

Little Bite, Big Disease: Recognizing and Managing Tickborne Illnesses

Clinician Outreach and Communication Activity
(COCA) Call
May 24, 2016



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Objectives

At the conclusion of this session, the participant will be able to:

- ❑ Review the geographic distribution of Lyme disease, Southern tick-associated rash illness (STARI), Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis, and other emerging tickborne diseases.
- ❑ Define the symptoms of Lyme disease, STARI, Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis, and emerging tickborne diseases.
- ❑ Identify the serologic tests used to diagnose Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis, and emerging tickborne diseases.
- ❑ Describe the appropriate use of antibiotics in treating Lyme disease, STARI, Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis, and emerging tickborne diseases.

TODAY'S PRESENTER



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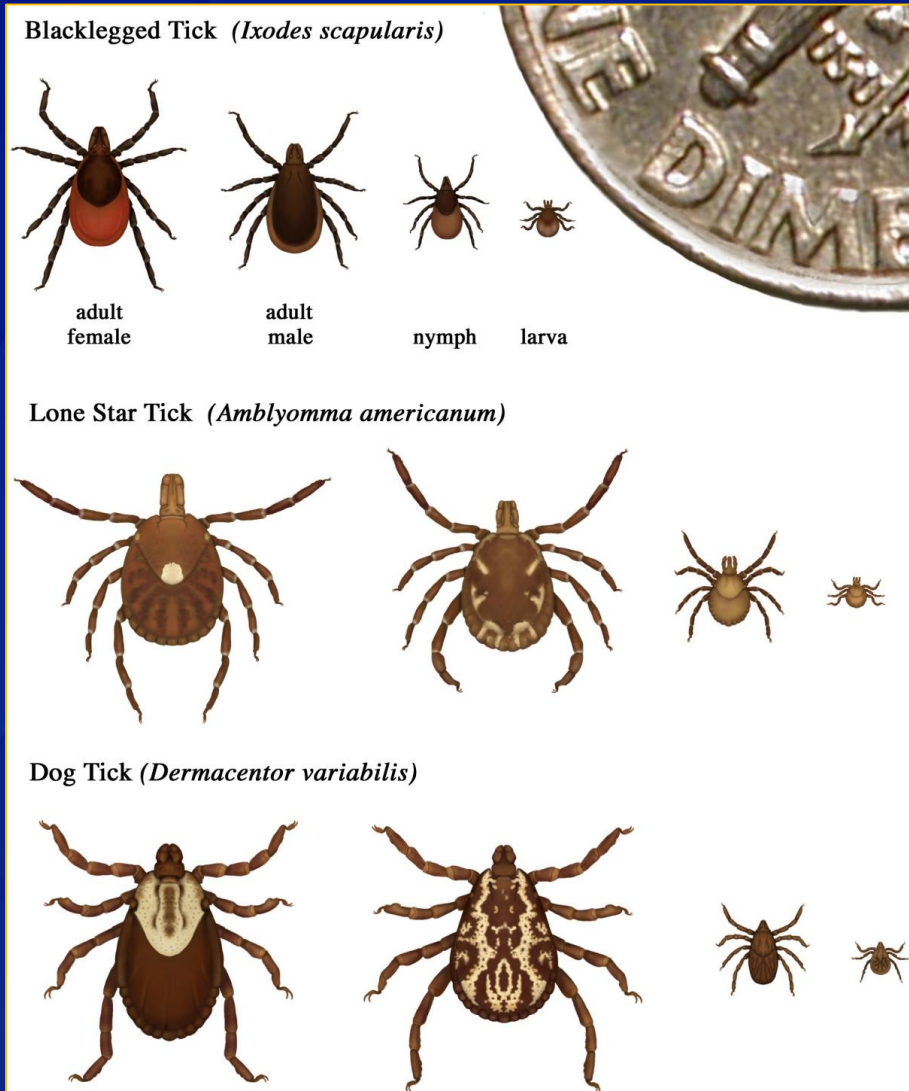
Leading Tickborne Diseases in the U.S.

- ❑ Lyme disease (*Borrelia burgdorferi*)
- ❑ Rocky Mountain spotted fever (*Rickettsia rickettsii*)
- ❑ Ehrlichiosis (*Ehrlichia chaffeensis*, others)
- ❑ Anaplasmosis (*Anaplasma phagocytophilum*)
- ❑ Babesiosis (*Babesia microti*)



For information on other tickborne diseases, visit www.cdc.gov/ticks

Selected Tick Vectors

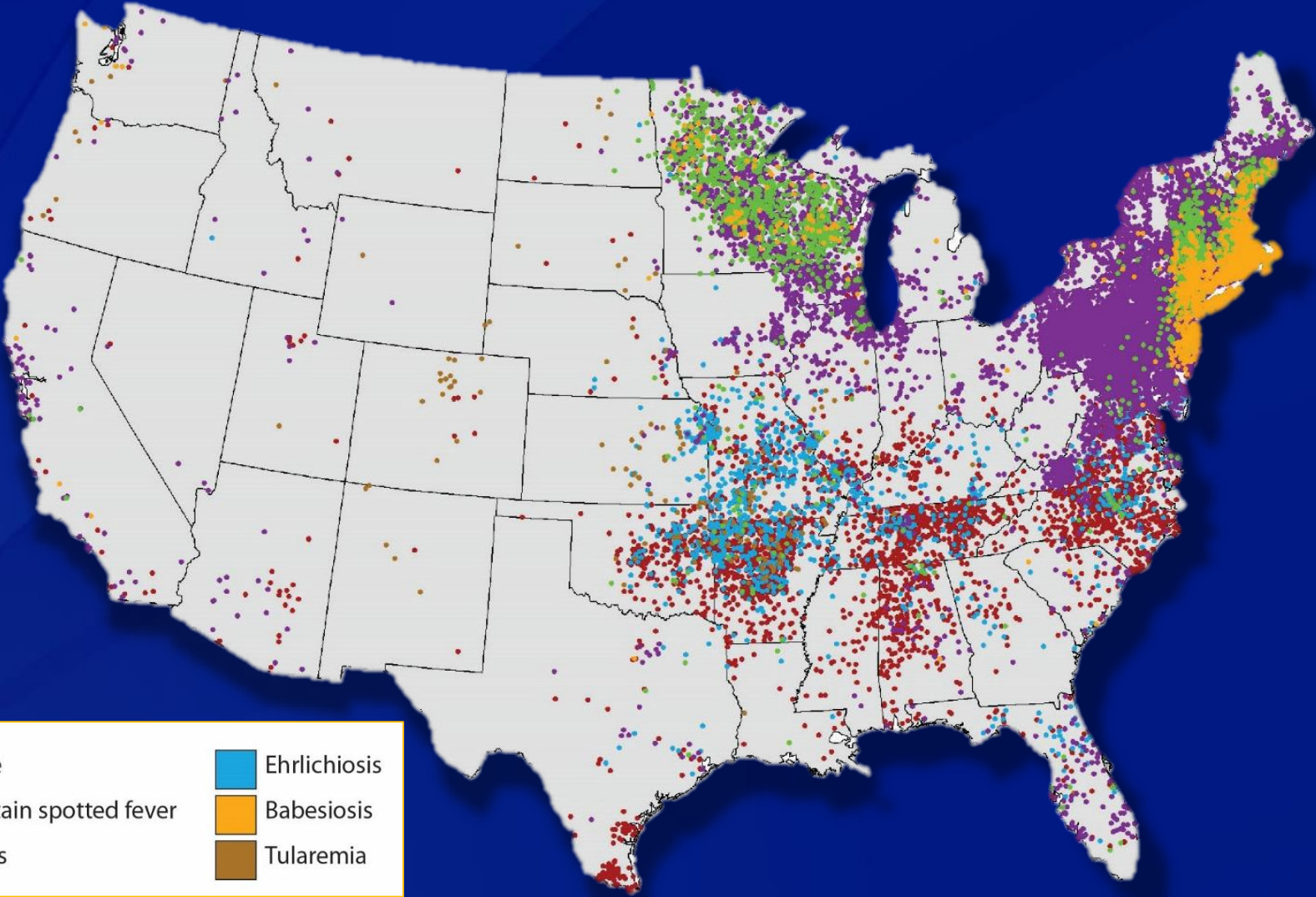



Transmit pathogens that cause the following diseases:

- Lyme disease
- Anaplasmosis
- Babesiosis
- Powassan virus disease
- Borrelia miyamotoi* disease
- Ehrlichiosis
- STARI
- Tularemia
- Rocky Mtn. Spotted Fever
- Tularemia

Distribution of Key Tickborne Diseases, 2014

Diseases are reported to CDC by county of residence. Each dot represents one case. The county where the disease was diagnosed is not necessarily the county where the disease was acquired.



