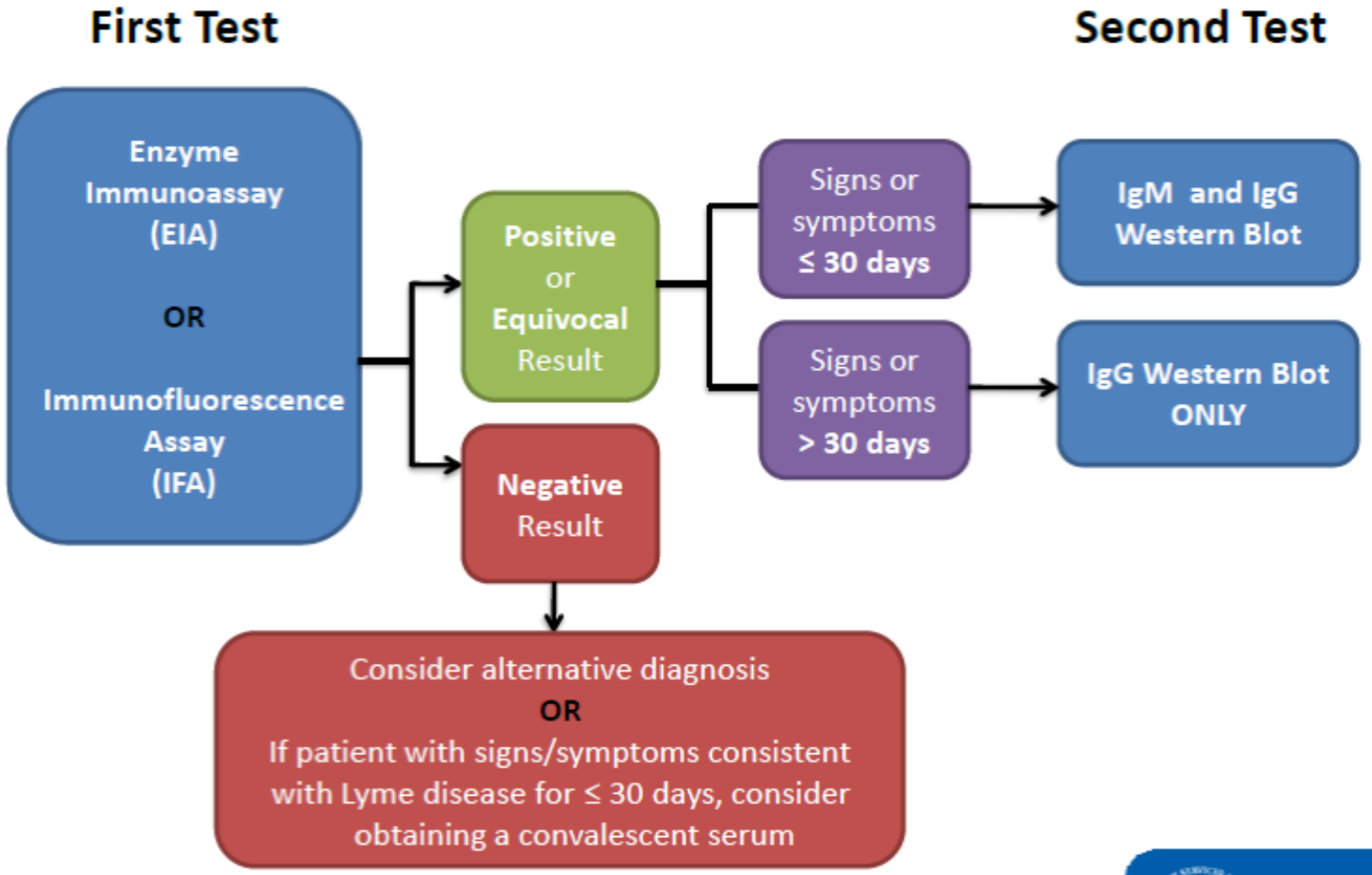
Patient B

An adolescent girl sought medical advice regarding years of muscle and joint pain, backaches, headaches, and lethargy. She had received a diagnosis of chronic fatigue syndrome,

*https://www.cdc.gov/lyme/treatment/prolonged/index.html.

