National recommendations for diagnosis and treatment of Lyme disease

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Indiana State Department of Health

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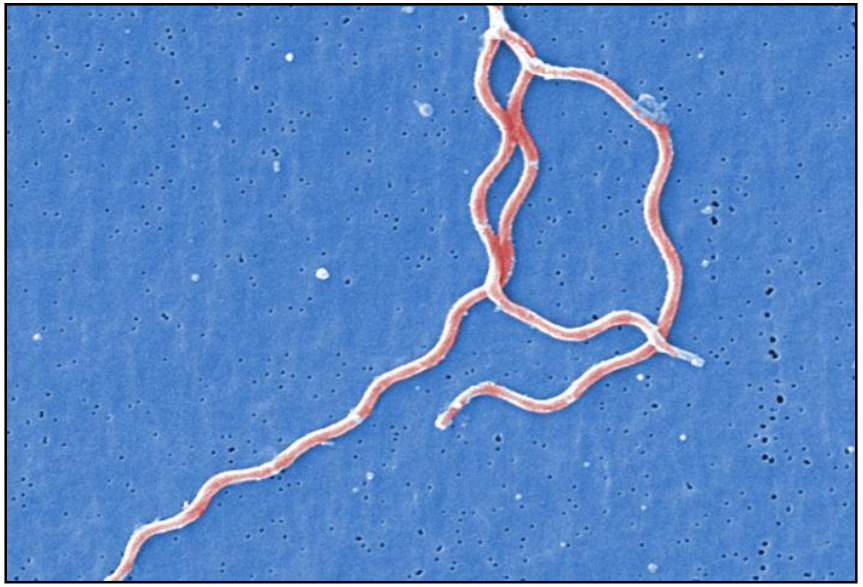
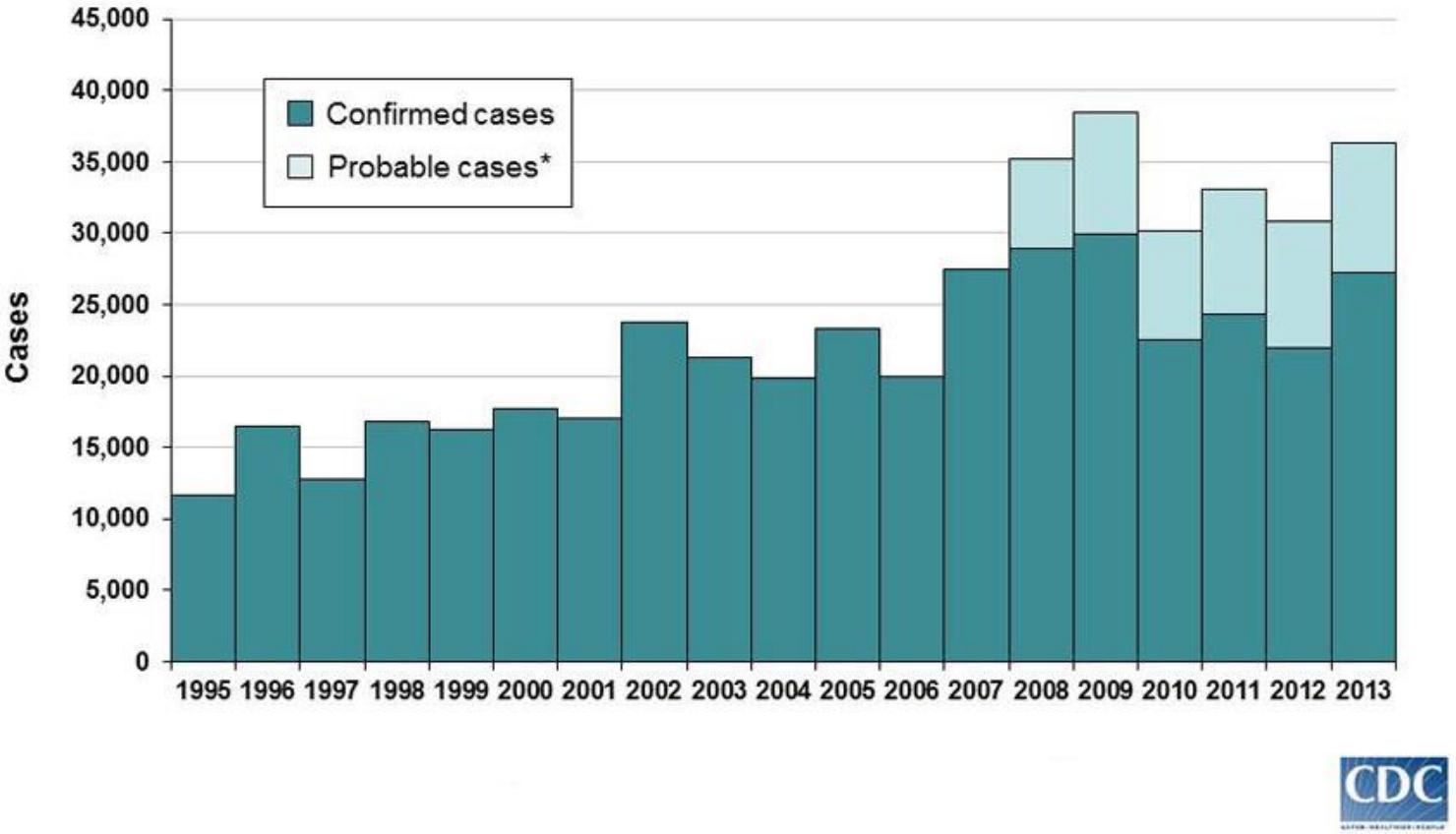