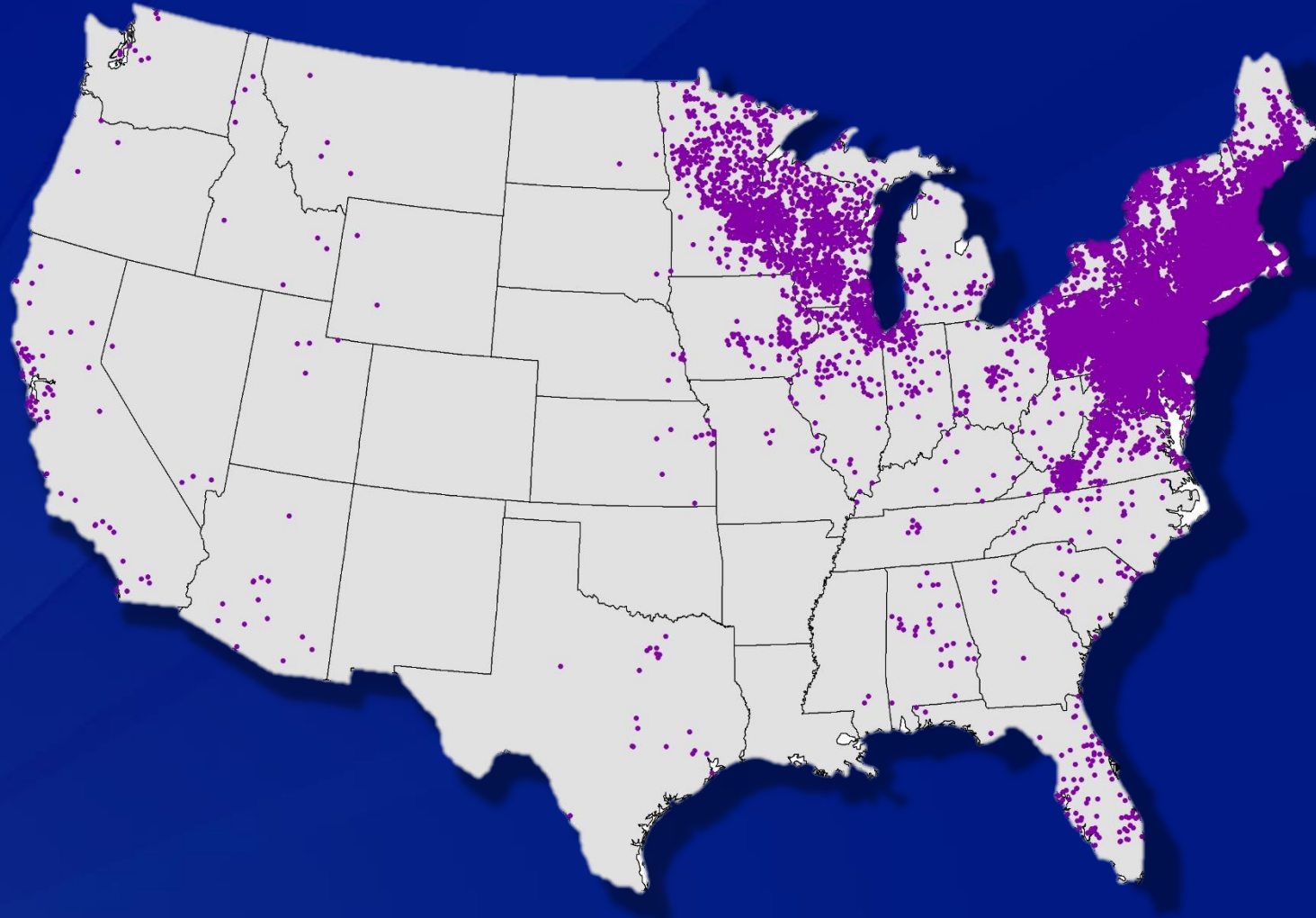
*** LAB ***


Lyme Disease

- ❑ Caused by spirochete *Borrelia burgdorferi* (and newly discovered *Borrelia mayonii*)
- ❑ Occurs in areas of North America, Europe, and Asia
- ❑ ~30,000 cases reported annually in US
- ❑ Transmitted in US by blacklegged ticks



Reported Lyme Disease Cases, 2014



Diseases reported to CDC by county of residence. Each dot represents one case. The county where the disease was diagnosed is not necessarily the county where the disease was acquired.

Erythema Migrans (EM)

- 70-80% of cases
- ~7-14 days after tick bite
- Expands over days
- Rarely painful
- Distinguish from allergic reaction



Atypical EM Presentations



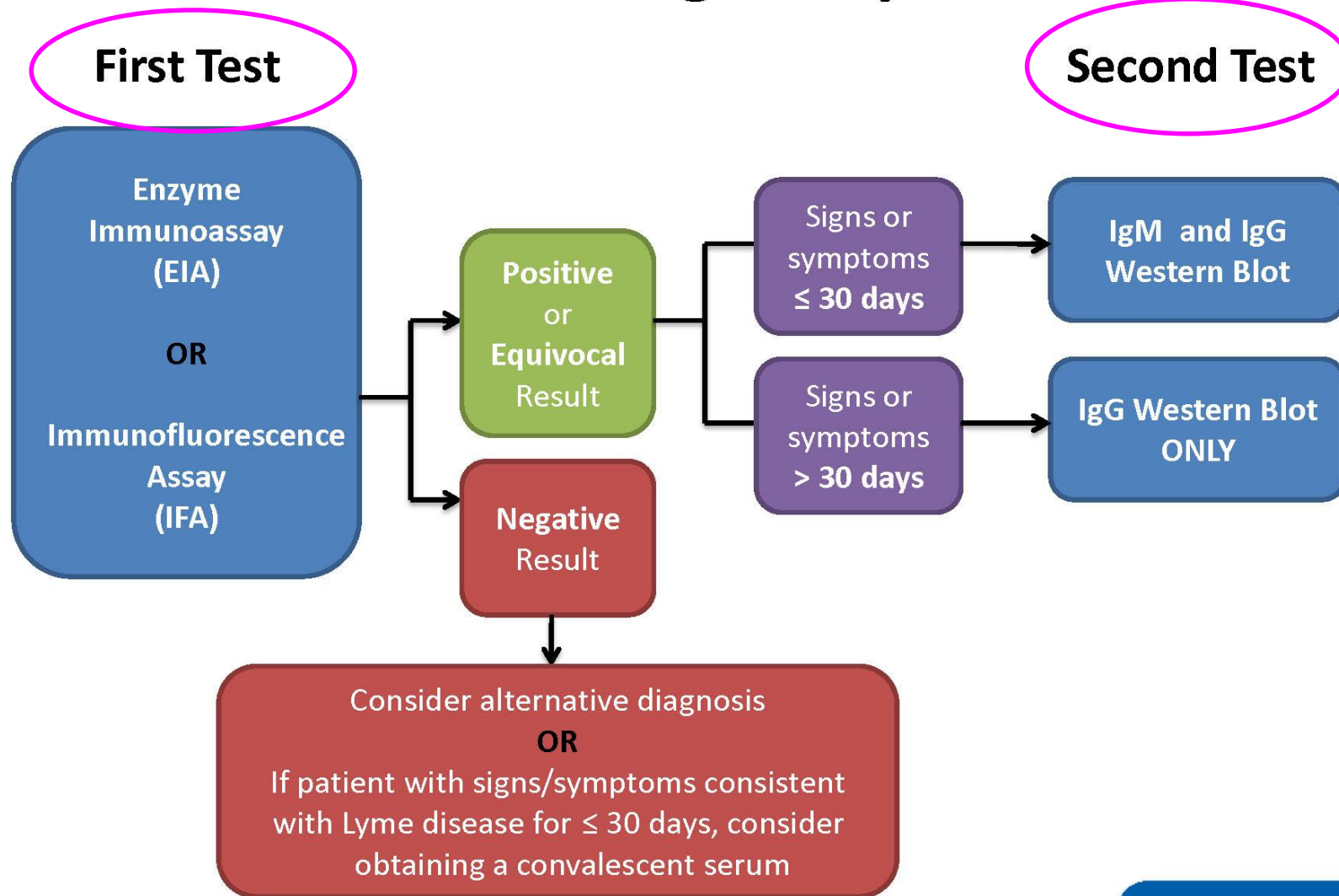
Nadelman RB, Wormser GP. Management of tick bites and early Lyme disease. Rahn DW, Evans J eds. *Lyme disease*. 1998; Philadelphia: American College of Physicians. 49-75.

Disseminated and Late Lyme Disease

- ❑ Facial palsy
 - Summer months
 - May be bilateral
- ❑ Meningitis
- ❑ Arthritis
 - Intermittent
 - Oligoarticular
- ❑ Late-stage neurologic
 - Peripheral neuropathy



Two-Tiered Testing for Lyme Disease



Sensitivity of Two-Tiered Serologic Testing

Lyme Disease Stage	Sensitivity (%)
EM rash (acute)	38
EM rash (convalescent)	67
Early neurologic	87
Late neurologic	100
Arthritis	97

Specificity of two-tiered testing is generally $\geq 95\%$

Bottom line:

- Good in later stages of disease
- Testing of patients with EM and exposure in an endemic area is not generally necessary

Additional Tests: Questionable Utility

- Single-tier Western blot tests without a previous EIA
- In-house criteria for interpretation of Western blots
- Capture assays for antigens in urine
- Tests for “cystic forms” of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- Novel culture techniques

More info on www.cdc.gov/Lyme

Concerns Regarding a New Culture Method for *Borrelia burgdorferi* Not Approved for the Diagnosis of Lyme Disease

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In 2005, CDC and the Food and Drug Administration (FDA) issued a warning regarding the use of Lyme disease tests whose accuracy and clinical usefulness have not been adequately established (1). Often these are laboratory-developed tests (also known as “home brew” tests) that are manufactured and used within a single laboratory and have not been cleared or approved by FDA. Recently, CDC has received inquiries regarding a laboratory-developed test that uses a novel culture method to identify *Borrelia burgdorferi*, the spirochete that causes Lyme disease. Patient specimens reportedly are incubated using a two-step pre-enrichment process, followed by immunostaining with or without polymerase chain reaction (PCR) analysis. Specimens that test positive by immunostaining or PCR are deemed “culture positive” (2). Published methods and results for this laboratory-developed test have been reviewed by CDC. The review raised serious concerns about false-positive results caused by laboratory contamination and the potential for misdiagnosis (3).

CDC recommends that laboratory tests cleared or approved by FDA be used to aid in the routine diagnosis of Lyme disease.

A complete searchable list of such tests is available online (4).

When evaluating testing options, providers and their patients

When laboratory testing is indicated, CDC recommends two-tier serologic testing for the diagnosis of Lyme disease. Two-tier testing consists of an FDA-cleared enzyme immunoassay (EIA) that, if positive or equivocal, is followed by an FDA-cleared immunoblot test, commonly known as a “Western blot” test. Results are considered positive only when both the EIA and Western blot are positive (5). Culture and PCR of clinical specimens are recommended only in certain rare circumstances (6).

CDC encourages researchers to work with FDA to develop new or improved tests for the diagnosis of Lyme disease. As with any diagnostic test, it is critical that new tests for Lyme disease have adequate analytical and clinical validation to avoid misdiagnosis and improper treatment of patients.

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References

1. CDC. Notice to readers: caution regarding testing for Lyme disease. MMWR 2005;54:125.

Prognosis

- Most patients treated with antibiotics recover completely
- In patients with persistent or recurrent joint swelling, re-treatment with a second 4-week course may be needed
- Some patients – particularly those diagnosed with later stages of disease – may have persistent symptoms of fatigue, muscle aches, reduced concentration
 - Preferred term for this is Post-treatment Lyme Disease Syndrome (PTLDS)
 - Placebo-controlled trials have not shown a sustained benefit of extended antibiotic treatment

Prevention – Talk About It!

- ❑ Avoid tick habitat
- ❑ Use DEET and wear permethrin-treated clothing
- ❑ After being outdoors:
 - **Tumble clothes in the dryer on high heat for 5-10 min**
 - Shower within 2 hrs – washes away unseen nymphs
- ❑ Daily tick checks – remove attached ticks ASAP
- ❑ Treat pets appropriately for ticks year-round

Nelson *et al.* The heat is on: Killing blacklegged ticks in residential washers and dryers to prevent tickborne diseases. *Ticks Tick Borne Dis.* 2016 Apr 28.

