CDC PUBLIC HEALTH GRAND ROUNDS

Emerging Tickborne Diseases





Accessible version: https://youtu.be/aI5EM3yh--0

March 21, 2017

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

Expanding Diversity and Distribution of Tickborne Diseases

Rebecca Eisen, PhD

Research Biologist

Division of Vector-Borne Diseases

National Center for Emerging and Zoonotic Infectious Diseases

The Basics of Tickborne Diseases

- **All known tickborne infectious diseases are diseases of animals that can be transmitted to humans via a tick vector (e.g., zoonoses)**
  - Ticks can maintain the pathogens through transmission to their offspring
  - Ticks can acquire infection through feeding on infectious hosts
- **Humans are incidental hosts, infected by the bite of infected ticks**

Ticks Can Transmit Diverse Types of Bacteria in the United States

Bacterial Diseases (9)	Pathogens (14)	Tick Genera (5)
Anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes* spp.
Borrelia miyamotoi disease	*Borrelia miyamotoi*	*Ixodes* spp.
Ehrlichiosis	*Ehrlichia chaffeensis* *Ehrlichia ewingii* *Ehrlichia muris eauclarensis*	*Amblyomma* spp. *Ixodes* spp.
Lyme disease	*Borrelia burgdorferi* *Borrelia mayonii*	*Ixodes* spp.
Rickettsia parkeri rickettsiosis	*Rickettsia parkeri*	*Amblyomma* spp.
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor* spp. *Rhipicephalus* spp.
Pacific Coast tick fever	*Rickettsia philipii*	*Dermacentor* spp.
Relapsing fever	*Borrelia hermsii* *Borrelia parkeri* *Borrelia turicatae*	*Ornithodoros* spp.
Tularemia	*Francisella tularensis*	*Amblyomma* spp. *Dermacentor* spp.

Eisen RJ, Kugeler KJ, Eisen L et al. (2017) ILAR J, in press.

Other Types of Pathogens Ticks Can Transmit

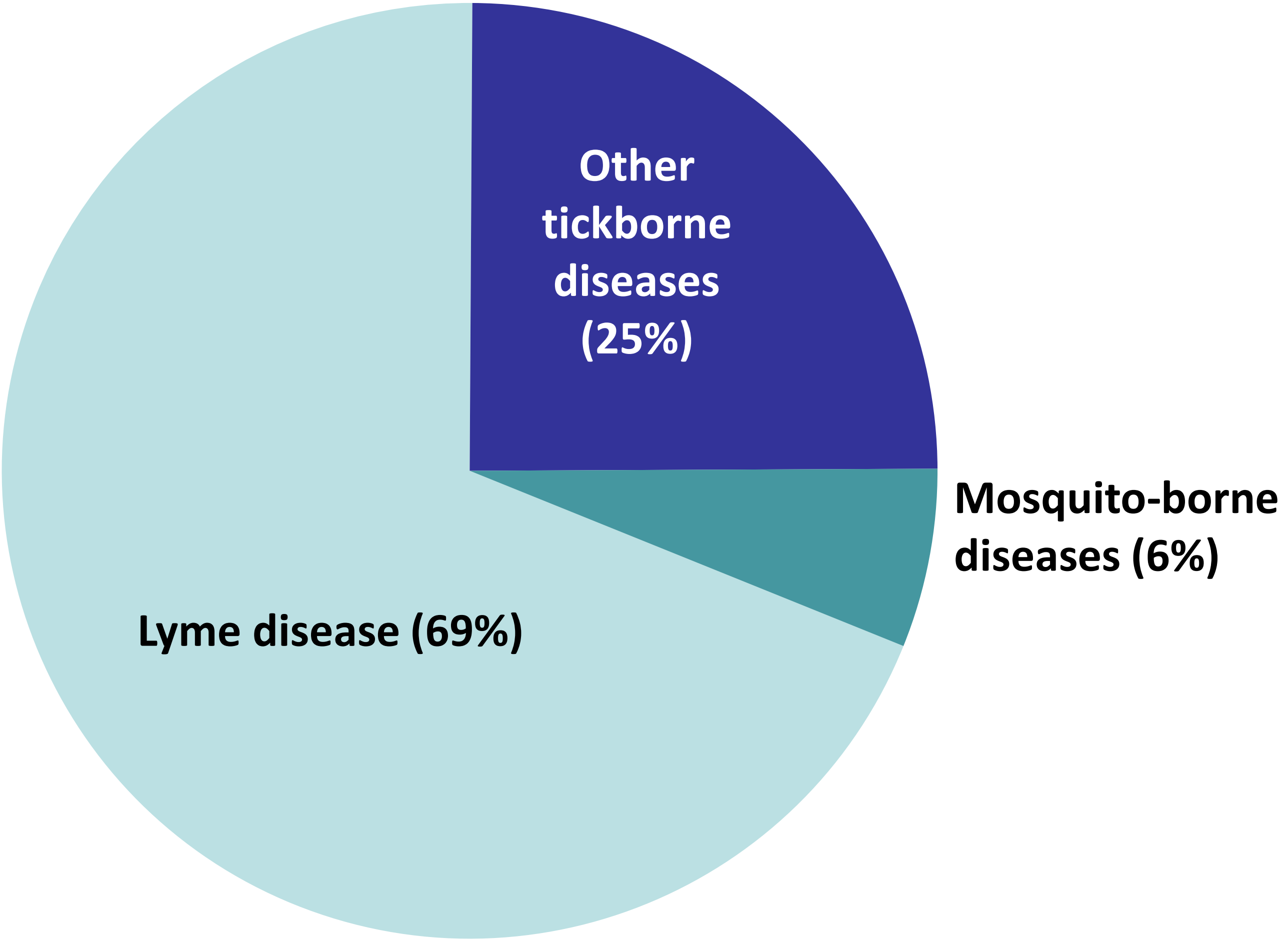
Diseases (4)	Pathogens (4)	Tick Genera (3)
Viruses		
Colorado tick fever	Colorado tick fever virus (Coltivirus)	*Dermacentor* spp.
Heartland virus disease	Heartland virus (Phlebovirus)	*Amblyomma* spp.
Powassan encephalitis	Powassan virus (Flavivirus)	*Ixodes* spp.
Protozoa		
Babesiosis	*Babesia microti*	*Ixodes* spp.

Eisen RJ, Kugeler KJ, Eisen L et al. (2017) ILAR J, in press.

Overview of Trends

- Majority of vector-borne diseases in the U.S. are tickborne diseases
- Increasing number of tickborne disease cases over time
- Expanding geographic range of tickborne cases
- Growing number of tickborne agents recognized to cause human disease

Cases of Nationally Notifiable Vector-borne Diseases Reported in the U.S., 2014



N= 48,519 cases

Adams DA, Thomas KR, Jajosky RA, et al. MMWR Morb Mortal Wkly Rep. 2016 Oct 14;63(54):1-152

Three Species Cause Majority of Human Diseases

- ***Ixodes scapularis*** **(Blacklegged tick)**
- ***Amblyomma americanum*** **(Lone star tick)**
- ***Dermacentor variabilis*** **(American dog tick)**

Ixodes scapularis

Amblyomma americanum

Dermacentor variabilis

Distribution of *Ixodes scapularis* (Blacklegged Tick)

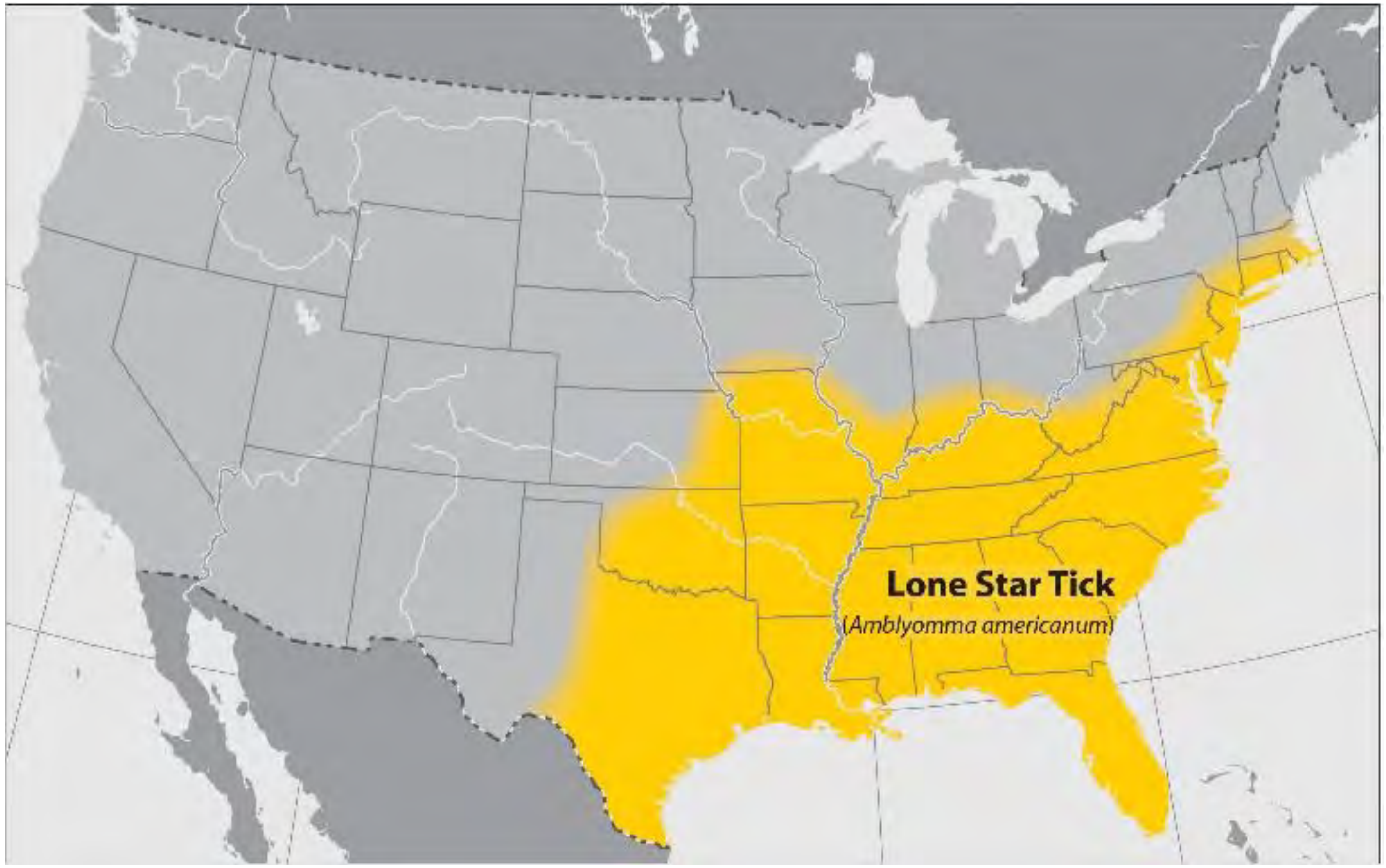
Transmits agents that cause:

- Anaplasmosis
- Babesiosis
- *Borrelia miyamotoi* disease
- Ehrlichiosis
- Lyme disease
- Powassan encephalitis