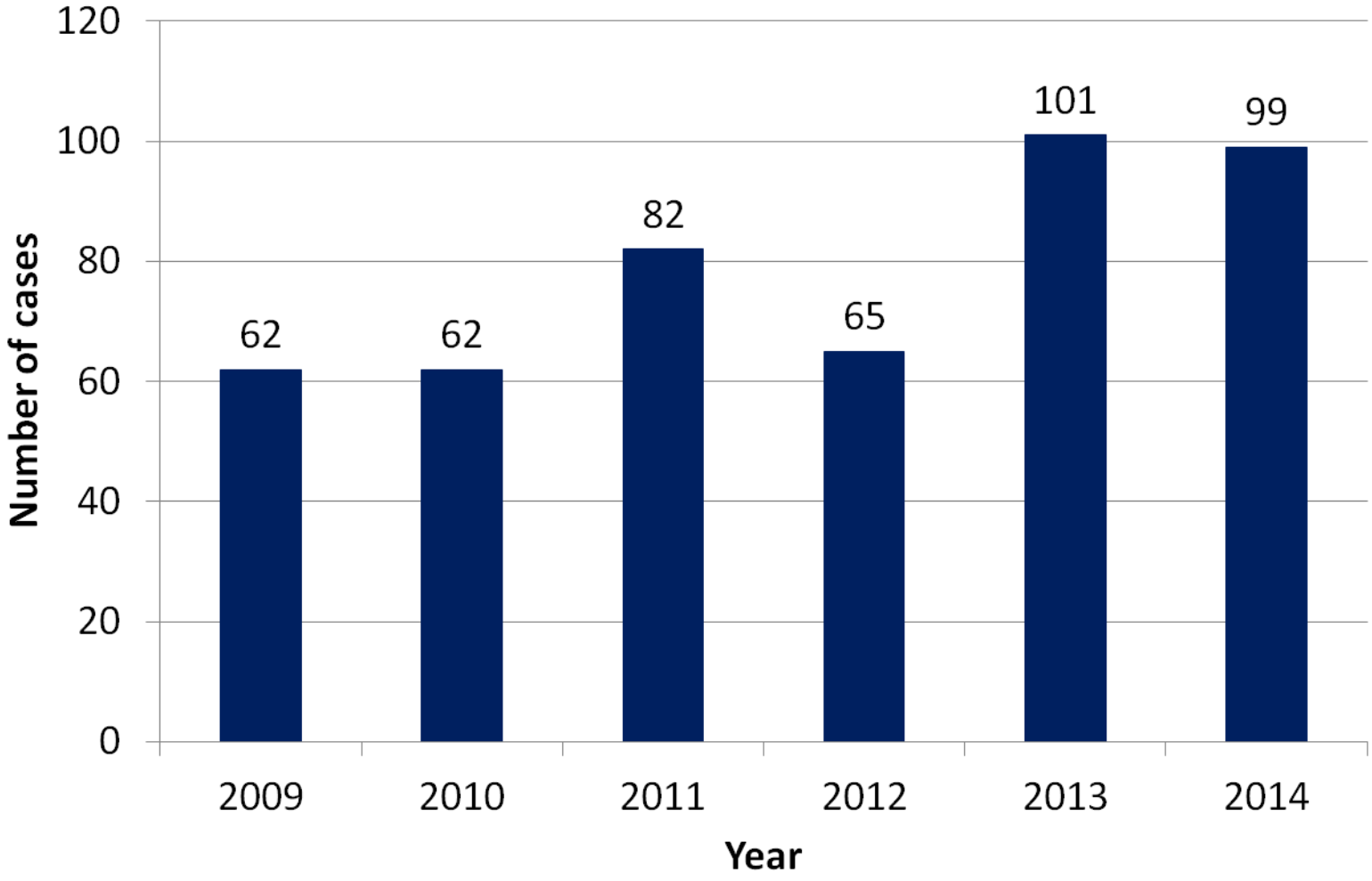
Borrelia burgdorferi.
Photo: Jamice Haney Carr, CDC.

EPIDEMIOLOGY

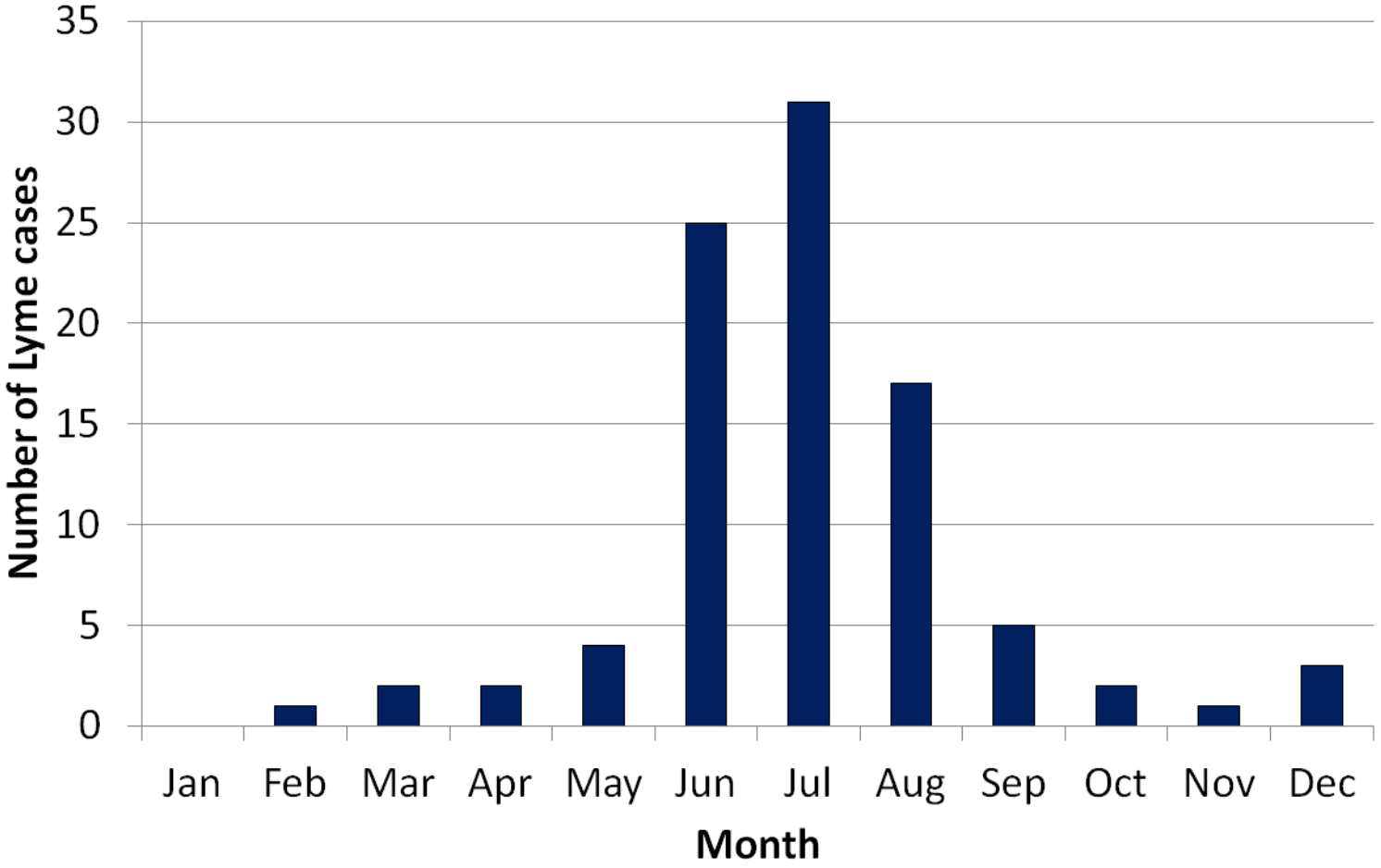
Cases of Lyme disease by year—US, 1995-2013