Antibiotic prophylaxis for patients with a tick bite

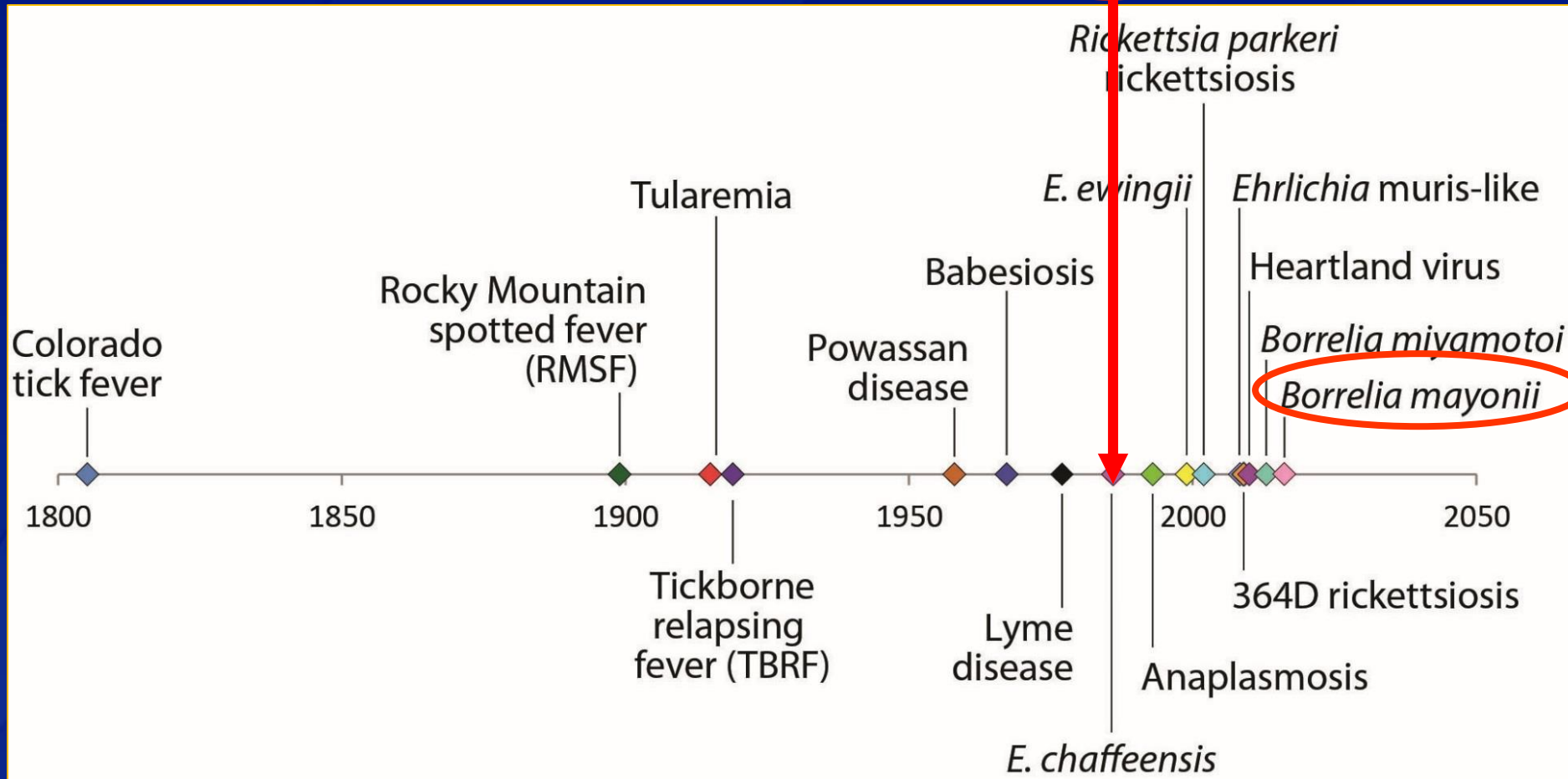
Single dose of doxycycline for prevention of Lyme disease when all of the following conditions are met:

- Highly endemic area
- Attached tick identified as an adult or nymphal *I. scapularis*
- Tick attached for > 36 hours based on engorgement or history
- Prophylaxis can be started within 72 hrs. of tick removal
- Doxycycline treatment is not contraindicated

Dose = 200 mg po x 1 for adults

Emerging Tickborne Diseases

STARI



STARI or Lyme Disease?

- ❑ Southern tick-associated rash illness (STARI)
 - Rash indistinguishable from Lyme disease EM
 - May be accompanied by fatigue, fever, headache, muscle and joint pains
 - Follows bite of lone star tick, *Amblyomma americanum*
- ❑ Also known as Master's disease
- ❑ Cause of STARI is not known



Southern Tick-associated Rash Illness (STARI)



Life stages of lone star tick
(*Amblyomma americanum*)

Treatment of STARI

- ❑ It is not known whether antibiotic treatment is necessary or beneficial for patients with STARI
- ❑ STARI has not been linked to arthritis, neurologic disease, or chronic symptoms
- ❑ Nevertheless, because STARI resembles early Lyme disease, physicians will often treat patients with oral antibiotics

Lantos et al. Empiric antibiotic treatment of EM-like skin lesions as a function of geography: a clinical and cost effectiveness modeling study. *Vector Borne Zoonotic Dis* 2013;13(12):877-83.

Borrelia miyamotoi

- ❑ Relapsing fever spirochete
- ❑ Detected in *I. scapularis* ticks in CT in 2001
- ❑ First report of human infection in 2011 (Russia)
- ❑ First report of human infection in U.S. in 2013
- ❑ Until very recently, 4 cases reported
 - All >60 years old and 2 immunocompromised
- ❑ Present in approximately 2% (up to 10.5%) of *Ixodes* spp. ticks in U.S.

Borrelia miyamotoi

- ❑ **Human blood samples from May 2013 – Oct 2014**
 - 11,515 samples tested (*B. miyamotoi* DNA in 0.8%)
 - 97 patients positive by 2 PCR assays (genus, species) → Clinical data on 51 patients
- ❑ **Onset in July/August**
- ❑ **Most patients experienced fever (96%), headache (96%), myalgia (84%), malaise (82%), and arthralgia (76%)**
- ❑ **Hospitalized (24%); Immunocompromised – ?**

Molloy *et al.* 2015



Borrelia mayonii: An Emerging Tickborne Pathogen

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Vectorborne Disease Program
Minnesota Department of Health

Lyme Disease

- Disease caused by bacteria in the *Borrelia burgdorferi* sensu lato (Bbsl) complex
 - In United States, *Borrelia burgdorferi* sensu stricto
 - In Europe, *Borrelia afzelii*, *Borrelia garinii*, and *Borrelia burgdorferi*
- The Bbsl complex does not include the relapsing fever group of *Borrelia* (e.g., *B. hermsii*, *B. miyamotoi*)

Lyme Disease Diagnosis

- Based on clinical presentation and a history of exposure to blacklegged ticks in an area where Lyme disease is endemic
- Serology
 - Two-tiered approach recommended, using FDA-approved tests
 - Not needed for early Lyme disease with single erythema migrans (EM) rash
 - Important for disseminated infections or illness without EM rash

Lyme Disease PCR Test

- Commercial assays are available to test blood, CSF, synovial fluid, and tissue
- Considered an adjunct test rather than for routine diagnostics
- Advantage of direct detection in acute illness – no need to wait for antibodies to develop
- Major disadvantage is low sensitivity
 - Blood is positive in only 50% of acute cases with EM
 - CSF is positive only 1/3 of patients with early neuroborreliosis

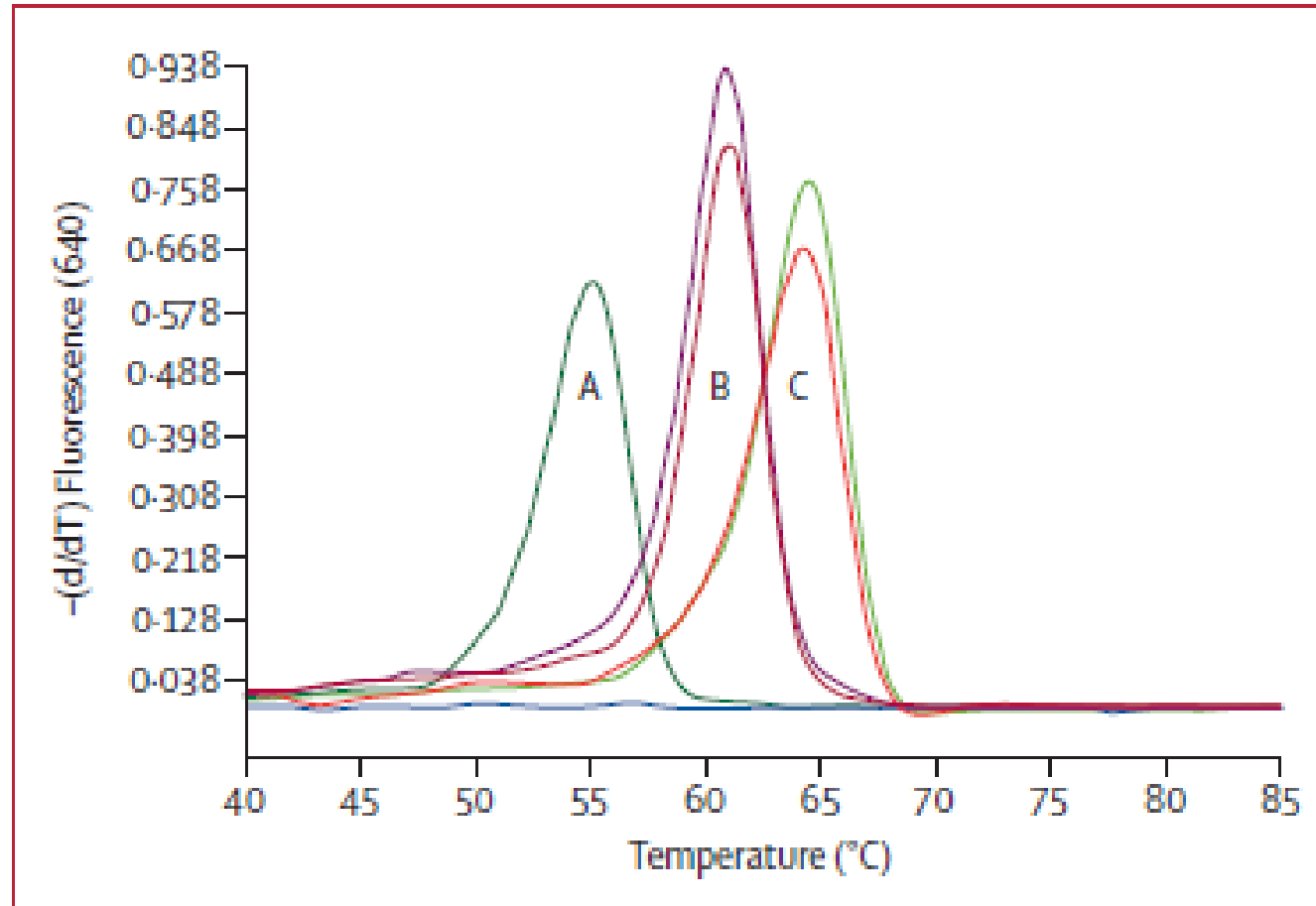
Index Case – June 2013

- 10-year-old male from northwestern Minnesota
- Presented with fever, headache, neck pain, myalgia, nausea/vomiting, and diffuse rash (not typical EM)
- Spent the week prior in Spooner, WI
- Patient was hospitalized for 4 days
- Treated with ceftriaxone for 1 day, followed by 21 days of amoxicillin
- Complete recovery