Adult female | Adult male | Nymph | Larva

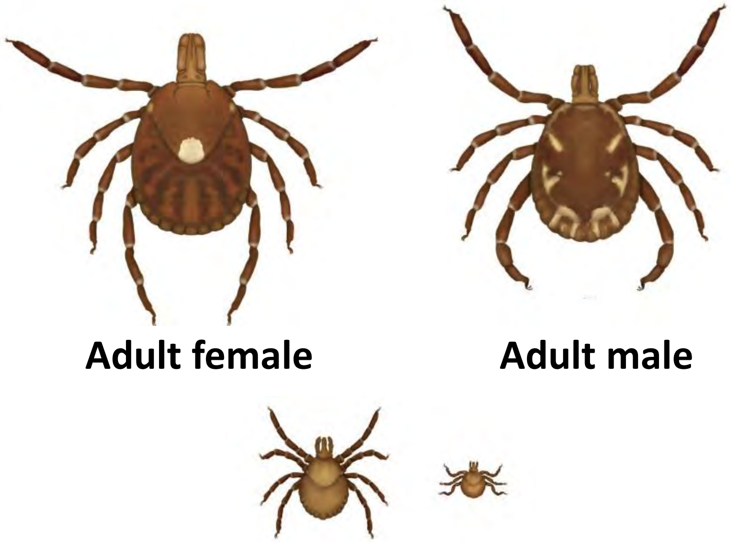
cdc.gov/ticks/geographic_distribution.html

Distribution of *Amblyomma americanum* (Lone star tick)



Transmits agents that cause:

- Ehrlichiosis
- Tularemia
- Heartland virus disease

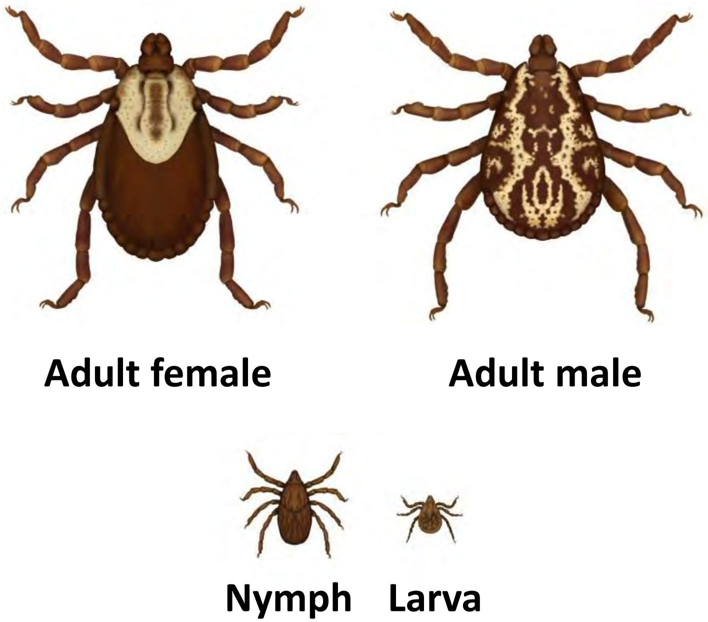


cdc.gov/ticks/geographic_distribution.html

Distribution of *Dermacentor variabilis* (American Dog Tick)

Transmits agents that cause:

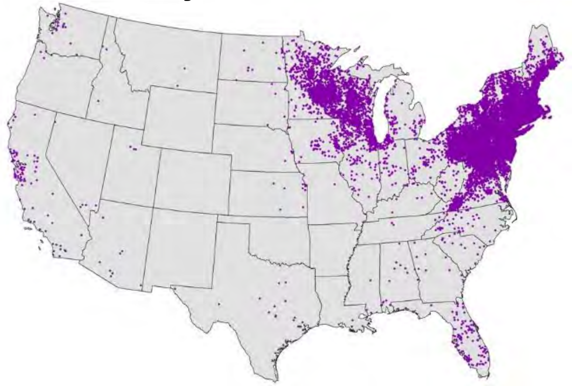
- **Rocky Mountain spotted fever**
- **Tularemia**



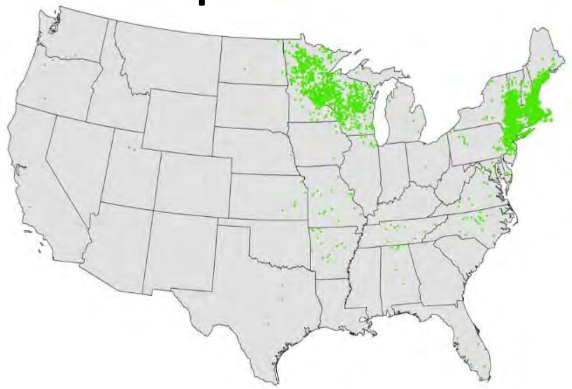
https://www.cdc.gov/ticks/geographic_distribution.html

Geographic Distribution of Nationally Notifiable Tickborne Diseases, 2015

Lyme disease



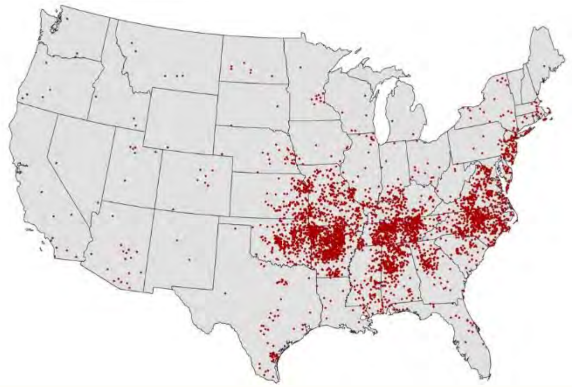
Anaplasmosis



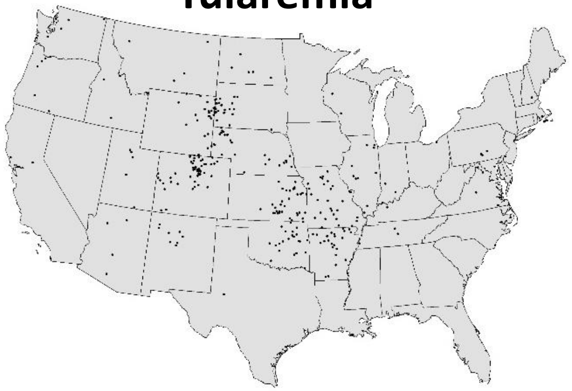
Babesiosis

Ehrlichiosis

Rocky Mountain Spotted Fever

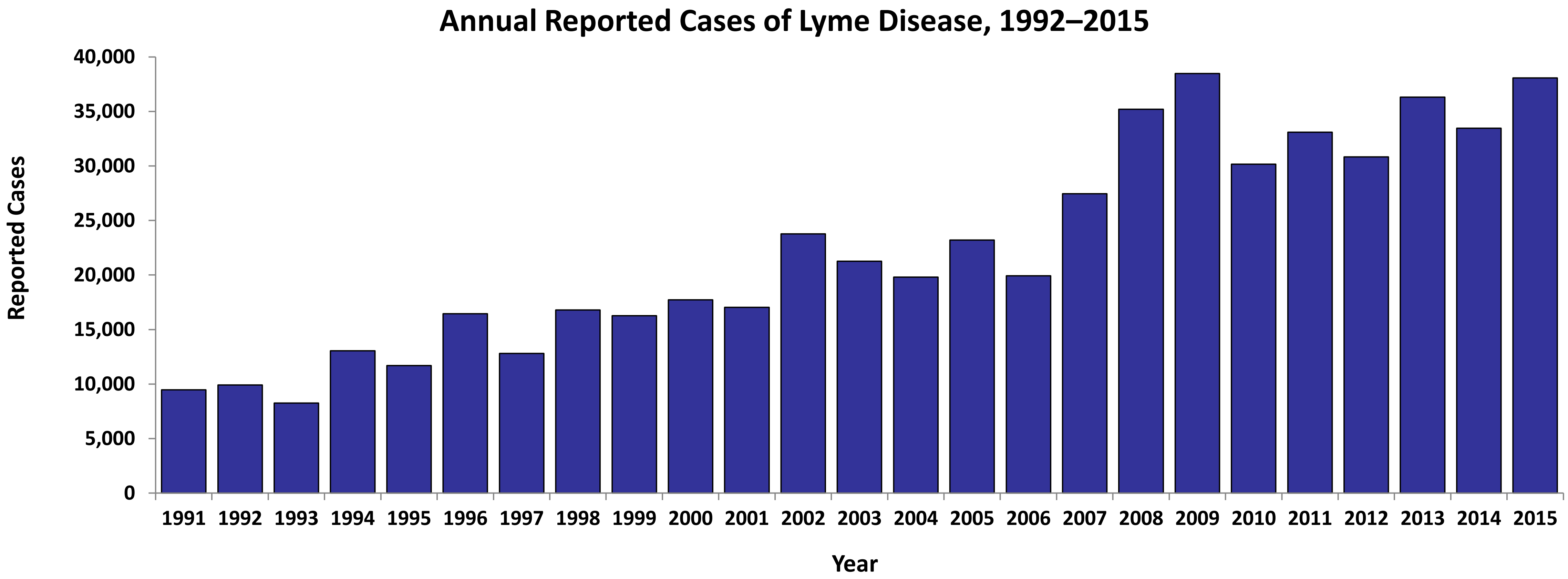


Tularemia



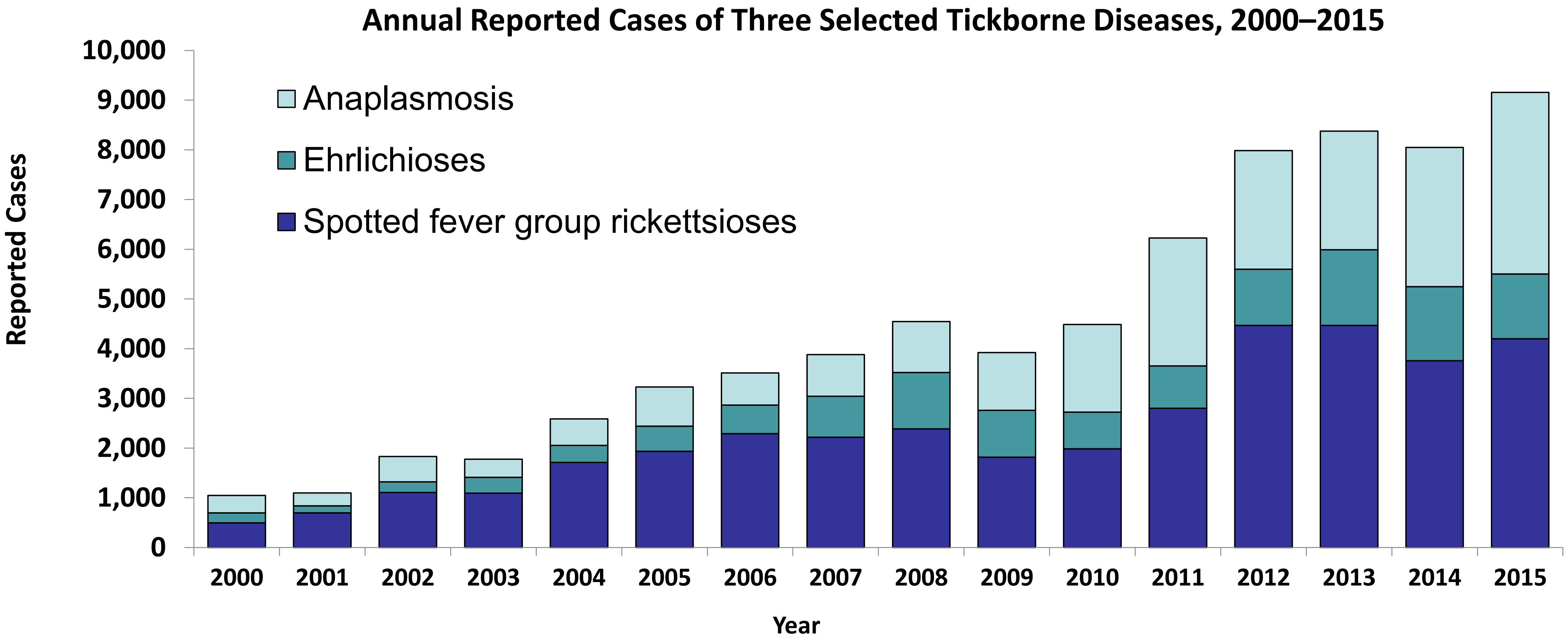
Each dot represents a reported case in the county of residence