- Report describes 5 cases with severe complications of prolonged IV antibiotic therapy
- Complications include septic shock resulting in death, sepsis due to CLABSI, osteomyelitis, parapspinal abscess and C.diff colitis
- One woman had delayed diagnosis of ALS, erroneously diagnosed as "chronic Lyme"

Two-Tiered Testing for Lyme Disease



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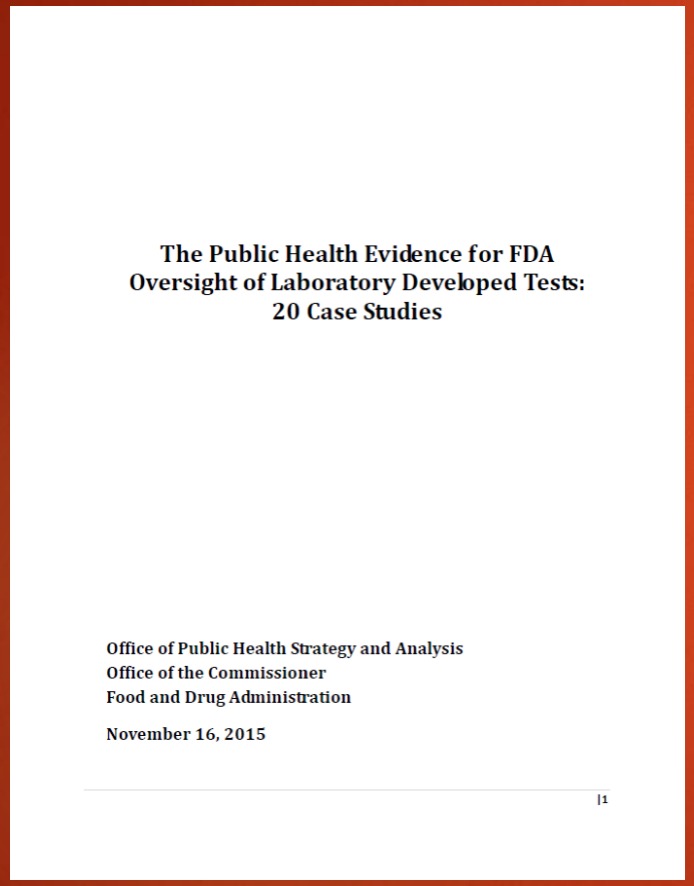
Lyme testing: What not to do



The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies

Office of Public Health Strategy and Analysis
Office of the Commissioner
Food and Drug Administration

November 16, 2015

|1

A. Tests that Yield Many Positive Results when the Disease or Condition is not Actually Present (False-Positives)

i. Lyme Disease Diagnostic Tests

Category	LDT Characteristics
LDT Name	Lyme disease antigen and culture tests
Description	Test to detect portions of the bacterium that causes Lyme disease or antibodies to the bacterium
Purpose	Diagnose Lyme disease
Target Population	Patients with symptoms suggestive of Lyme disease
Alternatives	Over 80 FDA-cleared diagnostic tests
LDT Problem 1	In clinical use, large numbers of patients with positive tests do not have Lyme disease
Clinical Consequence	Patients with false-positive tests may be treated with unnecessary medications; delayed diagnosis of true underlying condition
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards
Cost Impact of Inaccuracy	$1,226 per case

Testing for Lyme Disease

- Cell proliferation assays, Enzyme-Linked ImmunoSpot assays, cytokine measurements, complement split products, and lymphocyte transformation tests are not helpful and should not be used to diagnose Lyme
- Natural killer cell measurements are also not recommended
- Urine PCR tests are not recommended
- Performing a Lyme WB IgM without a screening test in appropriate clinical setting should be avoided
- Sensitivity and specificity of antibody tests increases with duration of infection. The CDC algorithm should be followed.