Diffuse Macular Rashes



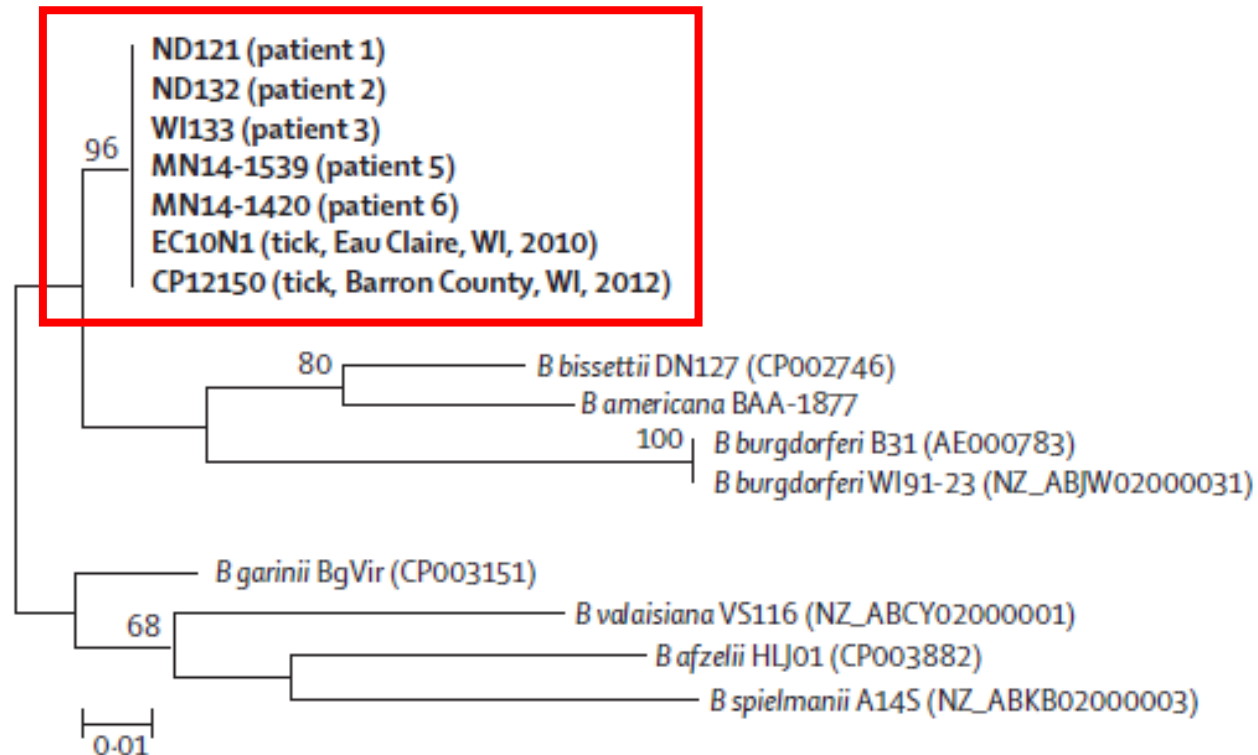
PCR Melting Temperature Analysis



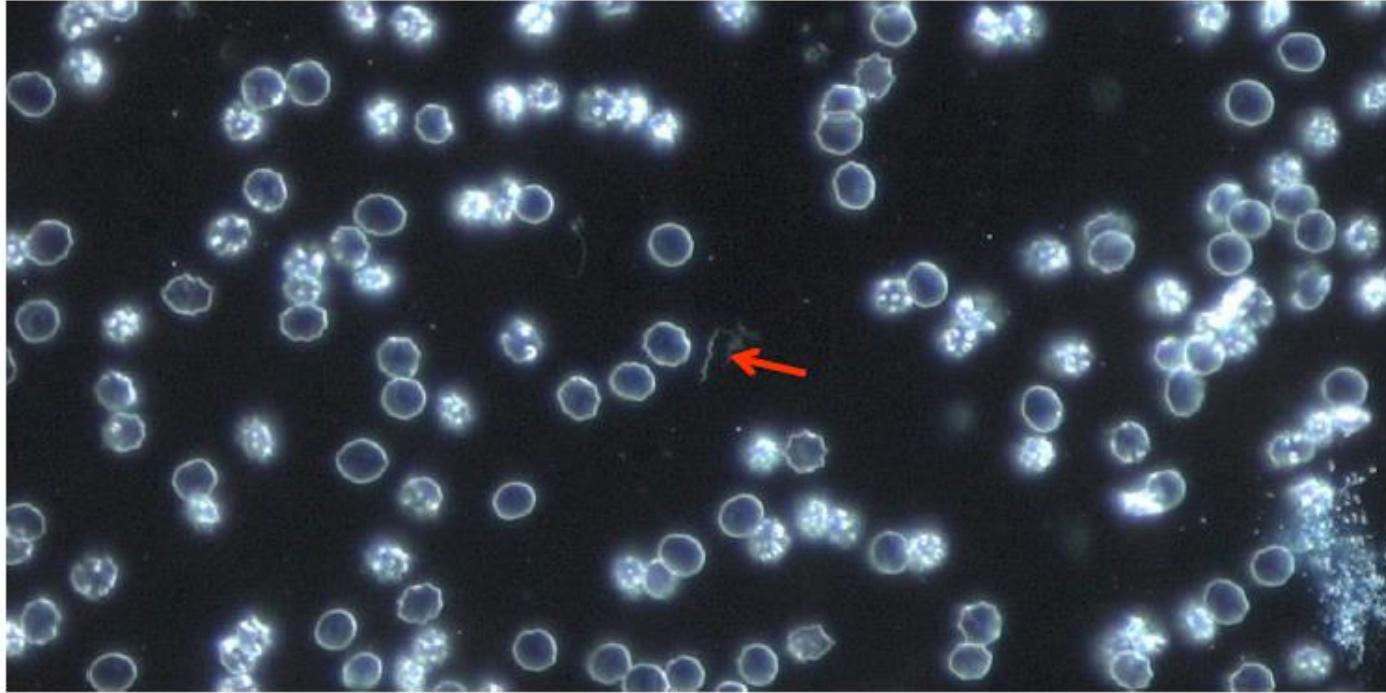
Additional Cases Identified

- PCR on whole blood positive
 - 11-year-old male from WI in July 2013
 - Retrospective review also identified a 65-year-old male from ND (exposure in MN) from July 2012
- Synovial fluid specimen from Mayo Clinic Eau Claire
 - 21-year-old woman from WI in June 2013
- Two additional cases in 2014