Human Lyme cases by year—Indiana, 2009–2014

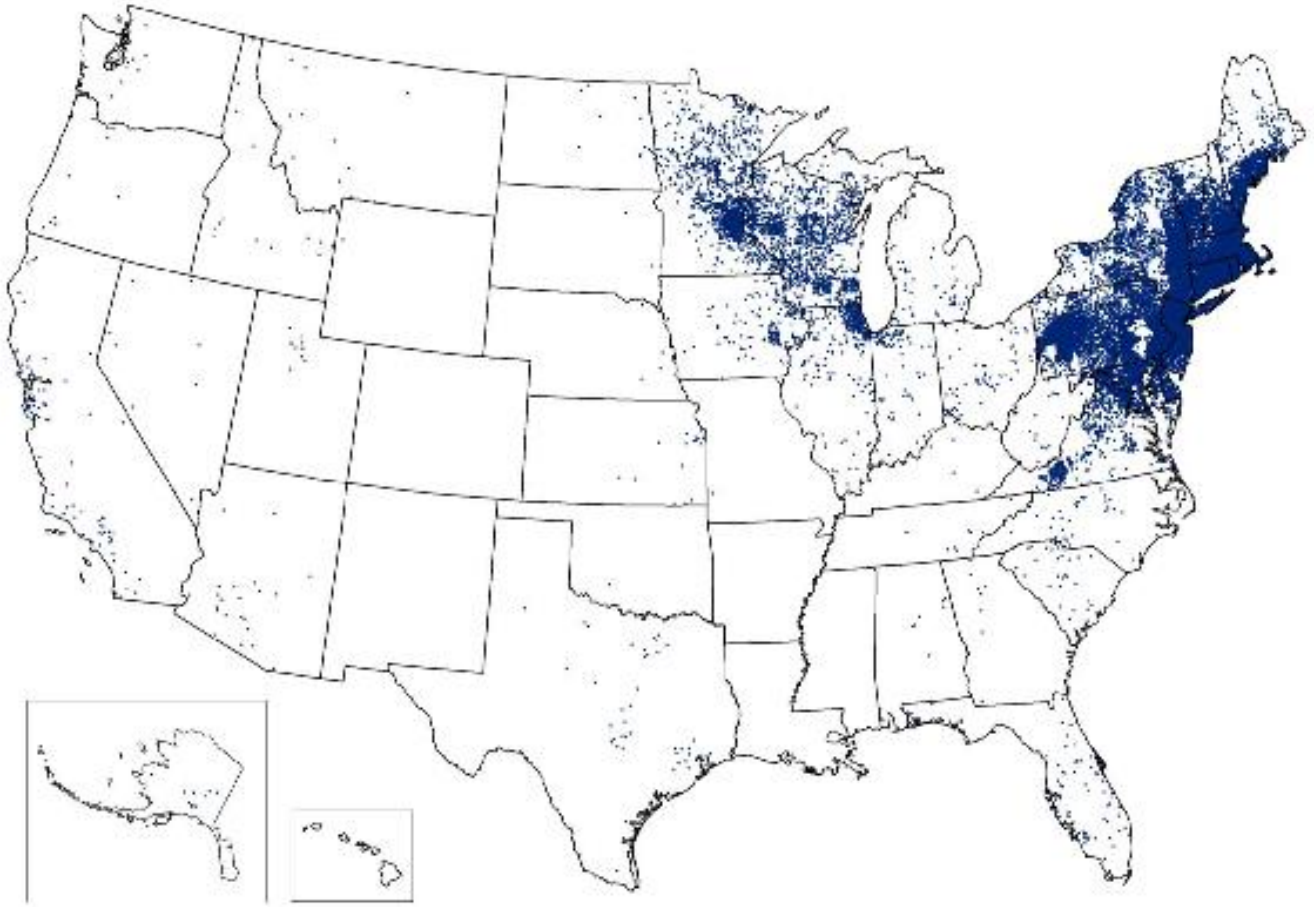


Human Lyme cases by month—Indiana, 2014



Reported Cases of Lyme Disease—United States, 2013

One dot is placed randomly within the county of residence for each confirmed case. Though Lyme disease cases have been reported in nearly every state, cases are reported based on the county of residence, not necessarily the county of infection.



1 dot placed randomly within county of residence for each confirmed case

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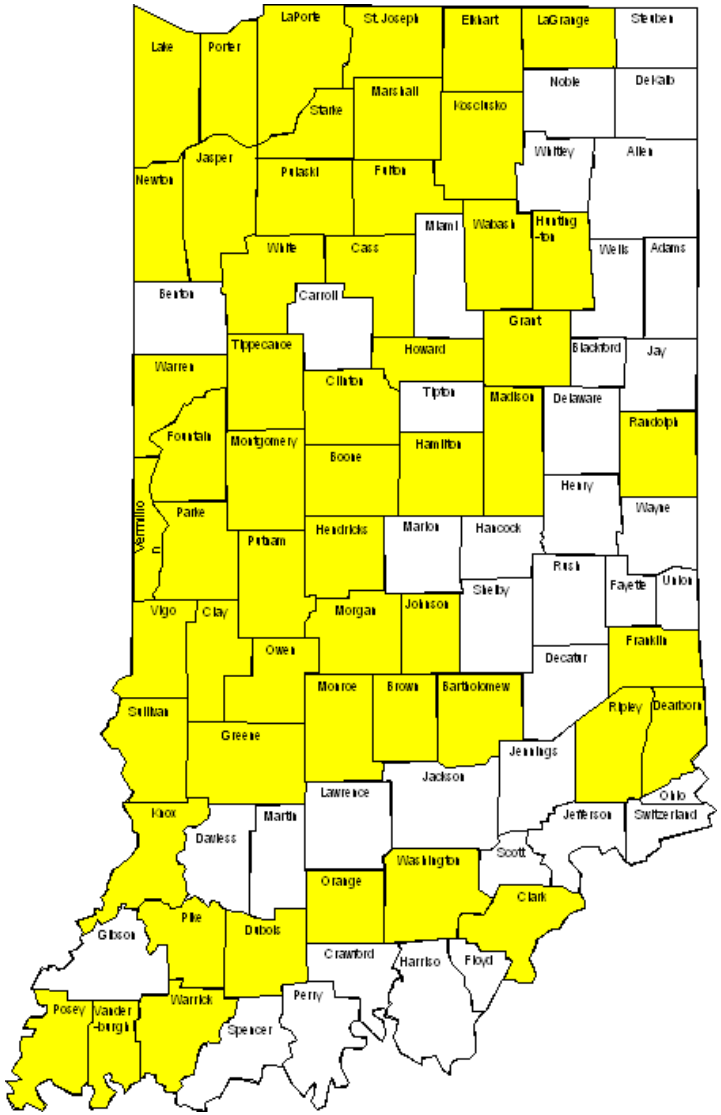
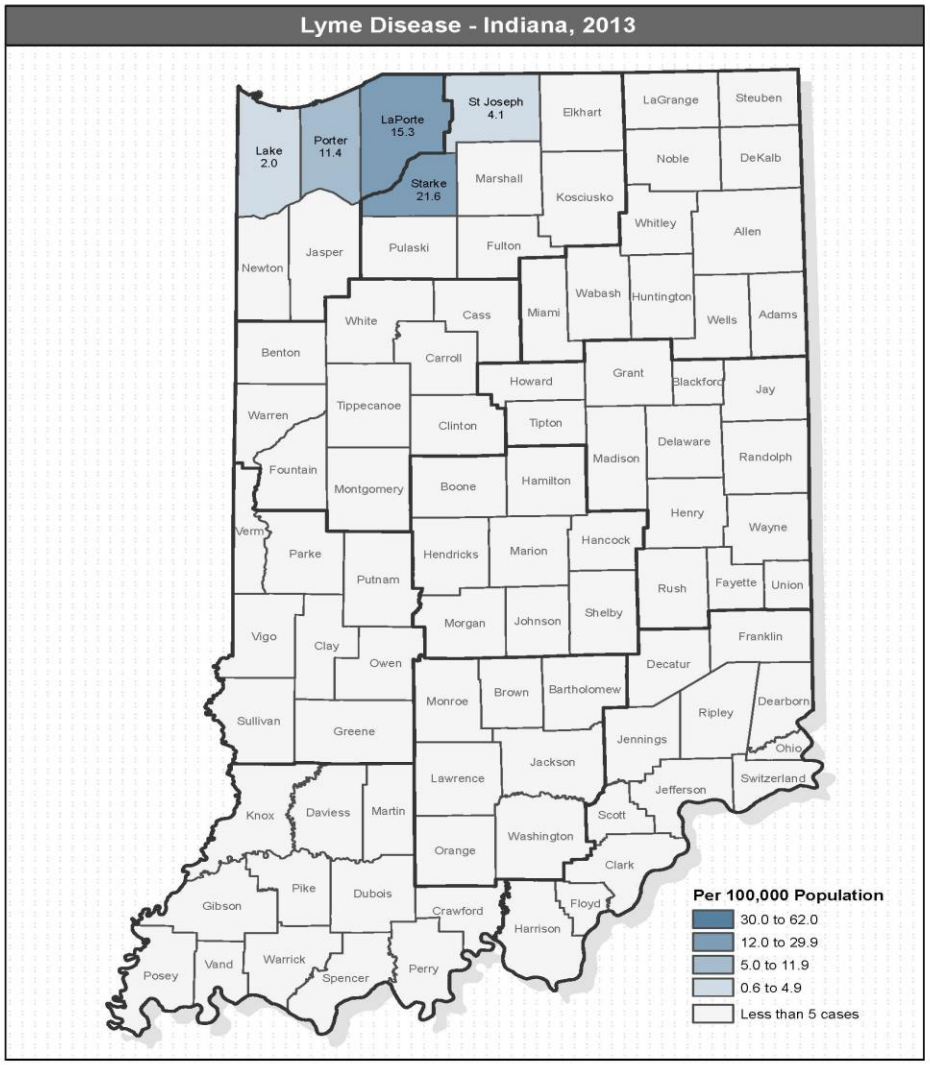
Distribution of *Ixodes scapularis*, IN