Cases of Lyme Disease Have Increased



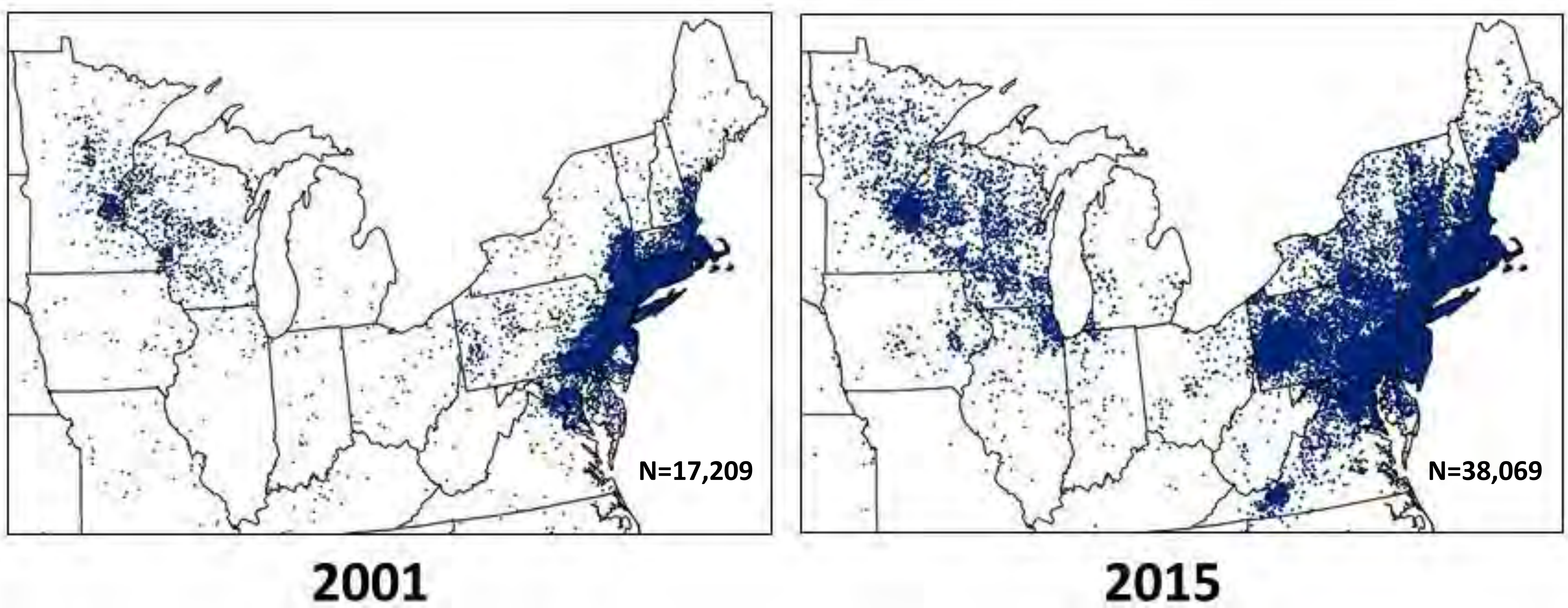
cdc.gov/mmwr/mmwr_nd/index.html
cdc.gov/mmwr/volumes/65/wr/pdfs/mm6546.pdf

Other Nationally Notifiable Tickborne Diseases Have Also Increased



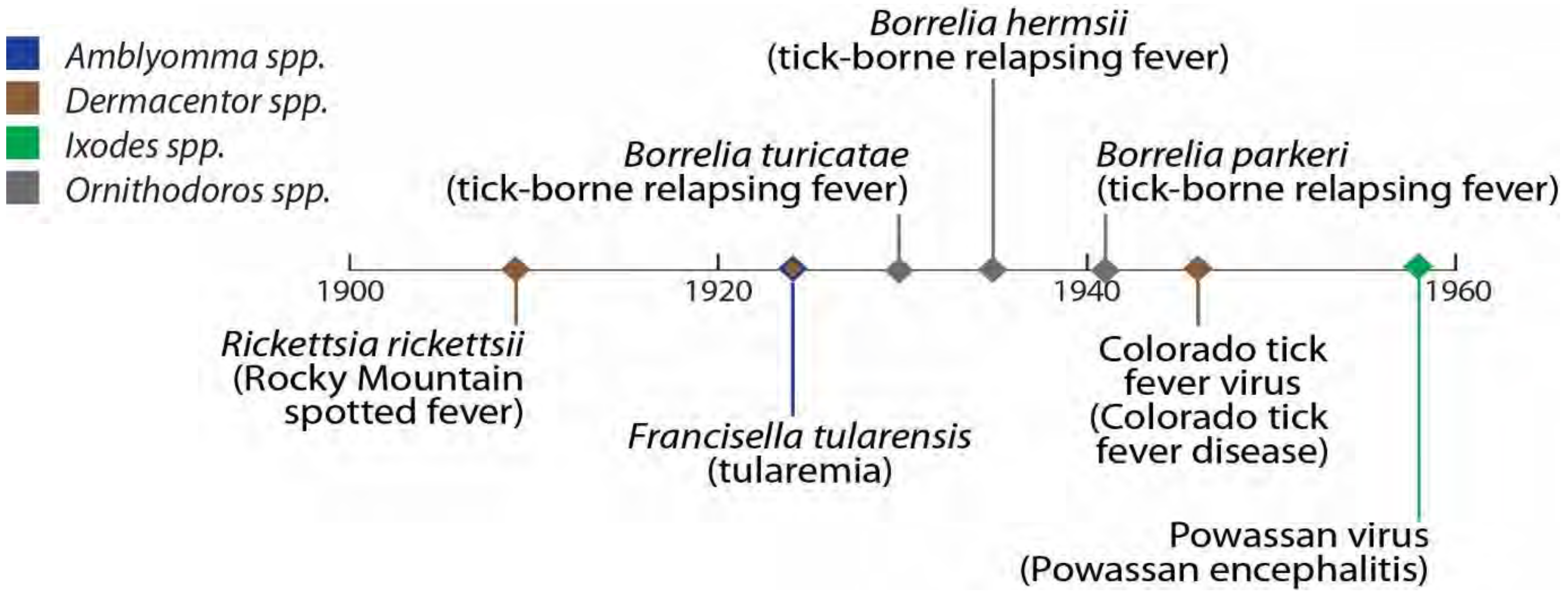
cdc.gov/mmwr/mmwr_nd/index.html
cdc.gov/mmwr/volumes/65/wr/pdfs/mm6546.pdf

Expanding Numbers and Geographic Distribution of Lyme Disease Cases Mirrors Other Tickborne Diseases



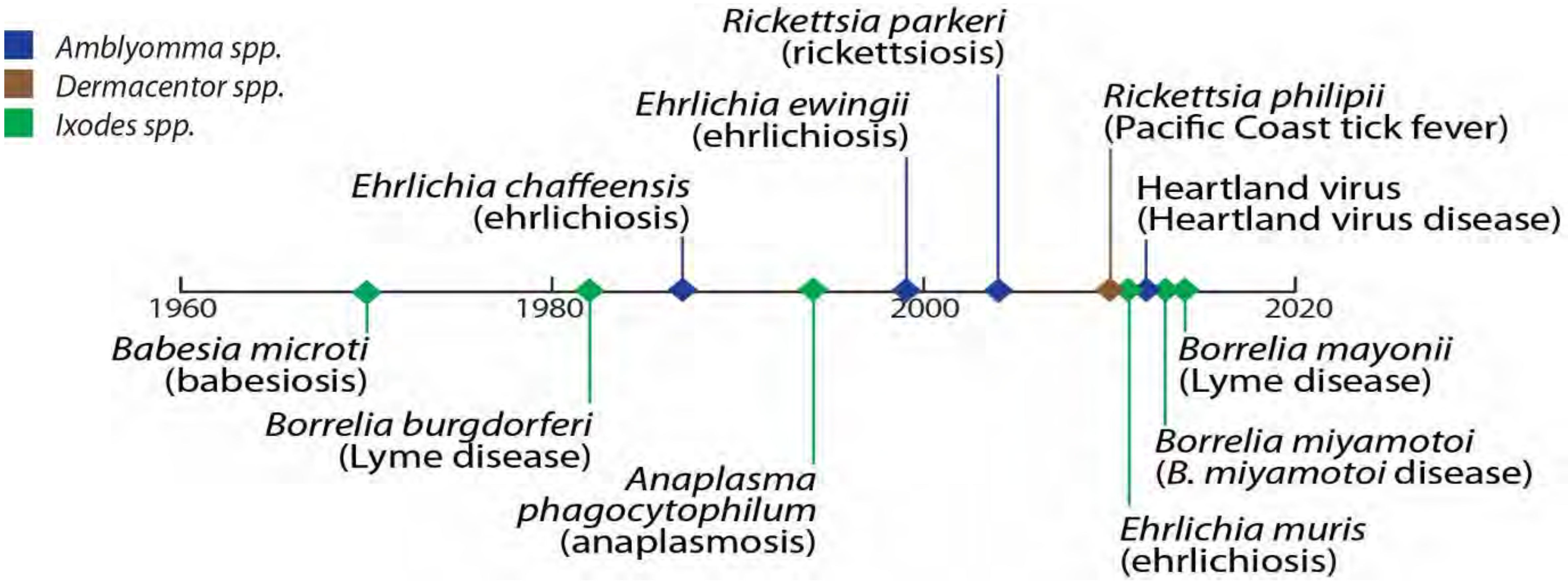
cdc.gov/lyme/stats/index.html

Discovery of Tickborne Pathogens as Causes of Human Disease By Year, 1909–1959



Year represents when tickborne pathogen was recognized as cause of human disease.
Adapted from: Paddock CD, Lane RS, Staples JE, Labruna MB. 2016. In: Mack A, Editor. Global health impacts of vector-borne diseases: workshop summary. National Academies Press. p. 221-257.

Discovery of Tickborne Pathogens Has Accelerated, 1960–2016



Year represents when tickborne pathogen was recognized as cause of human disease.

Adapted from: Paddock CD, Lane RS, Staples JE, Labruna MB. 2016. In: Mack A, Editor. Global health impacts of vector-borne diseases: workshop summary. National Academies Press. p. 221-257.