Sequence Analysis of Atypical *oppA1* PCR Products

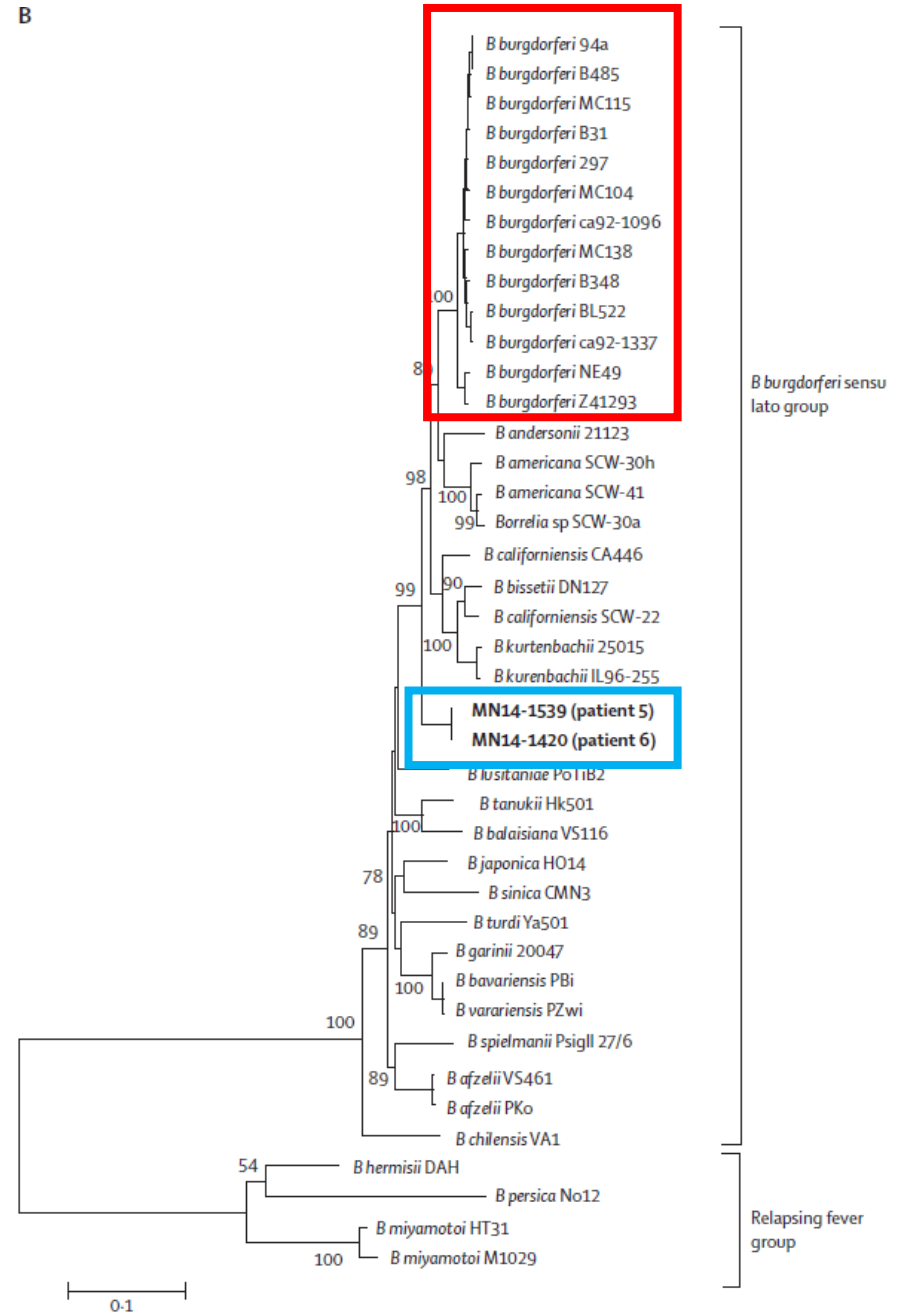


Dark Field Microscopy and Cultures



Phylogenetic Analysis

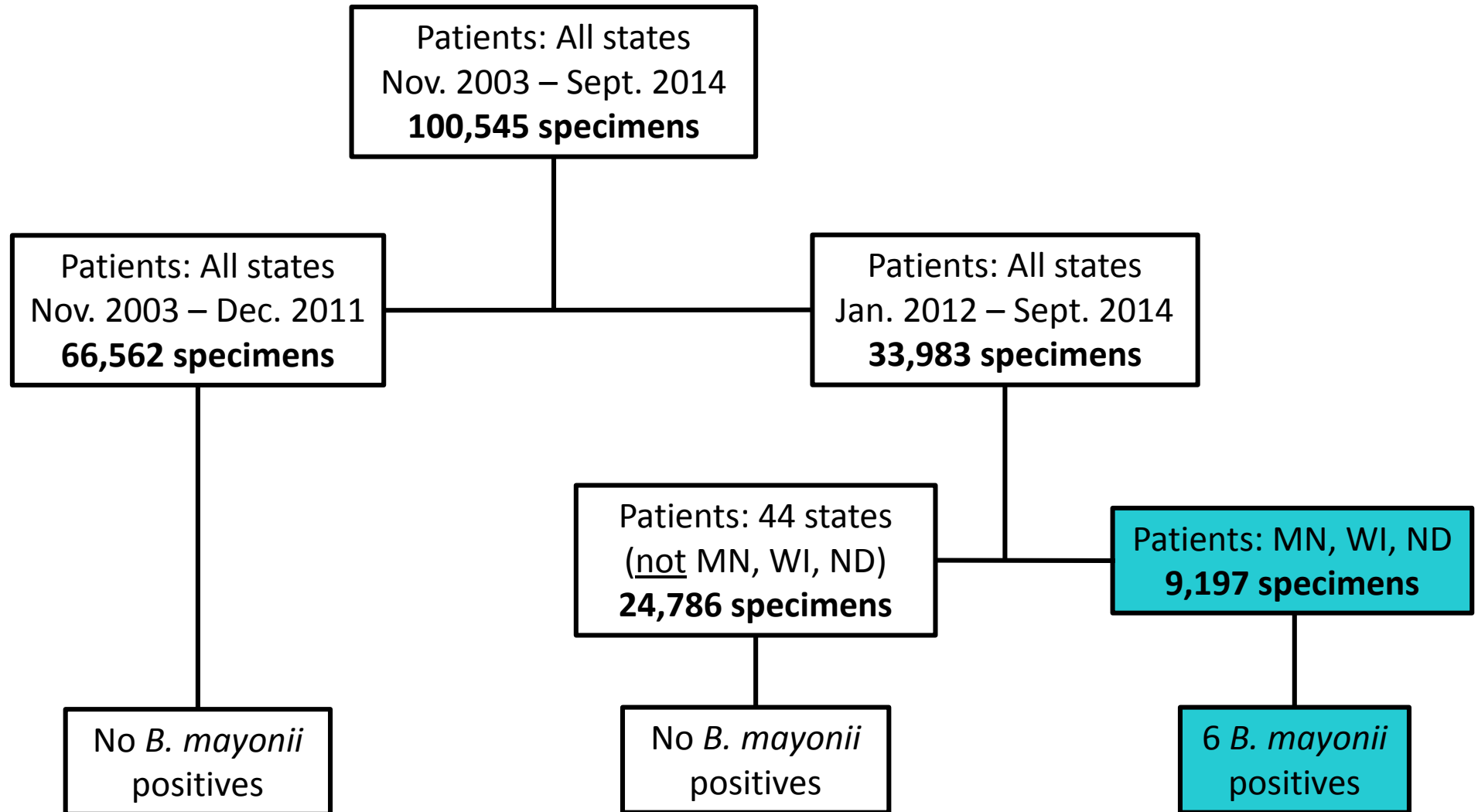
- 8 housekeeping genes:
 - uvrA*, *rplB*, *recG*, *pyrG*, *pepX*, *clpX*, *clpA*, *nifS*



Multi-Locus Sequence Analysis (MLSA)

- 8-gene MLSA performed
- Previously used for defining Bbsl genospecies
- Highest pairwise similarity was to *B. burgdorferi* (94.9 to 95.2%)
 - Threshold for separating genospecies = 98.3% similarity
 - Results confirmed that this is a novel Bbsl genospecies
- Proposed name is *Borrelia mayonii*

Patient Samples Analyzed



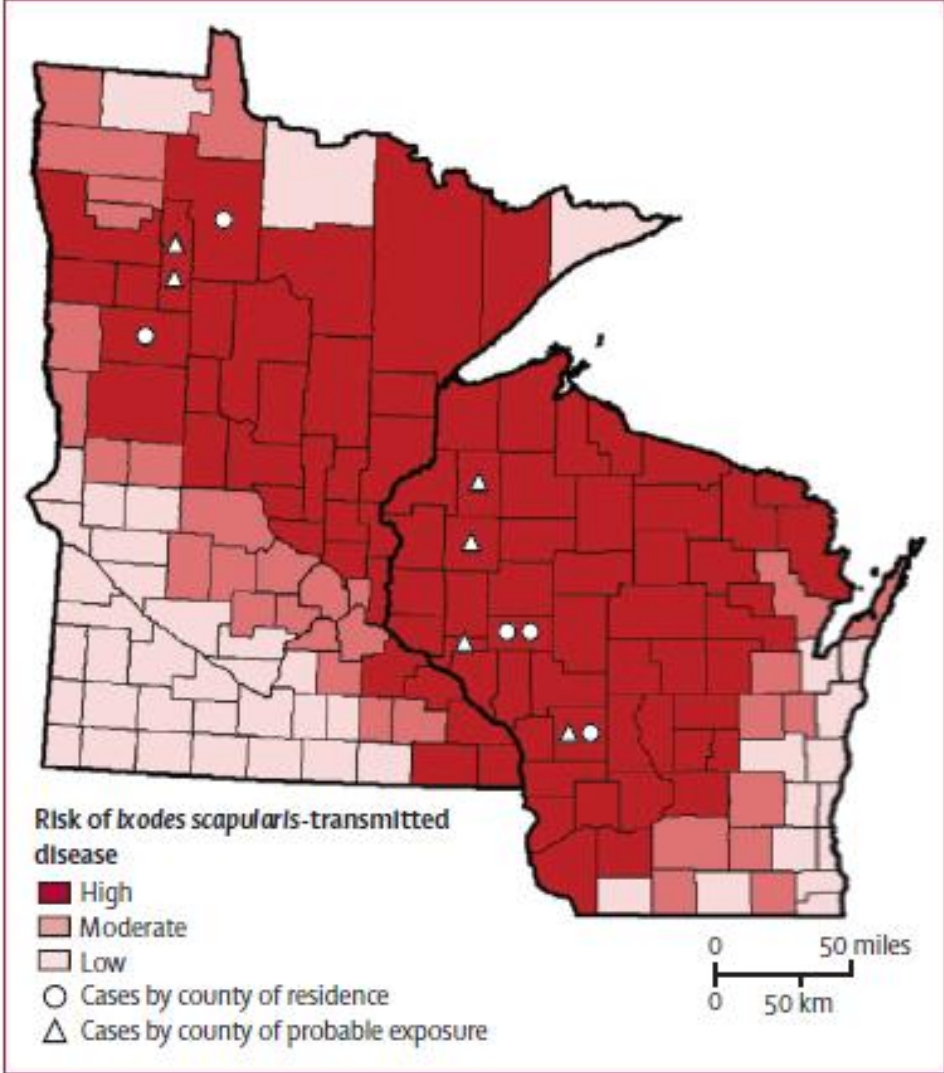
Clinical Features of Patients (n=6)

- Ages ranged from 10 to 67 years; 4 male, 2 female
- 2 patients had a known tick bite, but all reported exposure to ticks or tick habitat in Minnesota or Wisconsin
- 5 presented with an acute febrile illness
- 3 had potential neurologic involvement (confused speech, profound somnolence, visual difficulties)
- 4 had rash – only 1 was suggestive of an EM
- 1 had arthralgia

Patient Outcomes

- 2 of 6 patients were hospitalized
- All were treated with antibiotics recommended for treatment of Lyme disease
- 5 patients recovered completely, while 1 reported residual joint pain

Patient Exposure and Residence Locations



Routine Serologic Testing Results

Patient No.	Days from Illness Onset to Specimen Collection	Bb EIA-whole cell	Bb EIA-C6	Bb IgM Immunoblot Result (number of bands detected/possible bands)	Bb IgG Immunoblot Result (number of bands detected/possible bands)
1	6	N/A	Positive	Positive (2/3)	Negative (1/10)
3	2	N/A	Equivocal	Negative (0/3)	Negative (0/10)
3	29	N/A	Positive	Positive (3/3)	Negative (2/10)
3	104	Positive	Positive	Negative (0/3)	Negative (4/10)
4	266	Positive	Positive	Negative (1/3)	Positive (5/10)
5 ¹	3	Negative	Positive	Negative (0/3)	Negative (0/10)
5	32	Positive	Positive	Positive (2/3)	Negative (2/10)
6 ¹	1	Negative	Negative	Negative (0/3)	Negative (1/10)

¹ Specimen source was plasma rather than serum.