Posttreatment Lyme Disease Syndrome (PTLDS)

- Lyme disease is usually cured with antibiotic therapy, whether early or late
- Some will develop an ill-defined constellation of symptoms:
  - Fatigue, musculoskeletal pain, cognitive deficits
  - Symptoms may be persistent or intermittent
- When symptoms occur for more than 6 months after treatment of Lyme disease, this may be called PTLDS
- Objective physical findings are often not present, and no specific lab tests are available for this diagnosis
- Delay in initial diagnosis, severe symptoms,neurological symptoms at onset may lead to increase in frequency of PTLDS
- Estimates of frequency vary

PTLDS

- This is a diagnosis of exclusion
- It is important to rule out co-infection with other tickborne diseases
- Also look for underlying diseases such as autoimmune disease, fibromyalgia, depression
- Case definition proposed by IDSA includes persistent unexplained symptoms after treatment of documented Lyme disease, that began within 6 months of completion of treatment with currently recommended antibiotics
- If diagnosis of Lyme disease is based on presence of EM, this must be documented by an experienced health care practitioner

Exclusion Criteria for PTLDS

- A pre-existing diagnosis of CFS or Fibromyalgia
- Prolonged history of unexplained symptoms or somatic complaints prior to documented Lyme disease
- An underlying diagnosis that explains the symptoms: OSA, morbid obesity, psychiatric illness, autoimmune disease, substance abuse, etc.

Laboratory Testing and PTLDS

- Prior treatment with effective antibiotics is a part of the definition of PTLDS, so antibody tests may be negative
- Antibodies may also persist long after resolution of symptoms
- **Testing for Lyme is not recommended in cases where there is a prior established diagnosis of Lyme disease with appropriate treatment**
- CNS imaging is not helpful; nonspecific white matter changes may be present
- In patients with untreated late Lyme encephalopathy, neurocognitive testing and CSF evaluation is helpful. Objective cognitive deficits should be present and abnormal CSF

Treatment of PTLDS

- Repeated courses of antibiotics are not helpful and are not recommended
- Pharmacologic treatment of pain, sleep disorders, attention deficit, and postural orthostatic tachycardia syndrome (POTS)
- POTS is defined as the presence of chronic symptoms of orthostatic intolerance (≥6 months) accompanied by an increased heart rate (HR) ≥30 bpm within 10 minutes of assuming an upright posture (Figure 1) and in the absence of orthostatic hypotension (blood pressure [BP] fall >20/10 mmHg).1,2 In children and adolescents, a higher threshold (≥40 bpm) should be used since they have a greater physiological orthostatic tachycardia.3 Morning postural assessments will optimize diagnostic sensitivity (at the expense of specificity) for POTS
- Treatment of POTS includes optimizing fluid intake, eliminating or reducing medications that may contribute to symptoms

Raj SR, Levine BD. Postural tachycardia syndrome (POTS) diagnosis and treatment: basics and new developments. Cardiac rhythm management. 2013.

Recommended Lyme Treatments

- For early disease:
  - Doxycycline 100 mg po bid for 14 D
  - Amoxicillin 500 mg po tid for 14 D
  - Cefuroxime 500 mg bid for 14D
- For Lyme Arthritis: 28 D of doxycycline
- For neuroinvasive Lyme: ceftriaxone 2 grams once daily for 10-28D; alternate therapy includes cefotaxime, PCN or doxycycline

Anaplasmosis

Human Granulocytic Anaplasmosis

- transmitted by *Ixodes scapularis* tick
- Can cause severe illness and even death in otherwise healthy people
- There has been a large increase in cases in recent years
- Patients may resolve illness even without antibiotic therapy, but early treatment can avoid poor outcomes
- most cases occur in people who have a history of a tick bite (75%), but cases have also been described after butchering deer