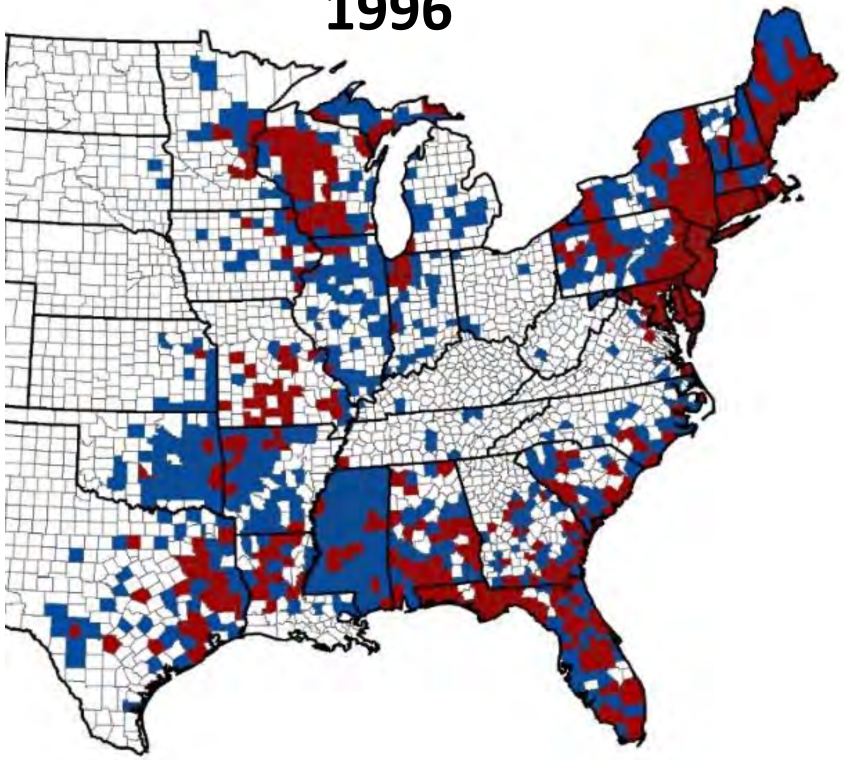
Explanation of Increasing Cases and Geographic Spread

- Improved diagnostics and clinical recognition
- Range expansion and population increases of ticks
- Lack of effective prevention strategies

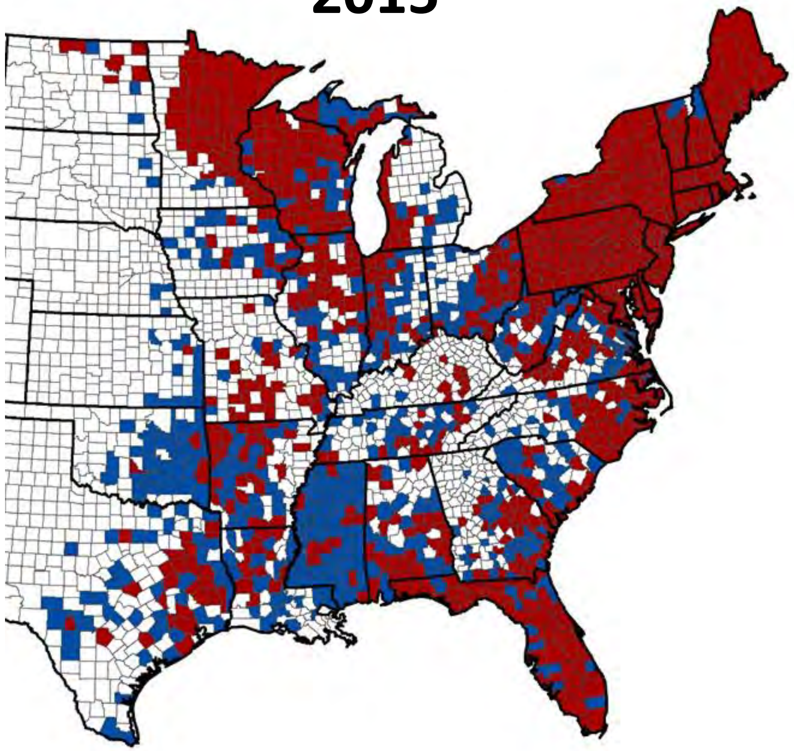
A blood-fed *Amblyomma americanum,* "Lone star tick"

Geographic Expansion of Ticks
Locations Where *Ixodes scapularis* Recorded

1996



2015



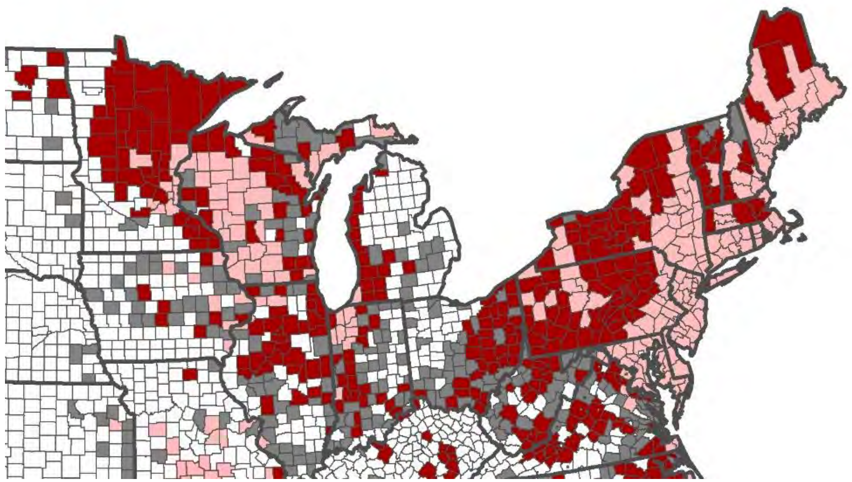
Established: >6 or more ticks or >1 life stage recorded in a single year

Reported: <6 individuals of a single life stage recorded in a single year

Dennis DT, Nekomoto TS, Victor JC, et al. J Med Entomol. 1998 Sep;35(5):629-38.
Eisen RJ, Eisen L, Beard CB. J Med Entomol. 2016 Mar;53(2):349-86.

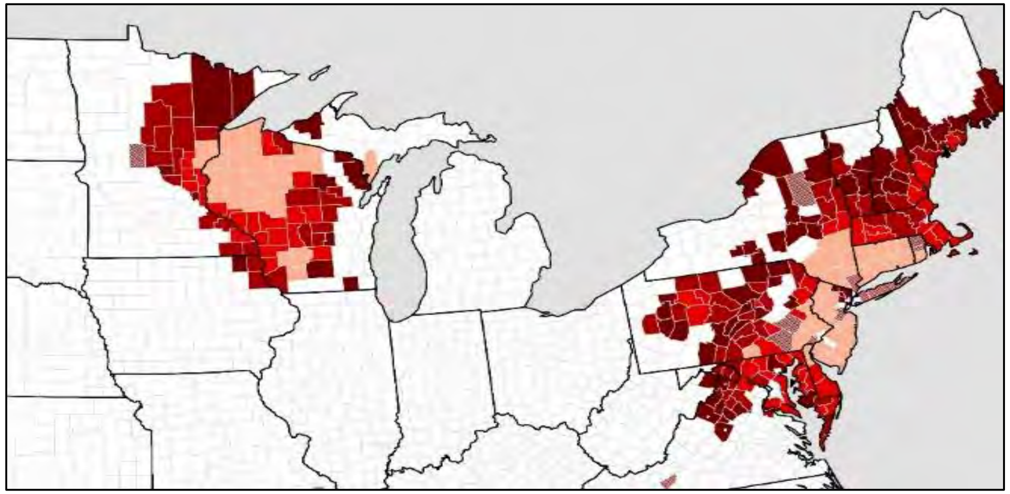
Geographic Expansion of Vectors Matches Increases in Tickborne Disease Cases

Changes in *I. scapularis* distribution, 1996–2015



Established as of 1996
Reported as of 2015
Established as of 2015

Time Period When County First Reached High Incidence of Lyme Disease



1993–1997
2003–2007
1998–2002
2008–2012

Established defined as: 6 or more ticks; or 1 or more; Reported defined as: 6 or more ticks or >1 life stage recorded in a single year

Adapted from: Eisen RJ, Eisen L, Beard CB. *J Med Entomol.* 2016 Mar;53(2):349-86.

Kugeler KJ, Farley GM, Forrester JD, et al. *Emerg Infect Dis*. 2015 Aug;21(8):1455-7.

Prevention in the Absence of Vaccines

- **Increasing human contact with ticks**
- **No human vaccines to prevent tickborne diseases in the U.S.**
  - No single effective, widely accepted method of preventing tickborne diseases
- **Prevention strategies include**
  - Personal protection
  - Environmental modification
  - Tick suppression

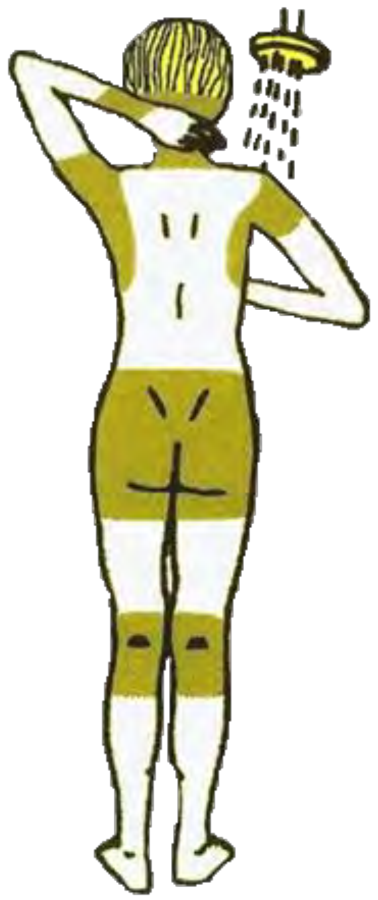
Prevention Through Personal Protection

- **Avoid tick habitat**
- **Repel ticks**
  - Use 20–30% DEET on exposed skin and clothing
  - Wear permethrin-treated clothing

cdc.gov/ticks/avoid/on_people.html
Eisen L, Dolan MC. *J Med Entomol*. 2016 Jul 20.

Prevention Through Personal Protection

- **Find and remove ticks from your body**
  - Bathe or shower as soon as possible after coming indoors
  - Every day check for and remove ticks on body, pets and outdoor gear
- **Tumble dry clothing**
  - Tumble dry clothes in a dryer on high heat for 10 minutes
  - If the clothes are damp, additional time may be needed
  - If the clothes require washing first, use hot water
    - Cold and medium temperature water will not kill ticks effectively



cdc.gov/ticks/avoid/on_people.html
Eisen L, Dolan MC. *J Med Entomol*. 2016 Jul 20.

Prevention Through Environmental Modification and Tick Suppression

- **Reduce the numbers of host-seeking ticks**
  - Landscape management
  - Kill host-seeking ticks with acaricides or biological agents

Acaricide Treatment of Vegetation

Eisen L, Dolan MC. *J Med Entomol*. 2016 Jul 20.

Prevention Through Environmental Modification and Tick Suppression

- **Host reduction or exclusion**
  - Install deer-proof fencing
- **Reduce the numbers of ticks on hosts**
  - Acaricide treatment of rodents or deer

Acaricide Treatment Station for Deer

As deer feed, a pesticide (acaricide) is applied topically.