Tick Collection

- *Ixodes scapularis* ticks collected
 - 2 sites in Wisconsin (2009-2010, 2013-2014)
 - 4 sites in Minnesota (2014-2015)
- PCR testing performed for both *B. burgdorferi* and *B. mayonii*
 - Wisconsin ticks – Mayo Laboratories
 - Minnesota ticks – Minnesota Department of Health Public Health Laboratory

Tick Testing Results, 2009 - 2015

	<i>Borrelia mayonii</i> No. pos/Total (%)		<i>Borrelia burgdorferi</i> No. pos/Total (%)	
	Adults	Nymphs	Adults	Nymphs
Minnesota <i>I. scapularis</i> ticks ¹	14/855 (1.6)	2/203 (1.0)	374/855 (43.7)	50/203 (24.6)
Wisconsin <i>I. scapularis</i> ticks ²	15/465 (3.2)	4/193 (2.1)	162/465 (34.8)	33/193 (17.1)

¹ Minnesota ticks tested were from 2014-2015.

² Wisconsin ticks tested were from 2009-2010 and 2013-2014.

Unique Features of *B. mayonii*

- Disease only identified in patients from the upper Midwest
 - Not detected in nearly 25,000 blood samples from other parts of the US
- Based on initial findings, seems to cause more severe disease than *B. burgdorferi*
- Rashes more diffuse than classic EM presentation
- Organism found primarily in whole blood
 - Historically, <0.1% of blood positive for *B. burgdorferi*

Summary

- Still much to learn about this newly identified species of *Borrelia* – unclear how common Lyme disease associated with *B. mayonii* really is, but research indicates it recently emerged
- Both Minnesota and Wisconsin are considered high-incidence states for Lyme disease, and have several endemic tickborne diseases
- Risk for tickborne diseases is highly seasonal – late spring through mid-summer is period of highest risk
- Tickborne diseases, including *B. mayonii*, should be considered in patients presenting with febrile illness after outdoor exposures in the upper Midwest

Acknowledgements

- Bobbi Pritt and colleagues at Mayo Clinic
- Division of Vectorborne Diseases, Centers for Disease Control
- Minnesota Department of Health Vectorborne Disease Program
- Minnesota Department of Health Public Health Laboratory
- Wisconsin Department of Health Services Vectorborne Program
- University of Wisconsin – Madison
- North Dakota Department of Health

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Tickborne Rickettsial Diseases

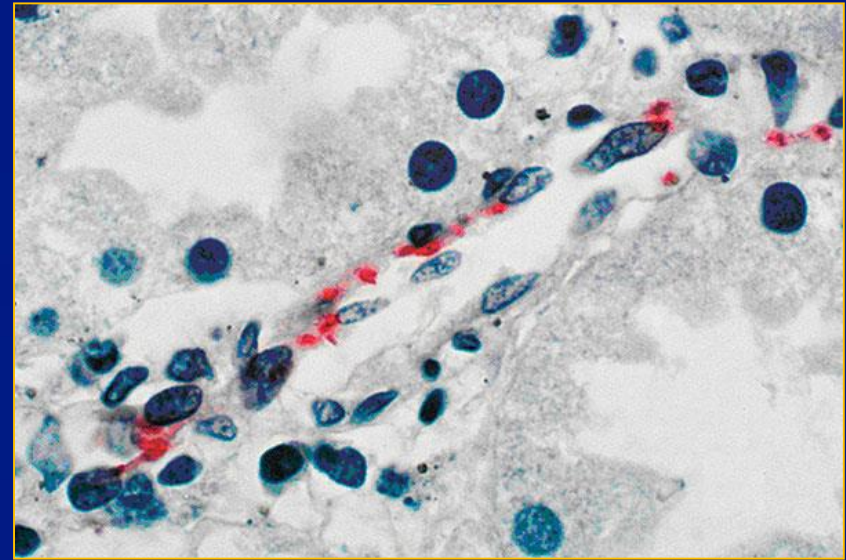
- ❑ Nonspecific early clinical signs make them difficult to diagnose
- ❑ Some are rapidly progressing and may be fatal
- ❑ Increasing incidence

But...

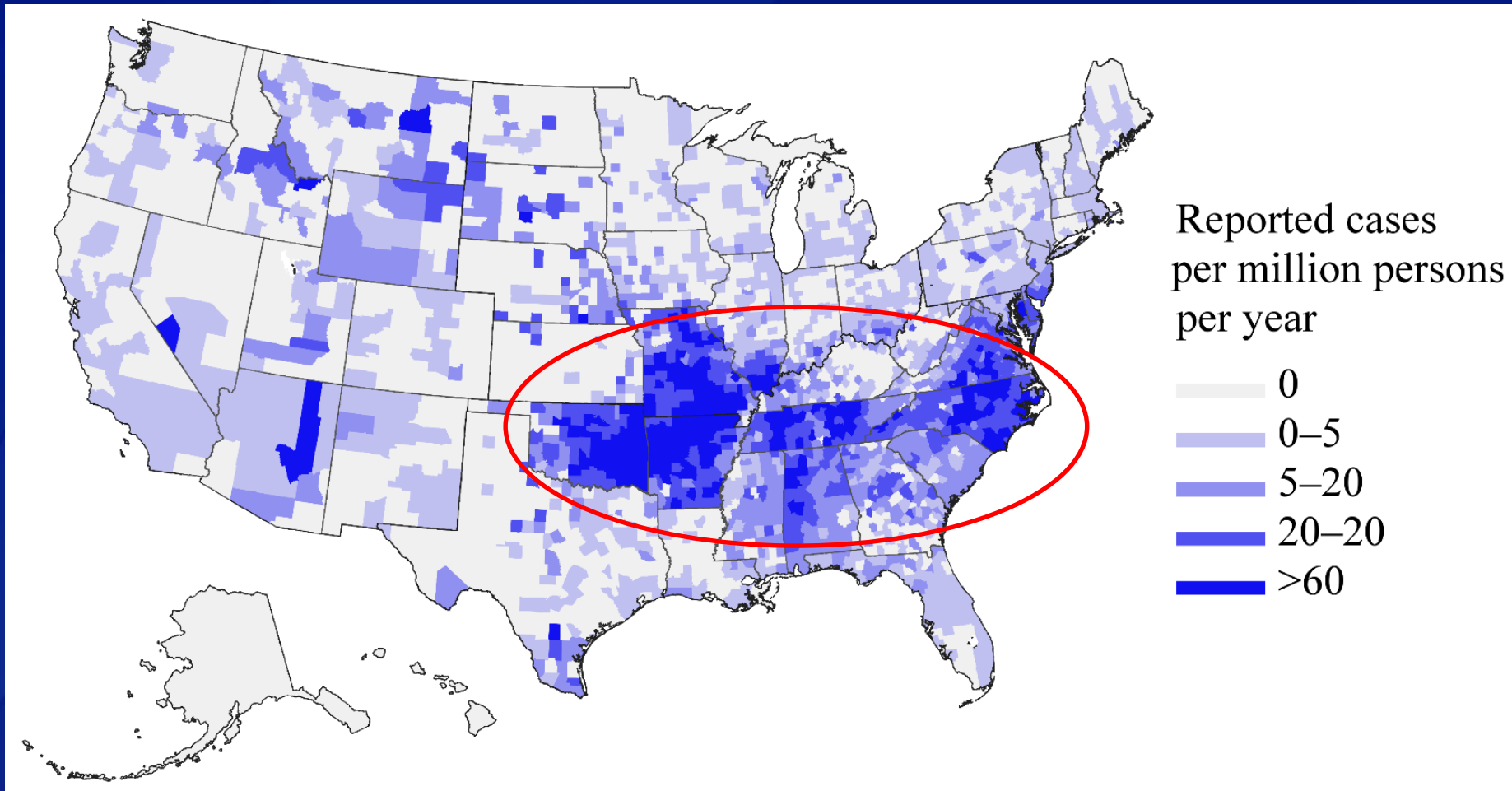
- ❑ Are all treated with doxycycline
- ❑ Use similar laboratory methods for diagnostic confirmation

Rickettsia rickettsii: Rocky Mountain spotted fever

- ❑ Gram-negative intracellular bacterium, endothelial cells
- ❑ Transmitted by *Dermacentor variabilis*, *Dermacentor andersoni*, and in some areas *Rhipicephalus sanguineus*
- ❑ Causes widespread vasculitis and multi-system organ failure
- ❑ Rapidly fatal, yet difficult to diagnose in early stage of illness (>20% case fatality rate in untreated cases)



Incidence of Spotted Fever Rickettsiosis, 2000-2013



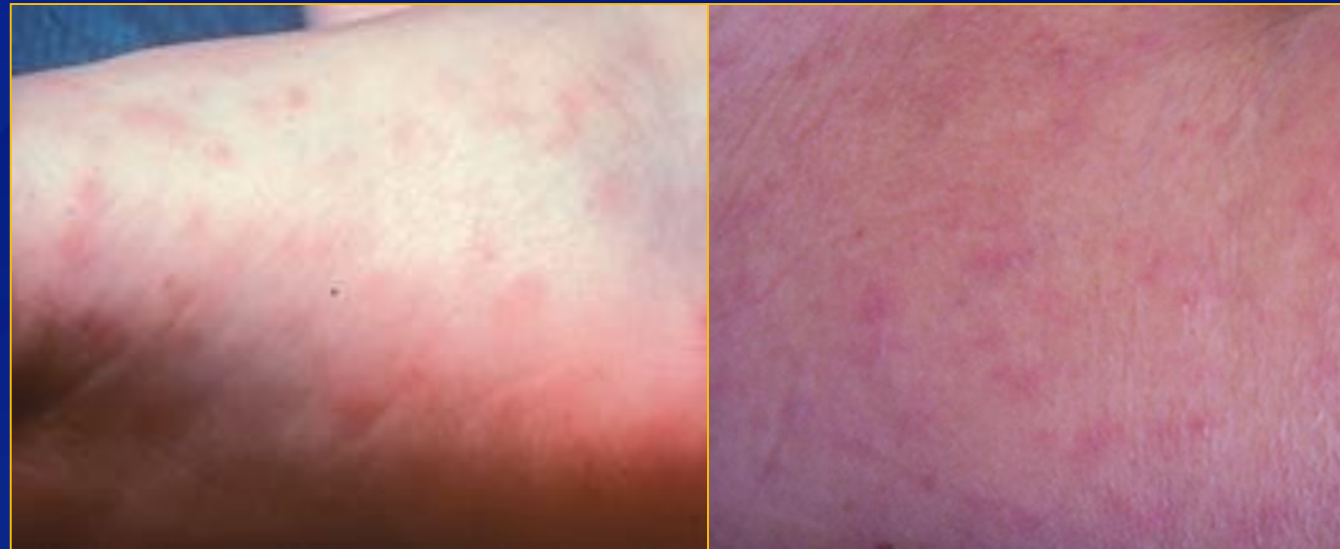
NOTE: Incidence based on national surveillance data 2000-2013. Surveillance reporting category changed to spotted fever rickettsiosis (including RMSF) in 2010.