Incidence of human Lyme disease—Indiana, 2013



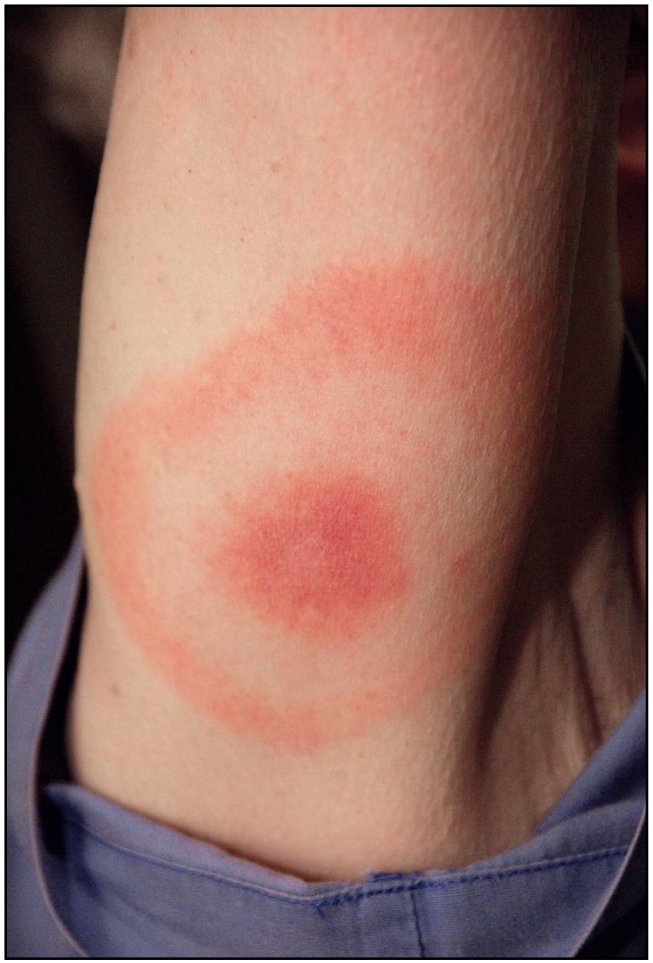
SIGNS AND SYMPTOMS

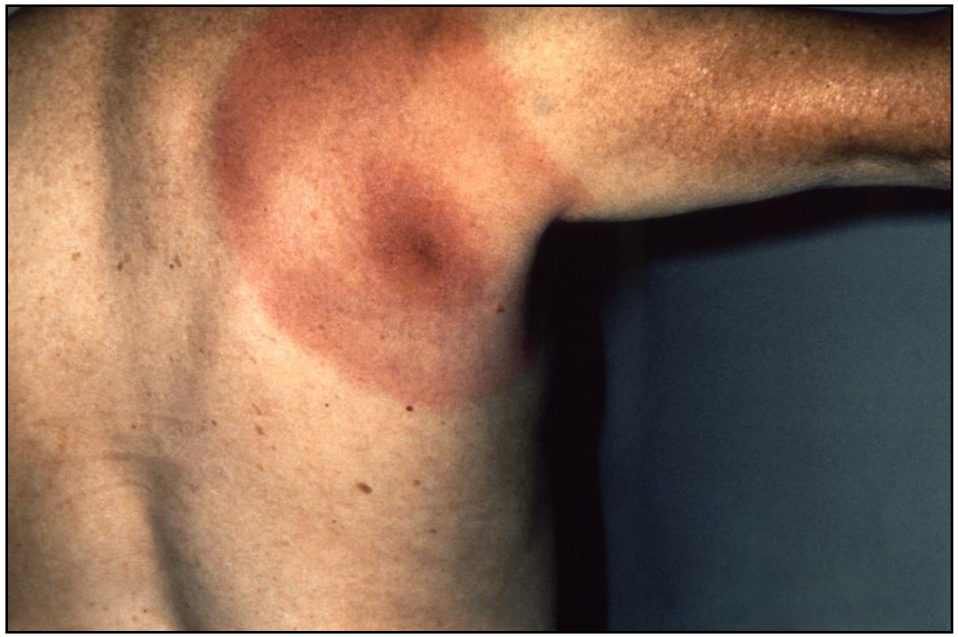
Early localized stage (3–30 days)

- Erythema migrans (EM) rash
- 70–80% of infected persons
- Up to 12 inch diameter
- Parts of the rash clear as it enlarges (“bulls-eye”)
- Warm to the touch
- Not itchy or painful
- Any area of the body

- Fatigue
- Chills
- Fever
- Headache
- Myalgia and arthralgia
- Swollen lymph nodes

Erythema migrans rash



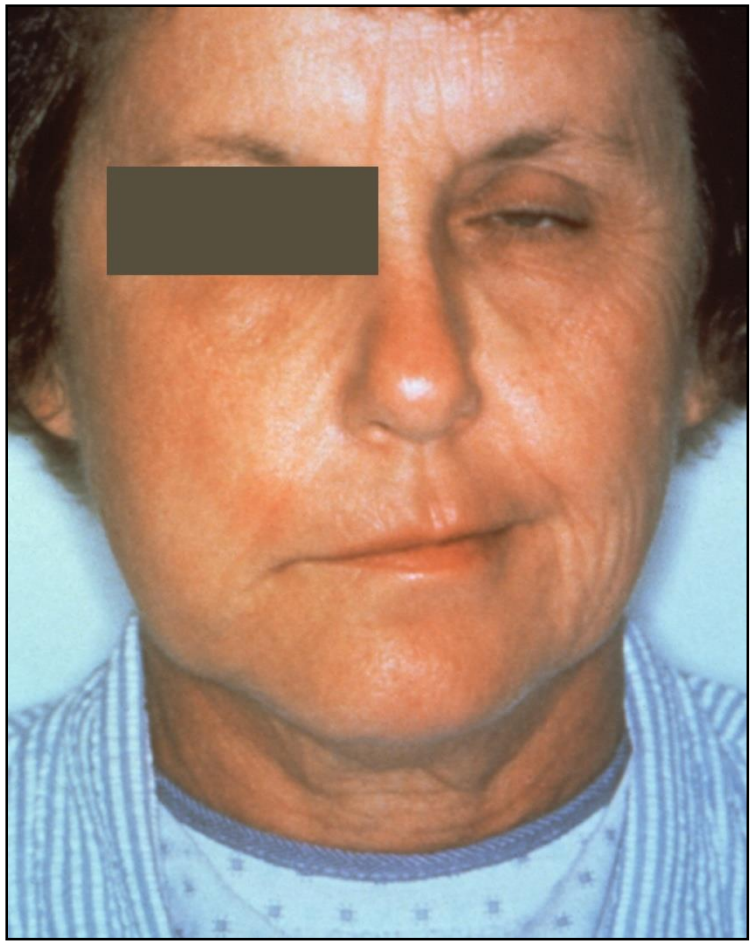


NOTE: A small, red bump at the bite site that goes away within a few days is NOT an EM rash

Photos: CDC.