Eisen L, Dolan MC. *J Med Entomol*. 2016 Jul 20.

Emerging Prevention Strategies

- Reduce the number of infected hosts
- Rodent-targeted methods to reduce infection in ticks
  - Vaccines
  - Antibiotics

Bait Box for Rodents

Attracted by the bait inside, rodents enter. Once inside, the rodent consumes the bait containing an oral vaccine or antibiotic.

Eisen L, Dolan MC. *J Med Entomol*. 2016 Jul 20.

Looking Forward

- **Recognition of more tickborne diseases and tickborne agents**

Looking Forward

- Recognition of more tickborne diseases and tickborne agents
- Continuing range expansion of ticks and associated tickborne diseases

Looking Forward

- **Recognition of more tickborne diseases and tickborne agents**
- **Continuing range expansion of ticks and associated tickborne diseases**
- **Importance of co-infections**
  - Single species can carry multiple disease agents

Looking Forward

- **Recognition of more tickborne diseases and tickborne agents**
- **Continuing range expansion of ticks and associated tickborne diseases**
- **Importance of co-infections**
  - Single species can carry multiple disease agents
- **Need for effective, widely-acceptable approaches to prevent tickborne diseases**

Tickborne Spotted Fevers – Old and New

Christopher D. Paddock, MD

Medical Officer, Rickettsial Zoonoses Branch

Division of Vector-Borne Diseases

National Center for Emerging and Zoonotic Infectious Diseases

A Long Time Ago, in A Valley Far, Far Away…

Image courtesy of Pete Ramberg

Rocky Mountain Spotted Fever
The First Recognized Tickborne Disease of Humans in the U.S.

Early RMSF patient with "spotted" rash

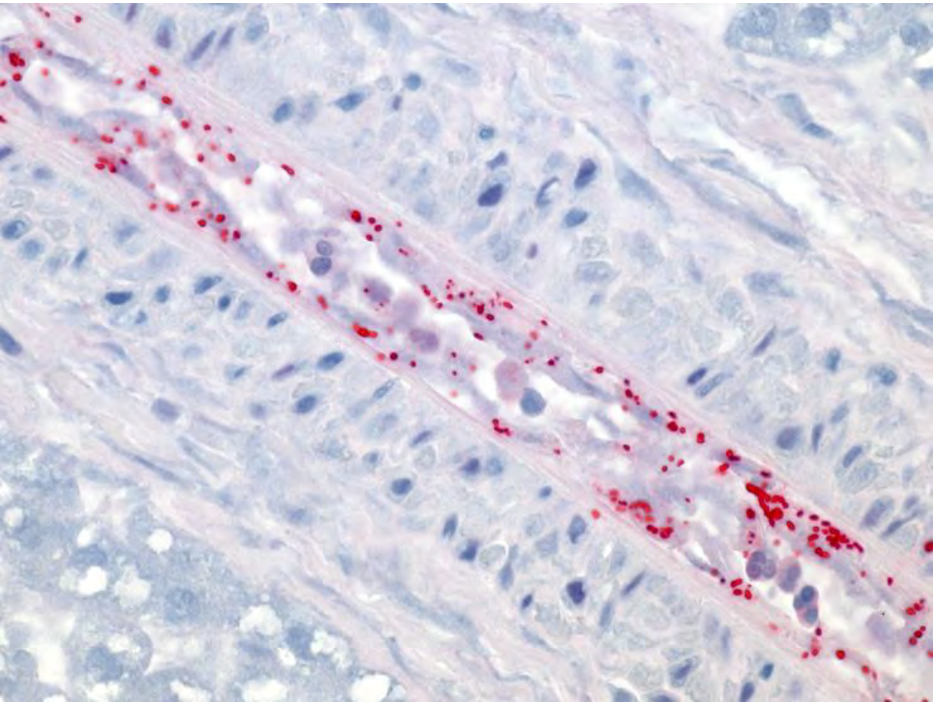
Years	Cases	Deaths	CFR
1880–1889	19	15	**79%**
1890–1899	99	70	**71%**
1900–1909	225	128	**57%**
1880–1909	343	213	**62%**

***Dermacentor andersoni*,**
the Rocky Mountain wood tick

CFR: Case fatality rate
RMSF:Rocky Mountain spotted fever

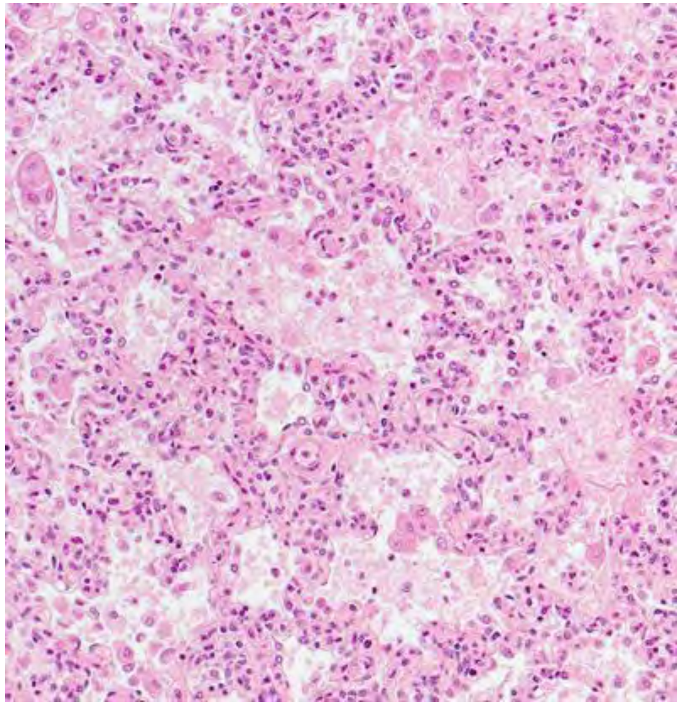
Philip RN. 2000. Rocky Mountain spotted fever in Western Montana. Anatomy of a Pestilence. Bitter Root Valley Historical Society, Hamilton, MT.

Why is Rocky Mountain Spotted Fever So Deadly?



Rickettsia rickettsii bacteria infecting endothelial cells of small blood vessel

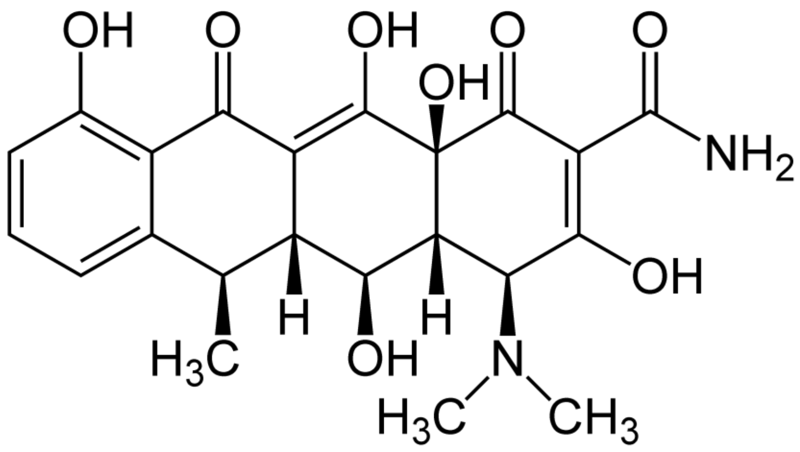
Petechial rash involving sole



Histologic section of lung from patient with fatal RMSF

The Favorable Impact of Doxycycline Therapy on Survival

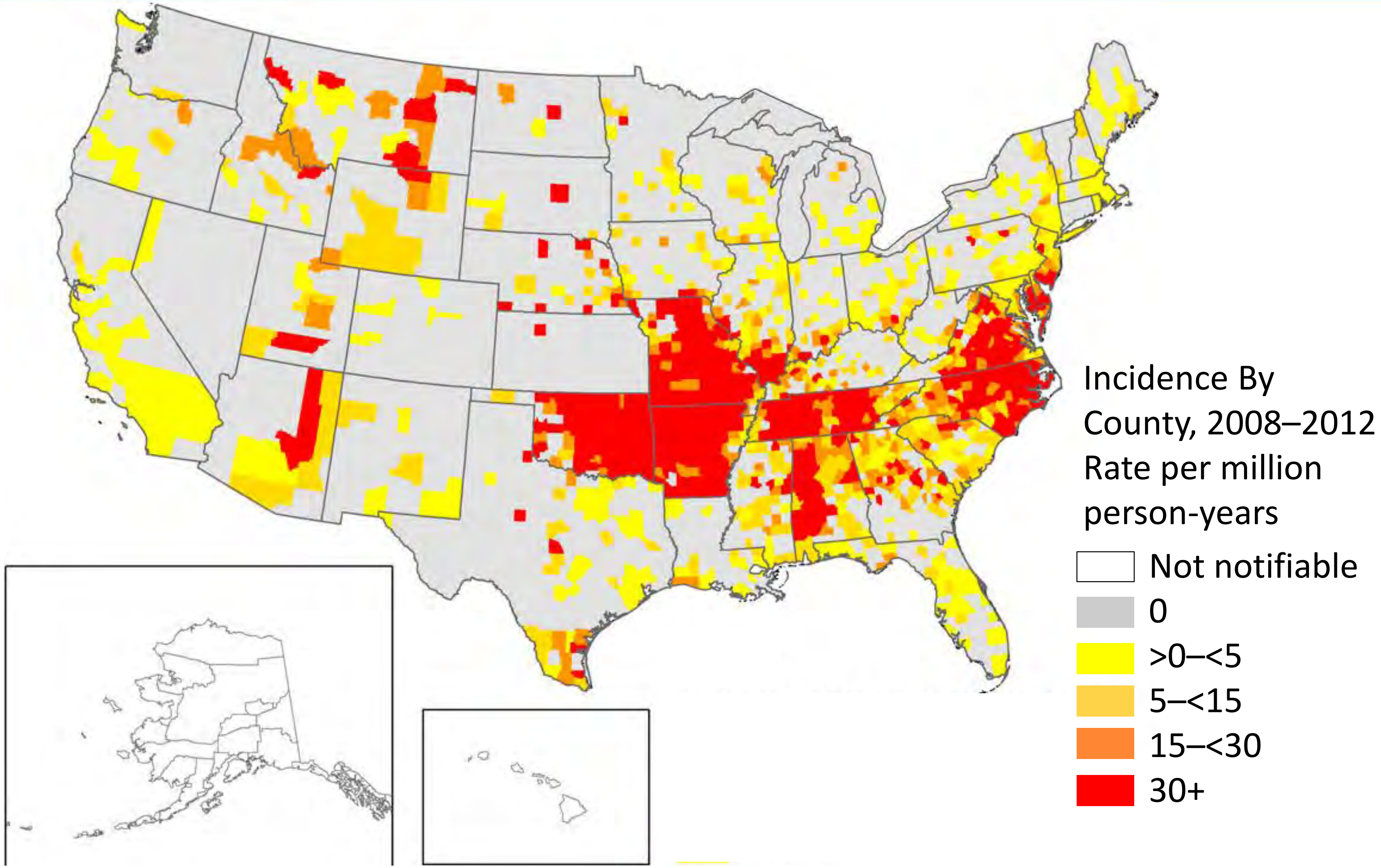
- **Discovery of tetracycline-class drugs resulted in dramatic reduction in case-fatality rates**
- **Doxycycline is the drug of choice for patients of all ages with RMSF and other tickborne rickettsial diseases**
- **Doxycycline should be initiated immediately if RMSF is suspected**
  - Delay of therapy (> 5 days) is the most important predictor of fatal outcome



Doxycycline

RMSF: Rocky Mountain spotted fever

Incidence of Spotted Fever Group Rickettsioses (including RMSF) in the United States, 2008–2012



***Dermacentor variabilis*, the American dog tick**

Drexler NA, Dahlgren FS, Heitman KN, et al. *Am J Trop Med Hyg*. 2016 Jan;94(1):26-34.