RMSF: Early Clinical Manifestations (Days 1-4)

- Day 1-2: Fever, headache, myalgia (*may be responsive to pain/fever meds*)
- Day 2-4: May develop respiratory signs (cough) and/or gastrointestinal signs (nausea, vomiting, abdominal pain)
- Day 2-4: Faint maculopapular rash (variable)

Initial Rash of RMSF

- ❑ Small (1-5 mm), blanching, pink macules, 2 to 4 days after onset of fever
- ❑ First appears on wrists, ankles, forearms, spreads centrally



RMSF: Late Clinical Manifestations (Day 5 or Later)

- Worsening systemic illness (cough, dyspnea, arrhythmias, hypotension, severe abdominal pain)
- Petechial rash may develop
- Thrombocytopenia, hyponatremia, elevated liver enzymes (AST, ALT) usually present
- Onset of neurologic signs (photophobia, altered mental status, seizures)
- Death

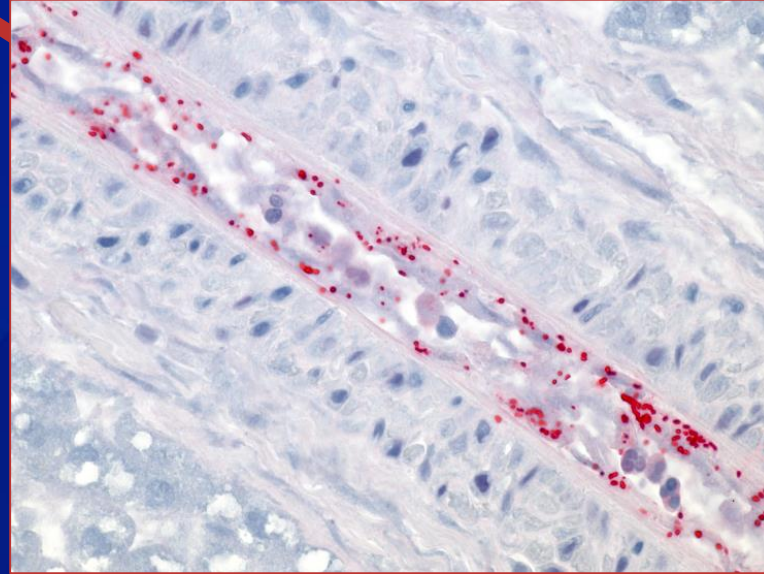
RMSF Petechiae



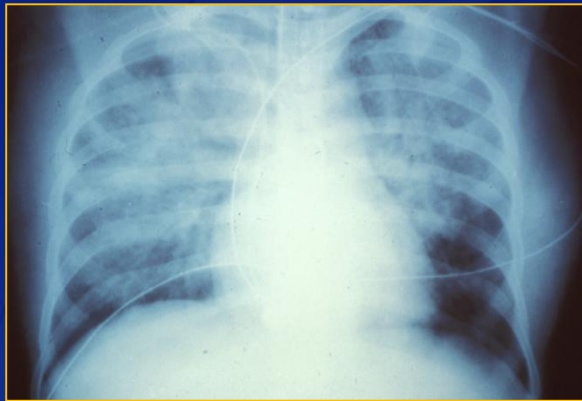
Petechiae on palms or soles typically do not appear until after 5th day of illness and indicates advanced disease



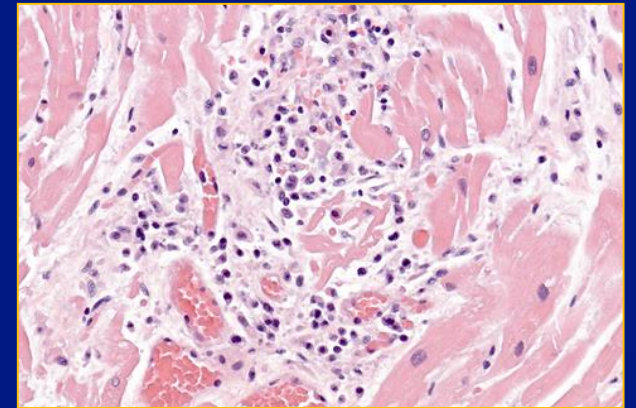
Gangrene



Cerebral edema



Pulmonary edema



Myocarditis

Photos courtesy of Dr. Chris Paddock and Dr. Gerardo Alvarez Hernandez

Risk Factors for Fatal Outcome

- ❑ Delayed onset or absence of rash
- ❑ Age <10 years or ≥60 years
- ❑ Chronic conditions with signs/symptoms that overlap with RMSF (i.e. alcoholism, chronic lung disease)
- ❑ Glucose-6-phosphate dehydrogenase deficiency
- ❑ Off-season onset (colder months, first and last cases of the year)
- ❑ **Delay in administration of effective therapy (doxycycline)**

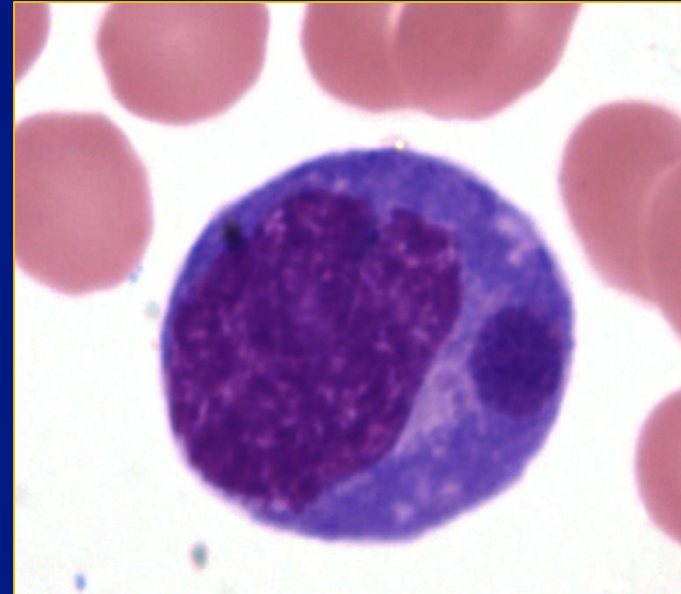
Other Pathogenic Tickborne Spotted Fever Rickettsioses

- ❑ ***Rickettsia parkeri* rickettsiosis:**
 - Transmitted by *A. maculatum*
 - Southeastern United States
 - Eschar-associated, febrile illness, no fatal cases
- ❑ ***Rickettsia* species 364D rickettsiosis:**
 - Transmitted by *D. occidentalis*
 - All cases have been reported out of California
 - Eschar-associated, febrile illness, no fatal cases
 - Rash not reported in few described cases

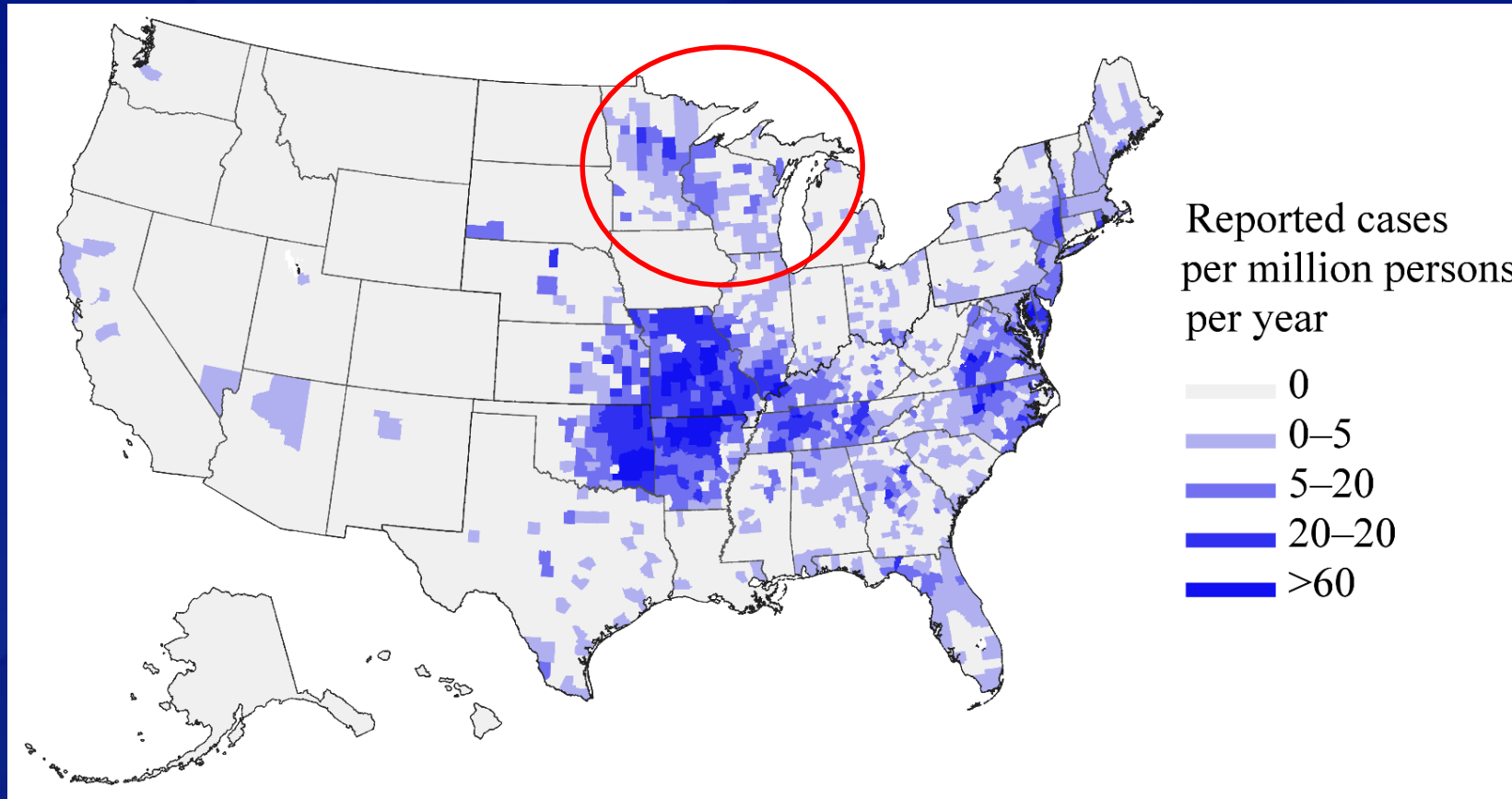


Ehrlichiosis

- ❑ Most commonly caused by *Ehrlichia chaffeensis* in United States
- ❑ Obligate intracellular bacteria which infect the peripheral blood leukocytes



Incidence of *Ehrlichia chaffeensis*, 2000-2013



NOTE: Incidence based on national surveillance data, 2000-2013

Symptoms—Ehrlichiosis

- ❑ Fever / chills
- ❑ Headache / malaise
- ❑ Muscle pain
- ❑ Nausea / vomiting / diarrhea
- ❑ Confusion
- ❑ Rash
 - In up to 60% of children, less than 30% of adults
- ❑ Thrombocytopenia, leukopenia and elevated liver enzymes

Severe clinical presentation may include multiple organ failure, septic shock, or respiratory failure.