Early disseminated stage (days–weeks)

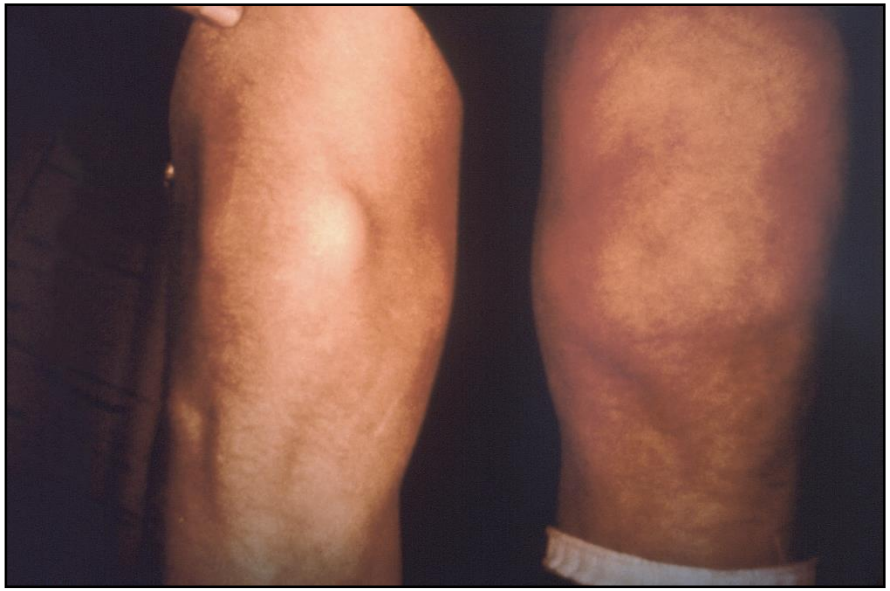
- Additional EM rashes in new locations
- Facial or Bell's palsy
- Meningitis
- Arthritis in large joints
- Shooting pains that may interfere with sleep
- Carditis (heart palpitations and dizziness)



Lyme-associated Bell's palsy.
Photo: CDC.

Late disseminated stage (months–years)

- Intermittent arthritis in large joints
  - 60% of untreated infections
- Neurologic complaints
  - Shooting pains, numbness, tingling in hands/feet
  - Cognitive problems
  - 5% of untreated infections



Lyme arthritis in the knees.
Photo: CDC.

Post-treatment Lyme disease syndrome (PTLDS)

- 10-20% of patients have symptoms lasting months to years after antibiotic treatment
  - Myalgia
  - Arthralgia
  - Cognitive impairment
  - Sleep disturbances
  - Fatigue
- These symptoms are currently thought to reflect an autoimmune process

DIAGNOSIS AND TESTING

Interpretation of diagnostic tests

Gold standard, or "truth"

	Lyme positive	**Lyme negative**
Test positive	True positives a	False positives b
Test negative	False negatives c	True negatives d

Test results

Interpretation of diagnostic tests

	Lyme positive	**Lyme negative**
Test positive	**True positives** **a**	False positives b
Test negative	False negatives c	True negatives d

Sensitivity: probability that a test will be positive when Lyme disease is present (true positive rate) (a/a+c)

False negative rate: probability that a test will be negative when Lyme disease is present (1-sensitivity)

Interpretation of diagnostic tests

	Lyme positive	**Lyme negative**
Test positive	True positives a	False positives b
Test negative	False negatives c	**True negatives** **d**

Specificity: probability that a test will be negative when Lyme disease is not present (true negative rate) (d/b+d)

False positive rate: probability that a test will be positive when Lyme disease is not present (1-specificity)

Interpretation of diagnostic tests

	Lyme positive	**Lyme negative**
Test positive	**True positives** **a**	False positives b
Test negative	False negatives c	True negatives d

Positive predictive value (PPV): the probability that Lyme disease is present if a test is positive (a/a+b)

Interpretation of diagnostic tests

	Lyme positive	**Lyme negative**
Test positive	True positives a	False positives b
Test negative	False negatives c	**True negatives** **d**

Negative predictive value (NPV): the probability that Lyme disease is not present if a test is negative (d/c+d)

Interpretation of diagnostic tests

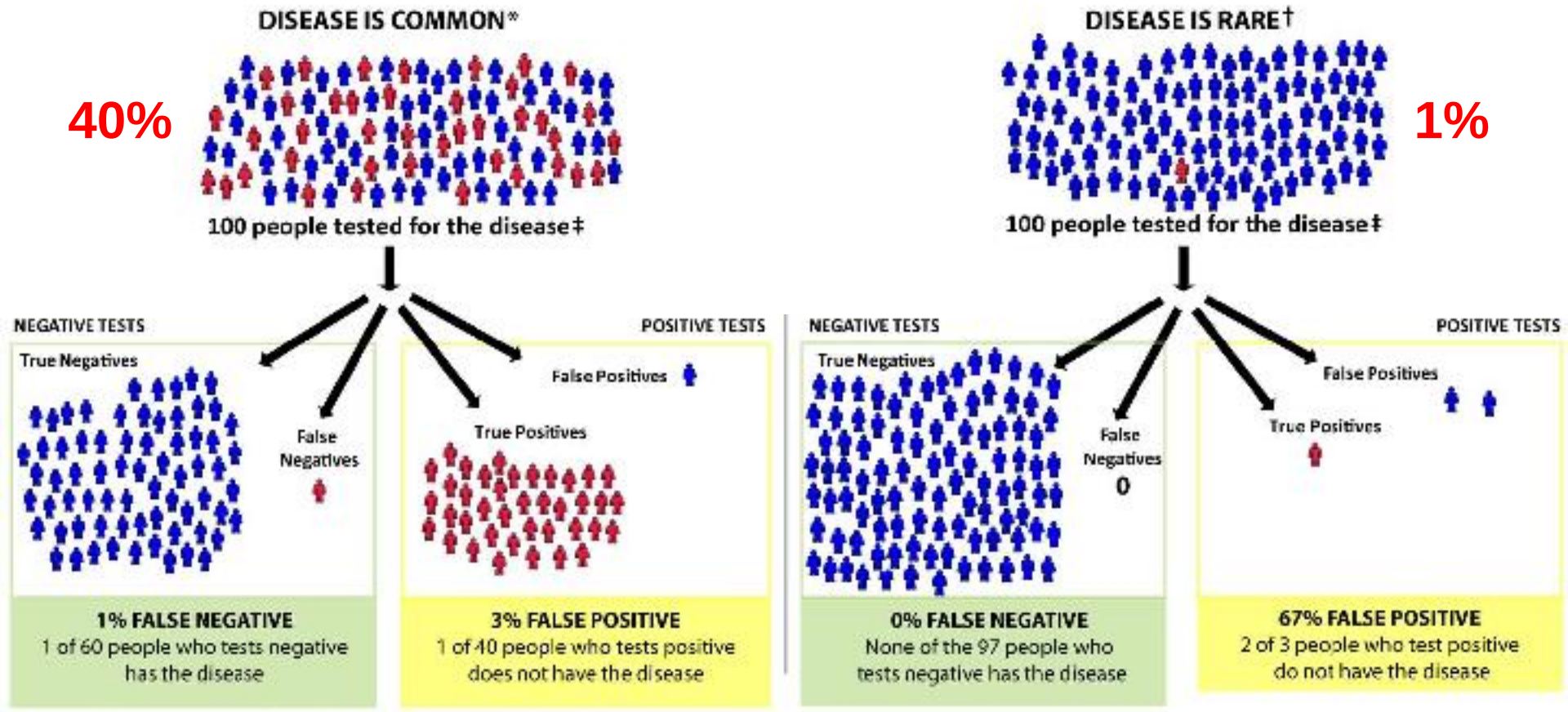
- Sensitivity and specificity are inversely related
- Sensitivity and specificity do not change for a given test
- PPV and NPV are dependent upon sensitivity and specificity AND the prevalence of disease in the population
- A test with excellent sensitivity and specificity might have poor predictive values if used in a population with low prevalence of disease