The Brown Dog Tick Emerges as an Unexpected Vector of Rocky Mountain Spotted Fever (RMSF) in Arizona

Rhipicephalus sanguineus, the brown dog tick

- Not considered important in the epidemiology of RMSF in the U.S. until 2004
- Cause of epidemic levels of RMSF in several American Indian communities in Arizona
- Outbreaks precipitated by large populations of free-roaming, tick-infested dogs

Demma LJ, Traeger MS, Nicholson WL, et al. N Engl J Med. 2005 Aug 11;353(6):587-94.

Community-Based Intervention Successfully Reduces the Number of Ticks and Cases of RMSF

- **Collaborative endeavor among tribal partners, IHS, private sector, Arizona DOH, USDA, Inter Tribal Council of Arizona, and CDC**
  - Yards treated with acaricide spray
  - Tick collars placed on dogs
- **Dramatic reduction in ticks on dogs and in the environment**
  - Ticks found on <1% of treated dogs vs. 64% of untreated dogs
- **43% reduction in cases of RMSF**

Placing tick collars on dogs

IHS: Indian Health Service
USDA: United States Department of Agriculture
Drexler N, Miller M, Gerding J, et al. *PLoS One*. 2014 Dec 5;9(12):e112368.

DHS: Department of Health Services
RMSF: Rocky Mountain spotted fever

A Second Pathogen Emerges from the Past

1939

OBSERVATIONS ON AN INFECTIOUS AGENT FROM *AMBLYOMMA MACULATUM*[1]

By R. R. PARKER, *Director, Rocky Mountain Laboratory*, GLEN M. KOHLS, *Assistant Entomologist, United States Public Health Service*, GEORGE W. COX, *Executive Officer, Texas State Department of Public Health*, and GORDON E. DAVIS, *Bacteriologist, United States Public Health Service*

Amblyomma maculatum,
the Gulf Coast tick

2004

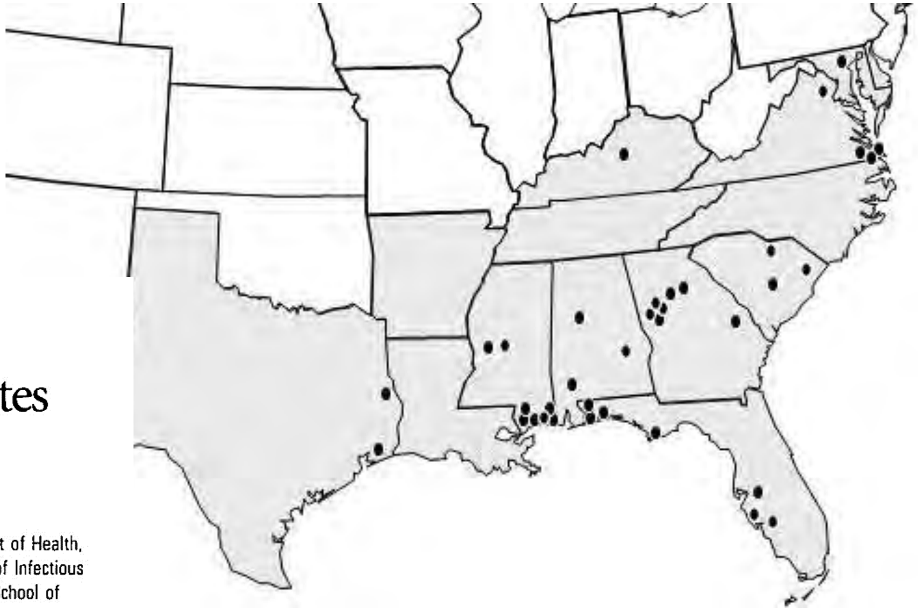
Rickettsia parkeri: A Newly Recognized Cause of Spotted Fever Rickettsiosis in the United States

Christopher D. Paddock,[1] John W. Sumner,[1] James A. Comer,[1] Sherif R. Zaki,[1] Cynthia S. Goldsmith,[1] Jerome Goddard,[2] Susan L. F. McLellan,[3] Cynthia L. Tamminga,[4] and Christopher A. Ohl[4,5]

[1]Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Mississippi Department of Health, Jackson, Mississippi; [3]Infectious Diseases Section, Tulane University Health Sciences Center, New Orleans, Louisiana, [4]Division of Infectious Diseases, Portsmouth Naval Medical Center, Portsmouth, Virginia; and [5]Section on Infectious Diseases, Wake Forest University School of Medicine, Winston-Salem, North Carolina

(See the editorial commentary by Raoult on pages 812–3)

2014



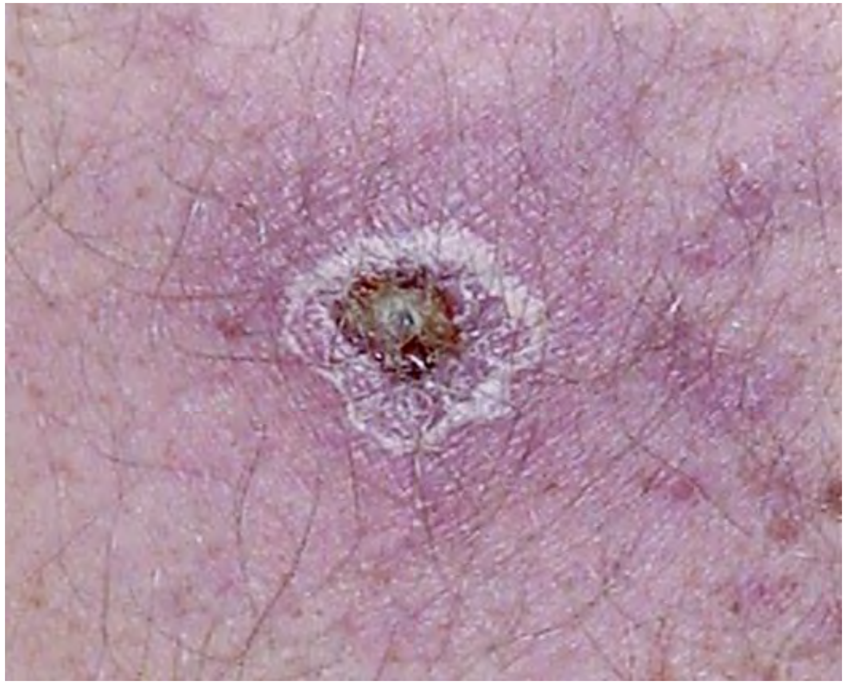
Parker RR, et al. *Pub Hlth Rep* 1939;54:1482–4.
Paddock CD, Sumner JW, Comer JA, et al. *Clin Infect Dis.* 2004 Mar 15;38(6):805-11.

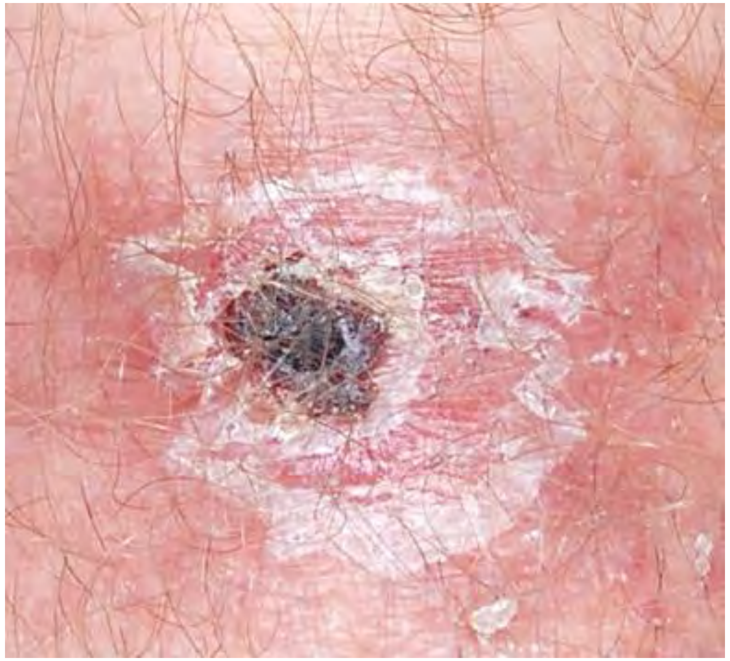
Rashes of Rocky Mountain Spotted Fever (RMSF) versus *Rickettsia parkeri* rickettsiosis

RMSF

R. parkeri rickettsiosis

Distinctive Eschars of *Rickettsia parkeri* Rickettsiosis





Paddock CD, Sumner JW, Comer JA, et al. *Clin Infect Dis.* 2004 Mar 15;38(6):805-11.
Cragun WC, Bartlett BL, Ellis MW, et al. *Arch Dermatol*. 2010 Jun;146(6):641-8.

RMSF versus *Rickettsia parkeri* rickettsiosis

Clinical Feature	RMSF (n = 398)	*R. parkeri* rickettsiosis (n = 21)
Fever	99%	100%
Headache	80%	86%
Any rash	92%	90%
Petechial rash	52%	14%
Pustular/vesicular rash	---	33%
Eschar	---	95%
Nausea/vomiting	66%	10%
Coma/seizure	27%	---
Death	8%	---

Paddock CD, Finley RW, Wright CS, et al. *Clin Infect Dis.* 2008 Nov 1;47(9):1188-96.
Cragun WC, Bartlett BL, Ellis MW, et al. *Arch Dermatol*. 2010 Jun;146(6):641-8.
Myers T, Lalani T, Dent M, et al. *Emerg Infect Dis.* 2013 May;19(5):778-80.
Ekenna O, Paddock CD, Goddard J. *J Miss State Med Assoc*. 2014 Jul;55(7):216-9.

Rickettsia parkeri rickettsioisis: How Much is Out There?