Other Ehrlichial Species

□ *Ehrlichia ewingii*

- Primarily reported out of Missouri, Arkansas
Indiana
- 51 cases between 2008-2012
- Transmitted by *A. americanum*



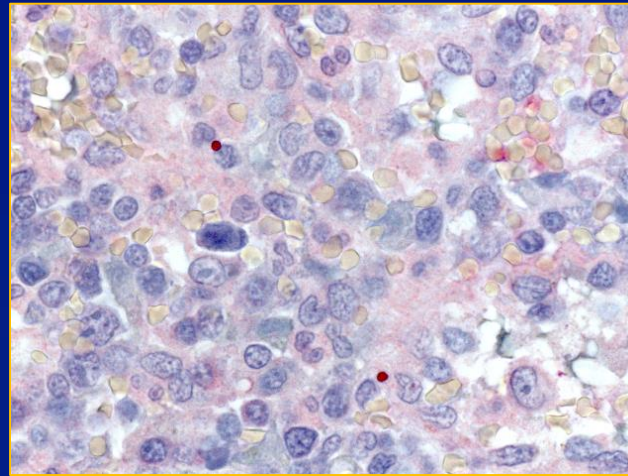
□ *Ehrlichia muris eauclairensis*

- First case confirmed in 2011
- 38 cases to date
- Suspected transmission by *I. scapularis*
- Wisconsin and Minnesota

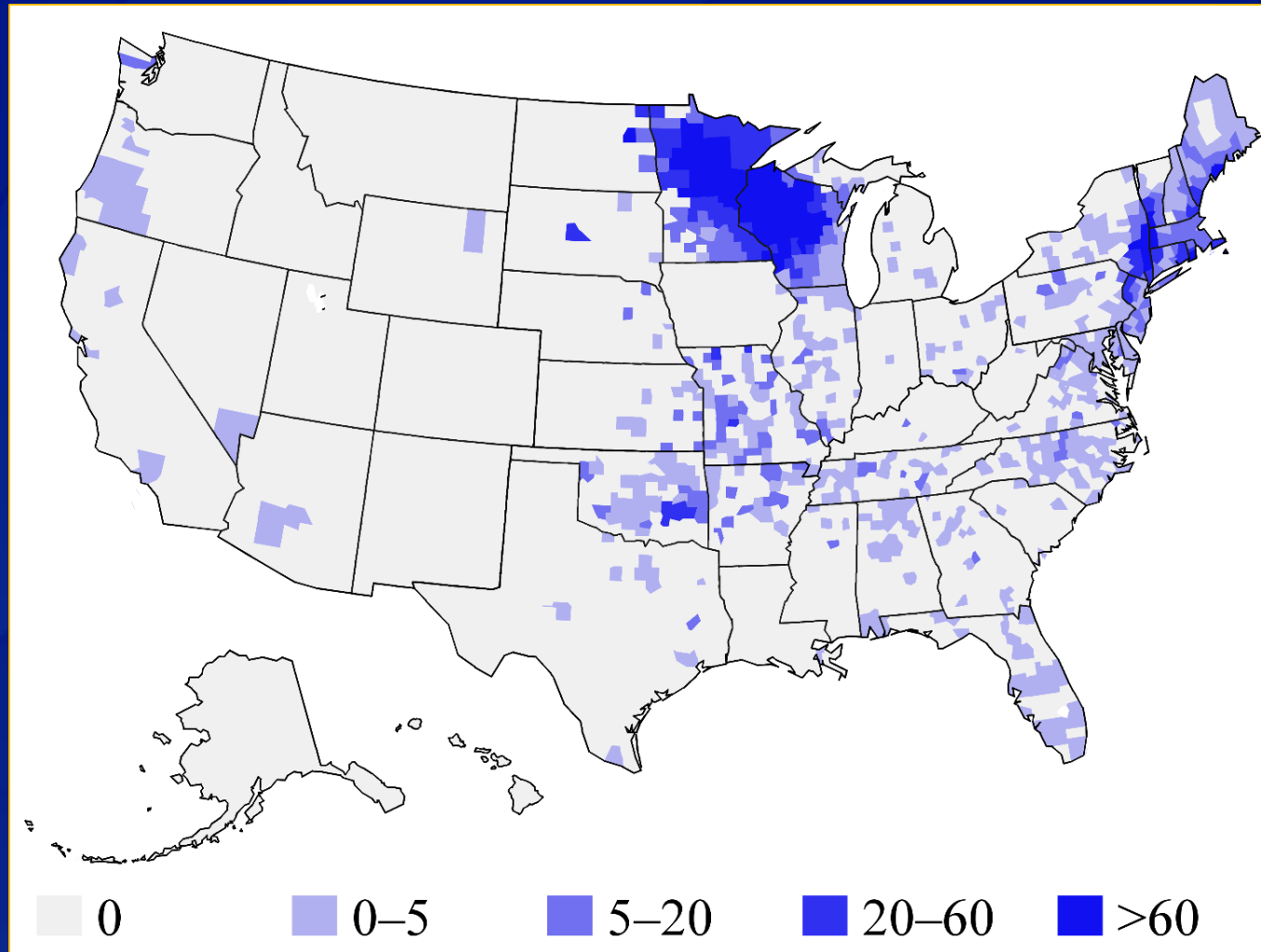


Anaplasmosis

- ❑ Caused by *Anaplasma phagocytophilum*
- ❑ Obligate intracellular bacteria which infect the peripheral blood leukocytes (predilection for granulocytes)



Incidence of Anaplasmosis, 2000-2013



NOTE: Incidence based on national surveillance data, 2000-2013

Symptoms—Anaplasmosis

- ❑ Fever / chills
- ❑ Headache/ malaise
- ❑ Muscle pain
- ❑ Thrombocytopenia, leukopenia, elevated liver enzymes and mild anemia

- ❑ Gastrointestinal symptoms
- ❑ Rash is uncommon

Severe clinical presentations may include respiratory failure, peripheral neuropathies, renal failure or toxic-shock-like syndrome.

Treating Rickettsioses—A Race Against Time

- ❑ Doxycycline is most effective treatment of **RMSF and other rickettsial diseases** in patients of all ages
- ❑ Treatment should be initiated early in patients of all ages with suspected rickettsial disease, before diagnosis confirmed
- ❑ Rapid treatment can prevent death and disability



Doxycycline Tooth Staining Study

- ❑ **Short term doxycycline use does not:**
 - Darken shade of teeth
 - Cause visible staining of teeth
 - Increase risk of enamel hypoplasia
- ❑ Doxycycline can be safely administered to children without fear of tooth staining at dose and duration recommended for rickettsial diseases

Todd SR, Dahlgren FS, Traeger MS, et al. No visible dental staining in children treated with doxycycline for suspected rocky mountain spotted Fever. The Journal of pediatrics **2015**; 166(5): 1246-51.



Confirming a Rickettsial Infection

- ❑ Treatment decisions must be made by clinical suspicion
- ❑ Do not base treatment decisions on (or wait for) confirmatory test results
- ❑ Laboratory test selection will depend on level of disease progression, the suspected agent, and specimen availability

Testing Options

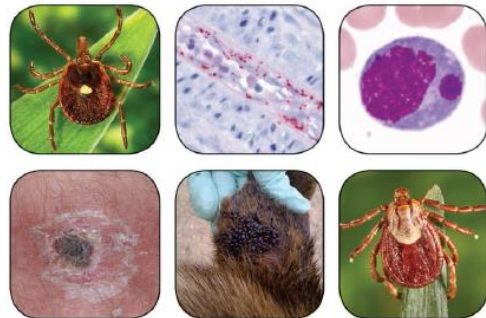
- ❑ **PCR of whole blood, skin, or tissue**
 - Sensitive for ehrlichiosis and anaplasmosis during acute illness
 - Generally insensitive for RMSF during acute illness until late in disease progression
 - Eschar swabs or biopsy sensitive specimens for detection of *R. parkeri* and *R. species 364D*
- ❑ **Serology (IFA)**
 - Requires both an acute and a convalescent sample to be interpretable
 - May be difficult to interpret due to cross-reactivity and antibody persistence
- ❑ **IHC of skin or tissue**
- ❑ **Microscopy for detection of morulae**
 - For ehrlichiosis and anaplasmosis only

The Most Important Points

- ❑ **Early symptoms are non-specific but can progress rapidly**
- ❑ **Early treatment with doxycycline is the best way to prevent severe disease, disability, and death**
- ❑ **Do not wait on confirmatory diagnostic test results to make a treatment decision**

**Diagnosis and Management of Tickborne
Rickettsial Diseases: Rocky Mountain Spotted Fever
and Other Spotted Fever Group Rickettsioses,
Ehrlichioses, and Anaplasmosis — United States**

A Practical Guide for Health Care and
Public Health Professionals



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>.



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Thank you

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**Updated guidelines on
treatment, diagnosis and
management of tickborne
rickettsial diseases:**

[http://www.cdc.gov/mmwr/
volumes/65/rr/rr6502a1.ht
m?s_cid=rr6502a1_w](http://www.cdc.gov/mmwr/volumes/65/rr/rr6502a1.htm?s_cid=rr6502a1_w)

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- “Click” ask

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- State your name
- Listen for the operator to call your name
- State your organization and then ask your question

Thank you for joining!
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