Understanding Test Results for Infectious Diseases

Consider the likelihood of disease ***before*** performing laboratory testing

The likelihood that a patient has a disease depends on many factors:

- **Has the patient been in an area where the disease is found?**
- **Does the patient have signs and symptoms typical of the disease?**
- **Does the patient have risk factors for contracting or developing the disease?**



Assuming sensitivity = 98% and specificity = 98%

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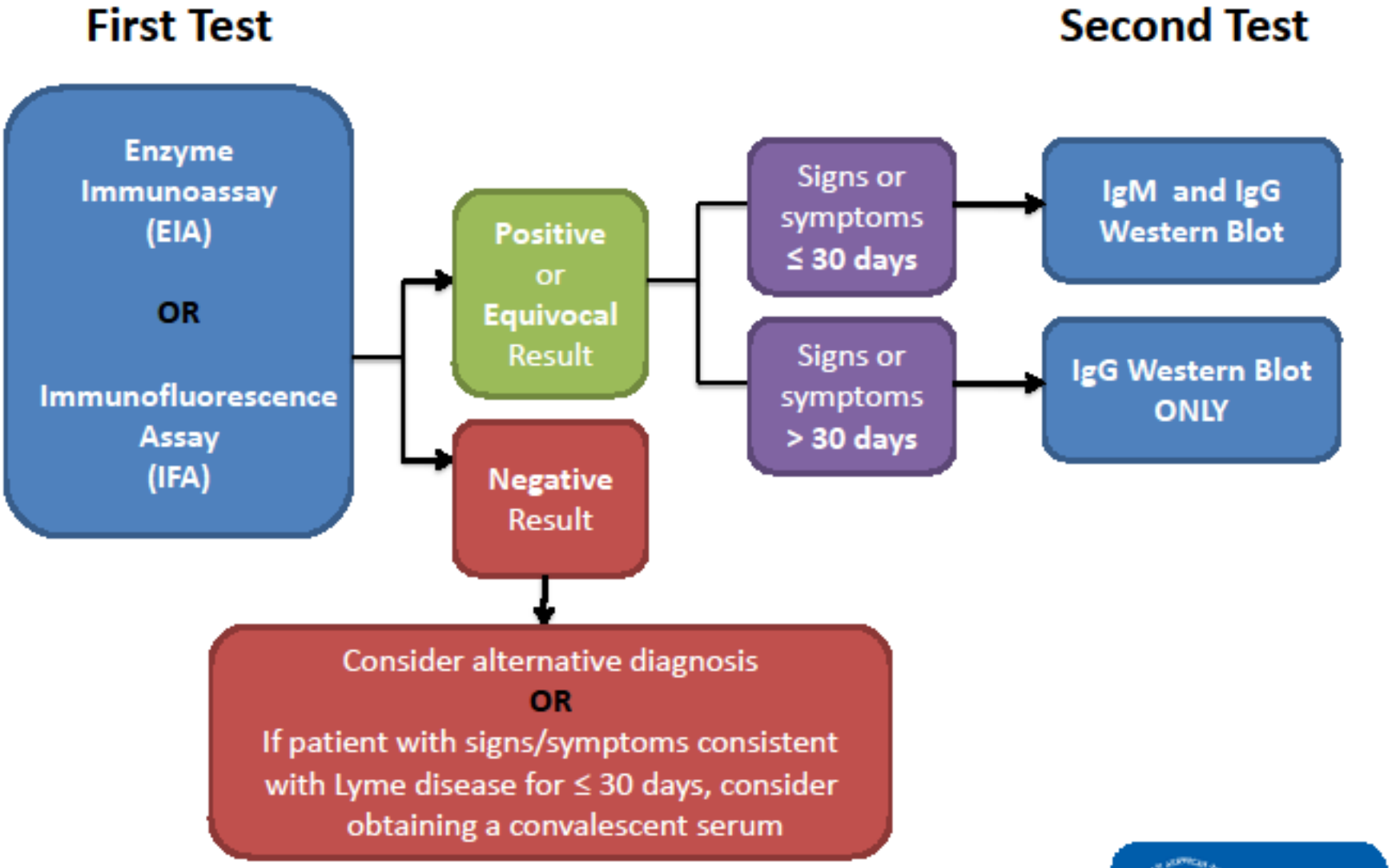
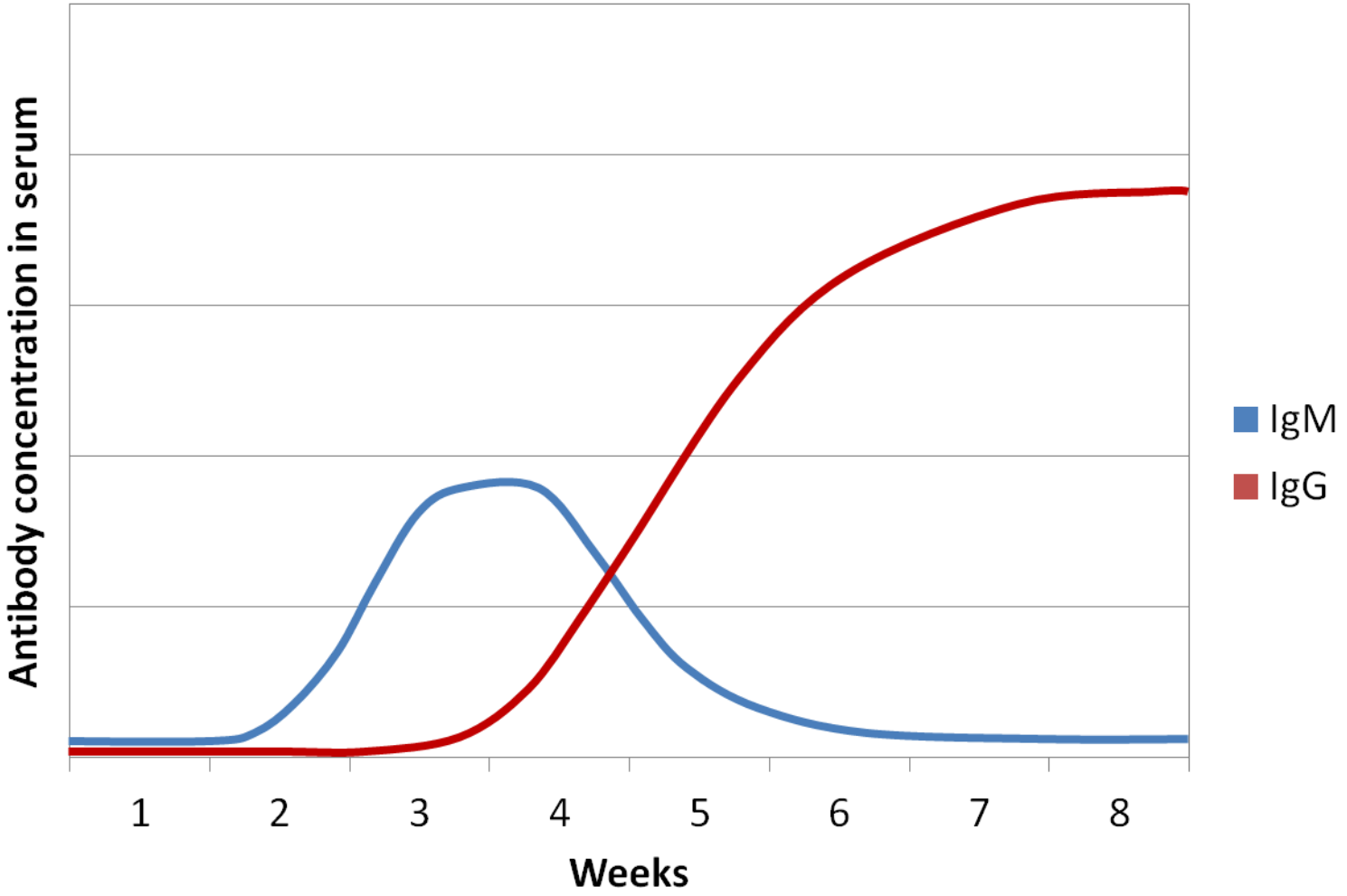
Factors affecting Lyme prevalence