- 5 cases identified by one clinician in Mississippi during 2007–2012

- 5 cases identified at one urgent care practice in Georgia during 2012–2014

Morbidity and Mortality Weekly Report

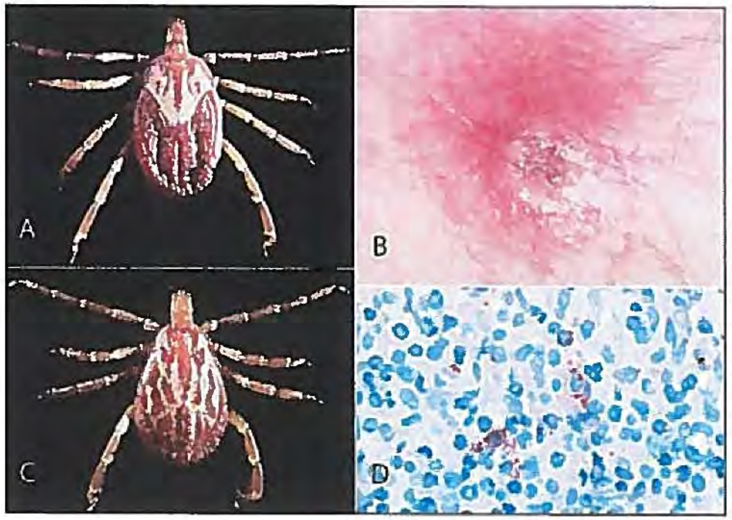
Notes from the Field

Rickettsia parkeri Rickettsiosis — Georgia, 2012–2014

Anne Straily, DVM[1,2]; Amanda Feldpausch, MPH[3]; Carl Ulbrich, DO[4]; Kiersten Schell[4]; Shannon Casillas, MPH[3]; Sherif R. Zaki, MD, PhD[5]; Amy M. Denison, PhD[5]; Marah Condit, MS[2]; Julie Gabel, DVM[3]; Christopher D. Paddock, MD[2]

During 2012–2014, five cases of *Rickettsia parkeri* rickett sis were identified by a single urgent care practice in Ge gia, located approximately 40 miles southwest of Atlanta. Symp m onset occurred during June–October, and all patients had a known tick bite. Patients ranged in age from 27 to 7_ years (median = 53 years), and all were male. The most commonly reported initial signs were erythema (n = 3) and swelling (n = 2) at the site of the bite. Two patients reported fever and a third patient reported a rash and lymphadenopathy without fever. Other symptoms included myalgia (n = 3), chills (n = 3), fatigue (n = 2), arthralgia (n = 2), and headache (n = 2). Eschar biopsy specimens were collected from each patient using a 4-mm or 5-mm punch and placed in 10% neutral buffered formalin or

FIGURE. Female (A) and male (C) Gulf Coast ticks (*Amblyomma maculatum*); (B) necrotic, ulcerated or scabbed lesion at the tick bite site, known as an inoculation eschar; and (D) immunohistochemical stain indicating the presence of a spotted fever group *Rickettsia* species in the tissue



Ekenna O, Paddock CD, Goddard J. *J Miss State Med Assoc*. 2014 Jul;55(7):216-9.
Straily A, Feldpausch A, Ulbrich C, et al. *MMWR Morb Mortal Wkly Rep.* 2016;65:718–719.

Percentage of Ticks Infected with *R. parkeri* Greater than Percentage of Ticks Infected with *R. rickettsii*

Frequency of *R. rickettsii* in *D. variabilis* vs. *R. parkeri* in *A. maculatum*

Dermacentor variabilis

Amblyomma maculatum

Pathogen	Location, years	No. (% infected)
R. rickettsii	North Carolina, 1982	2,123 (0.05)
	Ohio, 1984–1989	12,631 (0.06)
	Maryland, 2002	392 (0)
	Tennessee, 2007–2008	555 (0)
R. parkeri	Florida, 2005–2007	128 (22)
	Mississippi, 2008–2012	698 (15)
	North Carolina, 2009–2010	101 (31)
	Virginia, 2010–2011	293 (53)

Paddock CD, Fournier PE, Sumner JW, et al. *Appl Environ Microbiol*. 2010 May;76(9):2689-96.
Pagac BB, Miller MK, Mazzei MC, et al. *Emerg Infect Dis.* 2014 Oct;20(10):1750-2.
Ferrari FA, Goddard J, Paddock CD, et al. *Emerg Infect Dis.* 2012 Oct;18(10):1705-7.
Varela-Stokes AS, Paddock CD, Engber B, et al. *Emerg Infect Dis*. 2011 Dec;17(12):2350-3.
Nadolny RM, Wright CL, Sonenshine DE, et al. *Ticks Tick Borne Dis.* 2014 Feb;5(1):53-7.

Conclusions

- **Etiologic spectrum of tickborne rickettsioses in the U.S. has expanded during the past 15 years**

- **Rocky Mountain spotted fever and *R. parkeri* rickettsiosis share many clinical features but differ considerably in severity**

- **Doxycycline is the drug of choice for all tickborne rickettsioses and in patients of all ages**
  - Therapy should be initiated immediately, based on a presumptive diagnosis

Biggs HM, Behravesh CB, Bradley KK, et al. *MMWR Recomm Rep.* 2016 May 13;65(2):1-44.

Tickborne Viruses: Emerging Public Health Concern

Gregory D. Ebel, ScD

Associate Professor and Director

Arthropod-borne and Infectious Diseases Laboratories

Colorado State University

Worldwide Ticks Are Vectors For Diverse Array of Viral Pathogens and Diseases

Disease and Etiologic Agent	Signs and Symptoms	Geographic Location
Colorado Tick Fever Colorado Tick Fever	Flu-like symptoms (FLS), headache, rash	Western U.S.
Crimean-Congo Hemorrhagic Fever CCHF virus	FLS, hemorrhagic fever (HF)	Asia, Africa, and Europe
Omsk Hemorrhagic Fever Omsk hemorrhagic fever virus	FLS, HF	Southwestern Russia
Kyasanur Forest Disease Kyasanur forest disease virus	FLS, HF	Southern India, Saudi Arabia (aka Alkhurma disease in Saudi Arabia)
Tick-Borne Encephalitis Tick-borne encephalitis virus	FLS, encephalitis, HF	Temperate regions of Europe and northern Asia

Ticks Are Highly Efficient Vectors

- **Abundance**
  - One fully engorged female *Ixodid* yields several thousand offspring
- **Host preference**
  - At least two stages of feeding (usually larvae and nymphs) on the same host

A female *Ixodes scapularis* (Blacklegged tick) engorged with a host blood meal

Ticks Are Highly Efficient Vectors

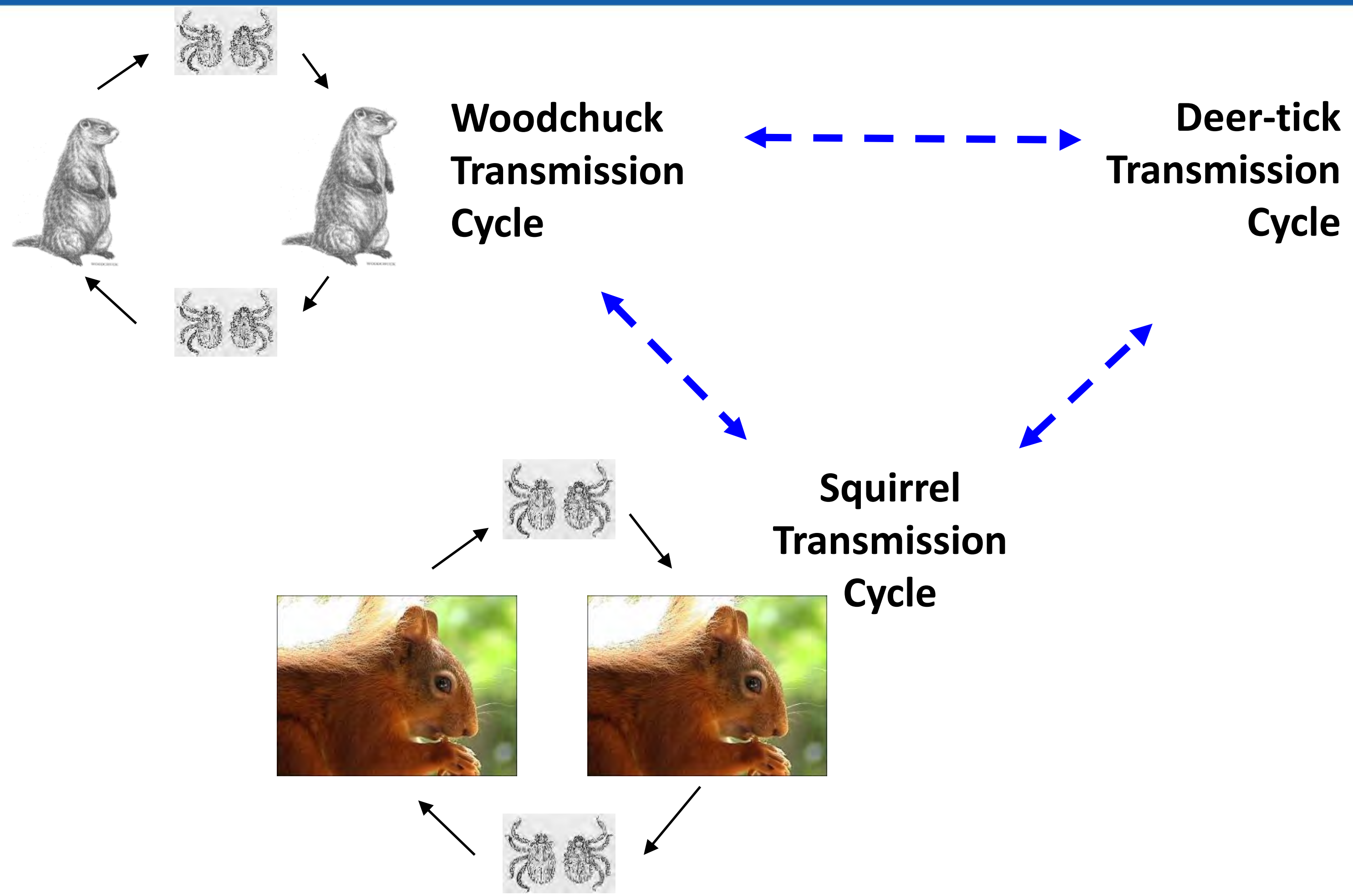
- **Longevity of ticks**
  - Once infected with a pathogen, ticks are likely to survive and to transmit pathogen to new host
    - Survival of pathogen's extrinsic incubation period
- **Modification of the site of attachment**
  - Pharmacology of tick saliva
- **Favorable gut environment**
  - Intracellular digestion of bloodmeal

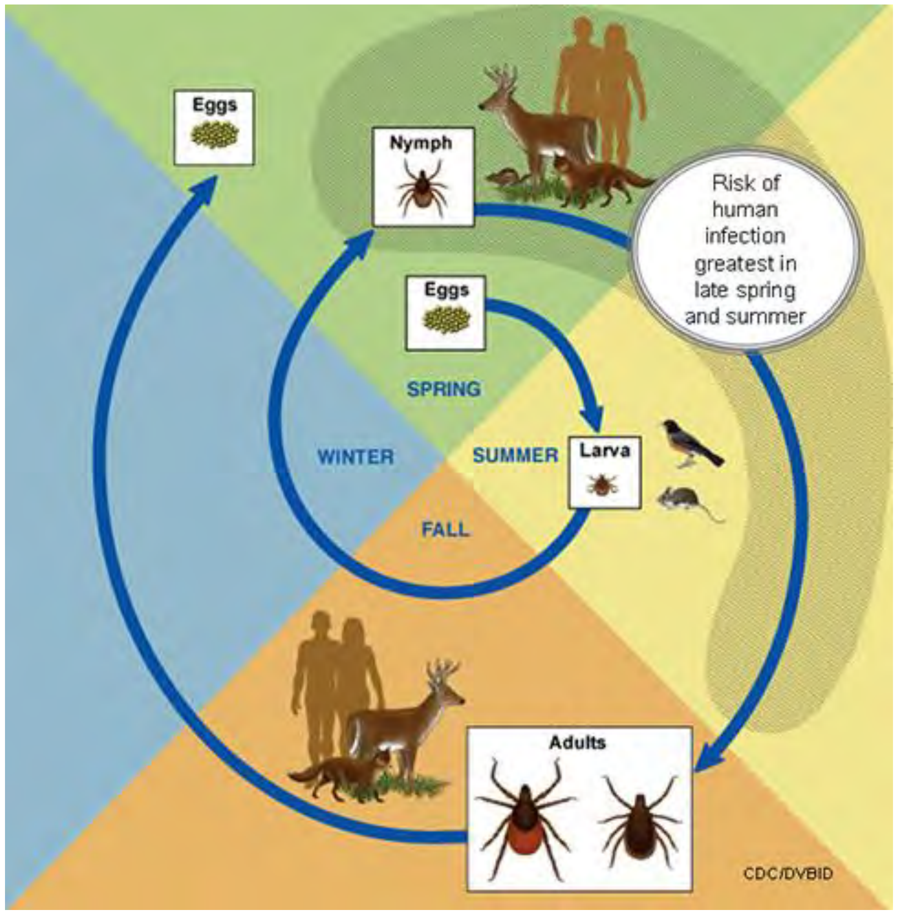
Emerging Tickborne Viruses in the United States