HGA

- patients present with non-specific febrile illness “viral illness”
- fever, nightsweats, rigors, myalgia and arthralgia are common
- 36% require hospitalization, half in the in ICU
- Severe headache and neck stiffness is commone, but CSF is usually normal
- Diarrhea, vomiting, confusion and rash are uncommon
- Elevated transaminases, leukopenia and thrombocytopenia are common

Diagnostic testing for HGA

- A peripheral blood smear may show morulae early in disease
- PCR from acute phase blood or isolation by culture is also possible, but not available in most labs
- Acute and convalescent serology demonstrating a 4 fold change is the most common and sensitive confirmatory lab test
- IgM is only reactive during first 6 weeks of infection
- IgG antibodies can persist for years
- Antibodies cross-react with *Ehrlichia chafeensis*, so must check both for definitive diagnosis
- Treatment is doxycycline

Babesiosis

Babesiosis

- Transmitted also by Ixodes ticks
- can also be transmitted through blood products and vertically during pregnancy
- causes severe disease in people with splenectomies
- All active stages of life cycle in Ixodes ticks can transmit infection
- Most cases occur in late summer
- Most cases occur in upper Midwest and Northeast

Clinical Manifestations of Babesiosis

- There is a high prevalence of asymptomatic infection in New England
- Incubation period is about 1-4 weeks after tick bite, 1-9 weeks after blood product receipt, but may be as long as 6 months
- Gradual onset of malaise, fatigue, fever, headache, chills, sweats, anorexia, myalgia, nausea, non-productive cough and arthralgia
- Depression is also common
- hepatomegaly and splenomegaly may be found
- Lab findings reflect hemolytic anemia; elevated transaminases and thrombocytopenia are common
- Illness usually resolves within a few weeks, but may be months

Diagnosis of Babesiosis

- Parasites may be detectable by DNA for more than a year after completion of therapy
- Parasites can be seen on peripheral smear and may be confused with falciparum malaria
- PCR is more sensitive and can detect a lower burden of organisms, also allows species identification
- If initial testing is negative and illness is sever, consider repeat testing

Babesiosis Treatment

- Mild to moderate disease can be treated with atovaquone, azithormycin, clindamycin plus quinine for 10 days
- partial or complete exchange transfusion may be needed for severe cases and for anyone infected with *Babesia divergens*

Severe Babesiosis

- usually occurs in those over 50 or with underlying comorbidities
- complications include ARDS, DIC, pulmonary edema, renal failure, and course may be prolonged even with appropriate antibiotic therapy
- fatal cases usually involve people who have had splenectomies

Tick Bite Prevention

- Use repellent that contains 20 percent or more DEET, picaridin, or IR3535 on exposed skin and reapply as indicated
- Use products that contain permethrin on clothing and gear
- Bathe or shower as soon as possible after coming indoors to wash off and more easily find ticks that are crawling on you.
- Conduct a full-body tick check using a hand-held or full-length mirror to view all parts of your body upon return from tick-infested areas. Parents should check their children for ticks under the arms, in and around the ears, inside the belly button, behind the knees, between the legs, around the waist, and especially in their hair.
- Examine gear and pets. Ticks can ride into the home on clothing and pets, then attach to a person later, so carefully examine pets, coats, and day packs.
- Tumble dry clothes in a dryer on high heat for 10 minutes to kill ticks on dry clothing after you come indoors. (wash first if indicated)

Prophylaxis

- A single dose of doxycycline 200 mg can be given
- consider when estimated attachment time of tick is >36 hours
- consider only when prophylaxis can be given within 72 hours of tick removal
- There is no evidence that prophylaxis prevents other tick borne disease.
- Treat if symptoms of disease present.

Conclusions

- Tickborne diseases and recognition of tickborne diseases is increasing
- Co-infection is often present
- Most are treated with doxycycline and response is good
- Avoid unnecessary testing and treatment for Lyme disease