- Geographic
  - Most Lyme disease cases are reported from 10 states in the Northeast and upper Midwest
  - Northwest Indiana has a geographic focus of moderate risk
- Symptomatic
  - Prevalence of Lyme is highest in patients with compatible symptoms
  - Prevalence of Lyme is lower in patients with non-specific symptoms (headache, fatigue, myalgia)

Two-Tiered Testing for Lyme Disease



Antibody kinetics in acute disease



Common errors in Lyme testing

- Testing a patient with nonspecific symptoms, or symptoms not compatible with Lyme disease
- Skipping the first test
- Interpreting a positive IgM Western Blot for a patient who has had symptoms for >30 days, especially if they are IgG negative
- Using tests not approved by the Food and Drug Administration or validated by CDC

SURVEILLANCE

National Lyme disease surveillance

- CDC conducts surveillance for conditions of public health importance as determined by the states
- Council of State and Territorial Epidemiologists (CSTE) includes Lyme disease on its list of notifiable diseases
- 410 IAC 1-2.3-47, 48, and 80 mandate that Lyme disease is notifiable in Indiana

Case definition

- Set of uniform criteria used to define a disease for public health surveillance
- Enable public health officials to count and classify cases consistently
- NOT intended for the diagnosis or clinical management of clinical cases
- Case definitions have sensitivity and specificity just like laboratory tests

Case definition criteria

- Clinical
  - Erythema migrans rash
  - Late manifestations affecting the musculoskeletal, nervous, or cardiovascular systems
- Laboratory
  - Positive culture for *Borrelia burgdorferi*
  - Positive two-tier testing (EIA/IFA + IgM WB; onset <30d prior)
  - Positive two-tier testing (EIA/IFA + IgG WB)
  - Positive single-tier testing (IgG WB)
  - CSF EIA/IFA > serum EIA/IFA

Surveillance case definition

- Confirmed case
  - Erythema migrans + known exposure
  - Erythema migrans + laboratory evidence
  - Late manifestation + laboratory evidence
- Probable case
  - MD diagnosis + laboratory evidence
- Suspect case
  - Erythema migrans with no exposure or lab evidence
  - Laboratory evidence with no clinical information

TREATMENT

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Gary P. Wormser,[1] Raymond J. Dattwyler,[2] Eugene D. Shapiro,[3,4] John J. Halperin,[3,4] Allen C. Steere,[5] Mark S. Klempner,[10] Peter J. Krause,[6] Johan S. Bakken,[11] Franc Strle,[12] Gerold Stanek,[14] Linda Bockenstedt,[7] Durland Fish,[8] J. Stephen Dumler,[13] and Robert B. Nadelman[1]

Divisions of [1]Infectious Diseases and [2]Allergy, Immunology, and Rheumatology, Department of Medicine, New York Medical College, Valhalla, and [3]New York University School of Medicine, New York, New York; [4]Atlantic Neuroscience Institute, Summit, New Jersey; Departments of [5]Pediatrics and [6]Epidemiology and Public Health and [7]Section of Rheumatology, Department of Medicine, Yale University School of Medicine, New Haven, and [8]Department of Pediatrics, University of Connecticut School of Medicine and Connecticut Children's Medical Center, Hartford; [9]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, and [10]Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts; [11]Section of Infectious Diseases, St. Luke's Hospital, Duluth, Minnesota; [12]Division of Medical Microbiology, Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland; [13]Department of Infectious Diseases, University Medical Center, Ljubljana, Slovenia; and [14]Medical University of Vienna, Vienna, Austria

Evidence-based guidelines for the management of patients with Lyme disease, human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis), and babesiosis were prepared by an expert panel of the Infectious Diseases Society of America. These updated guidelines replace the previous treatment guidelines published in 2000 (Clin Infect Dis 2000; 31[Suppl 1]:1–14). The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them. For each of these *Ixodes* tickborne infections, information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment. Tables list the doses and durations of antimicrobial therapy recommended for treatment and prevention of Lyme disease and provide a partial list of therapies to be avoided. A definition of post–Lyme disease syndrome is proposed.

EXECUTIVE SUMMARY

Background

Lyme disease is the most common tickborne infection in both North America and Europe. In the United States, Lyme disease is caused by *Borrelia burgdorferi*, which is transmitted by the bite of the tick species *Ixodes scapularis* and *Ixodes pacificus*. Clinical manifestations most often involve the skin, joints, nervous system, and heart. Extracutaneous manifestations are less commonly seen than in earlier years. Early cutaneous infection with *B. burgdorferi* is called erythema migrans, which is the most common clinical manifestation of Lyme disease. *I. scapularis* may also be infected with and transmit *Anaplasma phagocytophilum* (previously referred to as *Ehrlichia phagocytophila*) and/or *Babesia microti*, the primary cause of babesiosis. Thus, a bite from an *I. scapularis* tick may lead to the development of Lyme disease, human granulocytic anaplasmosis (HGA, formerly known as human granulocytic ehrlichiosis), or babesiosis as a single infection or, less frequently, as a coinfection. *Clinical findings are sufficient*

Received 21 August 2006; accepted 21 August 2006; electronically published 2 October 2006.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Reprints or correspondence: Dr. Gary P. Wormser, Rm. 245, Munger Pavilion, New York Medical College, Valhalla, NY 10595 (Gary_Wormser@nymc.edu).

Clinical Infectious Diseases 2006; 43:1089–134

1058-4838/2006/4309-0001$15.00

Treatment guideline history

- Nov 2006: Clinical Practice Guidelines released
- Nov 2006: Connecticut Attorney General (CAG) initiated an antitrust investigation against IDSA under pressure from Lyme activists
- Apr 2008: CAG agreed to end the investigation and IDSA agreed to review the guidelines
- Apr 2010: thorough review of the guidelines found that they were developed appropriately; no changes were recommended

Final Report of the Lyme Disease Review Panel of the Infectious Diseases Society of America (IDSA)

INTRODUCTION AND PURPOSE

In November 2006, the Connecticut Attorney General (CAG), Richard Blumenthal, initiated an antitrust investigation to determine whether the Infectious Diseases Society of America (IDSA) violated antitrust laws in the promulgation of the IDSA's 2006 Lyme disease guidelines, entitled "The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America" (the 2006 Lyme Guidelines). IDSA maintained that it had developed the 2006 Lyme disease guidelines based on a proper review of the medical/scientific studies and evidence by a panel of experts in the prevention, diagnosis, and treatment of Lyme disease. In April 2008, the CAG and the IDSA reached an agreement to end the investigation. Under the Agreement and its attached Action Plan, the 2006 Lyme Guidelines remain in effect, and the Society agreed to convene a Review Panel whose task would be to determine whether or not the 2006 Lyme Guidelines were based on sound medical/scientific evidence and whether or not these guidelines required change or revision.

The Review Panel was not charged with updating or rewriting the 2006 Lyme Guidelines. Any recommendation for update or revision to the 2006 Lyme Guidelines would be conducted by a separate IDSA group.

This document is the Final Report of the Review Panel.

REVIEW PANEL MEMBERS

Carol J. Baker, MD, Review Panel Chair
Baylor College of Medicine Houston, TX

William A. Charini, MD
Lawrence General Hospital, Lawrence, MA

Paul H. Duray, MD[1] (retired)
Westwood, MA

Paul M. Lantos, MD
Duke University Medical Center, Durham, NC

[1] Dr. Duray resigned from the Panel on October 7, 2009, due to family illness.

Treatment of Lyme disease

- Early Lyme disease
  - Erythema migrans: oral antibiotics (doxycycline, amoxicillin, cefuroxime axetil) for 14 days
  - Early neurologic Lyme disease: IV antibiotics (ceftriaxone) for 14 days
  - Lyme carditis: oral or IV antibiotics for 14 days
- Late Lyme disease
  - Lyme arthritis: oral antibiotics for 28 days
  - Late neurologic Lyme disease: IV antibiotics for 2–4 weeks

Treatment of PTLDS

- 10-20% of patients treated appropriately for Lyme disease will have lingering symptoms
- Often mischaracterized as “chronic Lyme”
- There is no evidence that PTLDS is due to persistent active bacterial infection
- Placebo-controlled clinical studies show that long-term antibiotic therapy is not beneficial
- Patients usually improve with time

Treatments NOT recommended

- High-dose antibiotic therapy
- Multiple, repeated courses of antibiotics
- Long-term (≥6 months) antibiotic therapy
- Combination antibiotic therapy
- Pulsed-dosing antibiotic therapy
- Vitamins or nutritional supplements
- Other alternative therapies

CONCLUSIONS

Conclusions

- The mainstream medical community agrees on national guidelines for diagnosis and treatment of Lyme disease
- A vocal minority of “Lyme-literate” physicians and patient activists reject these guidelines
  - Some patients diagnosed with Lyme disease do not meet national diagnostic criteria
  - Some patients diagnosed with Lyme disease receive inappropriate antibiotic therapy

Primum non nocere: "first, do no harm"

- Misapplication of diagnostic tests:
  - Results in unnecessary medical intervention
  - Causes emotional distress for the patient
  - Allows other diseases to go undiagnosed
- Inappropriate antibiotic treatment:
  - Has not been proven effective
  - Contributes to antibiotic resistance
  - Causes potentially serious complications
  - Incurs out-of-pocket expenses for the patient

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Death from Inappropriate Therapy for Lyme Disease

A 30-year-old woman died as a result of a large *Candida parapsilosis* septic thrombus located on the tip of a Groshong catheter. The catheter had been in place for 28 months for administration of a 27 month course of intravenous cefotaxime for an unsubstantiated diagnosis of chronic Lyme disease.

A 30-year-old woman was admitted to the Mayo Clinic (Rochester, MN) in May 1999 following a grand mal seizure. She reported a several-week history of anorexia that was accompanied by a 23-kg weight loss over an 8-month period; 4 days before admission, she noticed twitching of her upper extremities. She appeared ill and had a blood pressure of 124/82 mm Hg, a pulse rate of 85, a temperature of 37°C, and a respiratory rate of 20. The patient was confused and unable to provide a coherent history. She was icteric and had diffuse myoclonus. Cardiac auscultation revealed a prominent pulmonic second sound. A Groshong catheter was in place. Hepatosplenomegaly was noted.

Her family provided a pertinent medical history. She had had a history of bilateral knee pain since childhood. She resided in Iowa; however, she had lived in Westchester County, New York, until the age of 16 years and in northern California for a short period thereafter. In 1994, she underwent cholecystectomy and since that time she had had chronic abdominal pain, whole body pain, an episode of Bell's palsy, occasional headaches, and periods of what were described as "mental fogginess" and "transient numbness." She also reportedly had a periodic rash that was thought to be a possible "Lyme rash." In 1996, she was evaluated by an infectious diseases physician in New York who specializes in chronic Lyme disease and was diagnosed with chronic Lyme disease. This diagnosis was made despite 6 EIAs negative for *Borrelia burgdorferi*, 7 Western blot assays negative or indeterminate for *B. burgdorferi*, and 4 PCR assays of blood, 5 PCR assays of urine, and 1 PCR assay of CSF, all negative for *B. burgdorferi*. MRI of the brain, as well as CSF examination, had been unremarkable in 1996. One PCR assay of blood for the *ospA* gene (Boston Biomedica Inc., New Britain, CT) was reportedly positive in January 1997.

She was initially treated with oral doxycycline, and then, for an 8-month period (1995–1996), she was treated with iv ceftriaxone; this treatment was followed by courses of oral clarithromycin and minocycline as well as parenteral penicillin G benzathine. A Groshong catheter was placed in January 1997, and a prolonged course of therapy with iv cefotaxime (up to 4 g every 8 h) was started. Intravenous doxycycline (300 mg every 12 h) was added to this therapeutic regimen in 1998. The patient reported only partial relief of her chronic symptoms during administration of this antibiotic regimen. Therapy with iv antibiotics was discontinued 1 month before evaluation at our institution, when a family physician noted abnormal results of liver function tests and thrombocytopenia. Another infectious diseases physician was consulted; this physician thought that the patient did not have chronic Lyme disease.

The patient was also being treated for chronic diffuse body pain, with several pain medications, including sustained release morphine sulfate (300 mg t.i.d.) and immediate release morphine sulfate (~45 mg/d), according to the recommendations of a fourth physician in Illinois.

At our institution, laboratory tests revealed the following abnormal results: hemoglobin level, 6.3 g/dL; WBC count, 2.2×10^9 cells/L; platelet count, 16×10^9 cells/L; rare schistocytes and helmet cells on a peripheral blood smear; prothrombin time, 19.9 s; alkaline phosphatase level, 435 U/L; aspartate

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Clinical Infectious Diseases 2000;31:1107–9

1058-4838/2000/3104-0039$03.00

Feeling worse after treatment?

…maybe it’s not Lyme disease.

Watch:

https://www.youtube.com/watch?v=823jkRIaLgA#

Recommended resources

- CDC's Lyme disease page
  www.cdc.gov/lyme
- Infectious Diseases Society of America
  www.idsociety.org
- American Lyme Disease Foundation
  www.aldf.com

Call me anytime!

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