- **Powassan virus (*Flaviviridae: Flavivirus*)**
  - Isolated 1958, Powassan, Ontario
- **Sole North American representative of the tickborne encephalitis complex of the Flaviviruses**
- **Severe acute disease**
  - 10.5% case-fatality rate
- **Long-term sequelae**
  - 47% of cases experience hemiplegia, wasting, severe headaches, etc.
- **Transmission depends on ecological factors that are not well understood**

Artsob H. Powassan encephalitis. In: Monath T, ed. *The arboviruses: epidemiology and ecology. Volume IV.* Boca Raton, FL: CRC Press, 1988:29–49.
McLean DM, Donohue WL. *Can Med Assoc J.* 1959 May 1;80(9):708-11.

Diverse Vectors and Transmission Cycles Maintain Powassan Virus

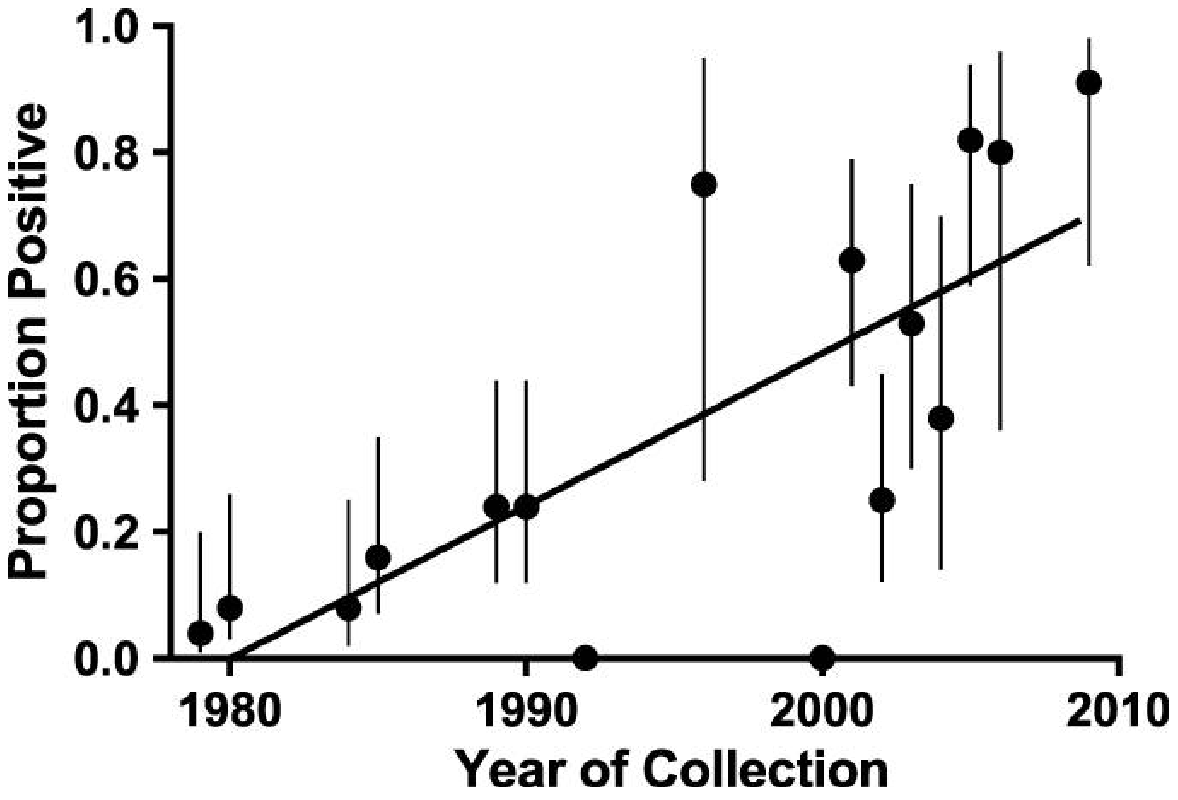




Deer tick-associated viruses appear to pose greatest public health risk

Infection Among Deer Is Increasing

Serological Prevalence of POWV in Hunter-killed Deer, 1979–2010



POWV: Powassan virus

Nofchissey RA, Deardorff ER, Blevins TM, et al. *Am J Trop Med Hyg*. 2013 Jun;88(6):1159-62.

Clinical Features of Powassan Virus Disease Consistent Through Time

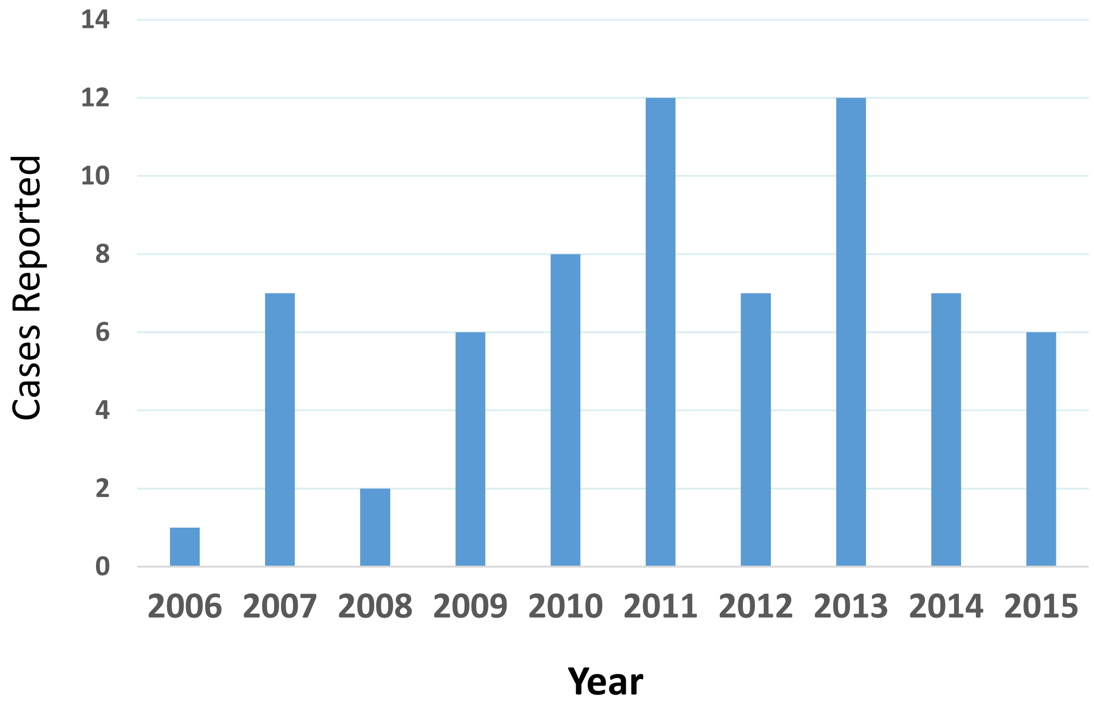
Demographic, Clinical Features and Outcomes of 8 Patients with Powassan Virus Encephalitis, 2013–2015

Patient Age and Gender	Exposure	Fever	Rash	Gastro-intestinal	Outcome
82 M	Outdoors	Y	N	Vomiting	Death
74 M	Outdoors, gardening	Y	N	None	Residual Deficits
21 M	Outdoors	Y	Y	Vomiting	Improved
67 M	Outdoors	Y	Y	Vomiting, diarrhea	Improved
65 F	Tick bite	Y	N	Vomiting	Improved
52 M	Tick bite	Y	N	None	Residual Deficits
49 M	Tick bite	Y	N	None	Death
44 M	Outdoors, hunting	N	Y	None	Improved

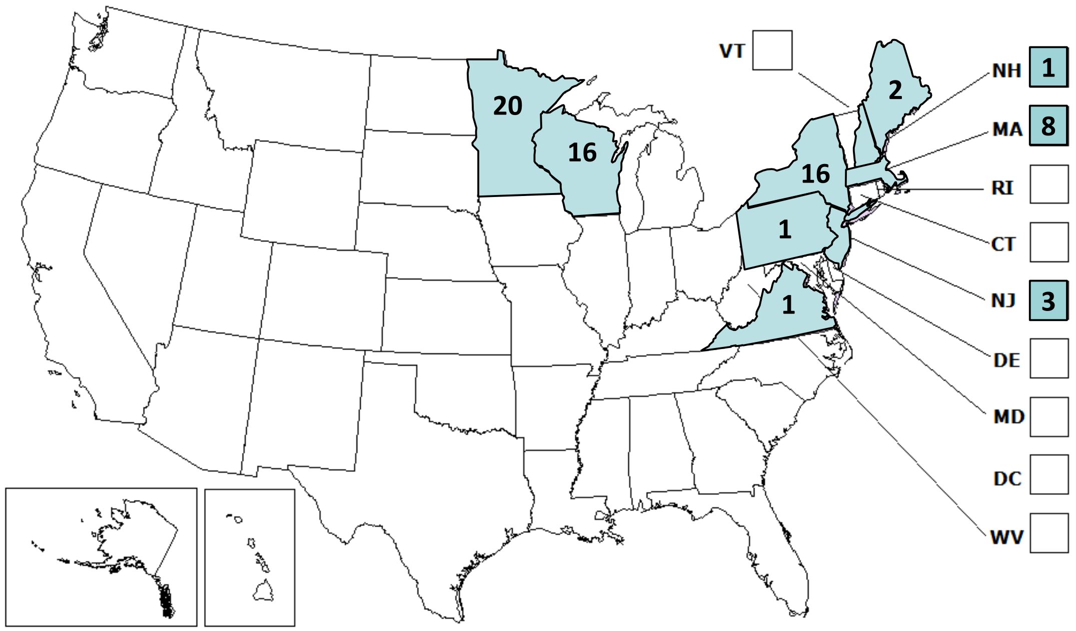
Adapted from: Piantadosi A, Rubin DB, McQuillen DP, et al. *Clin Infect Dis*. 2016 Mar 15;62(6):707-13.

Number and Geographic Distribution of Reported Powassan Virus Cases, 2006-2015

Powassan Virus Neuroinvasive Disease Cases Reported by Year, 2006–2015

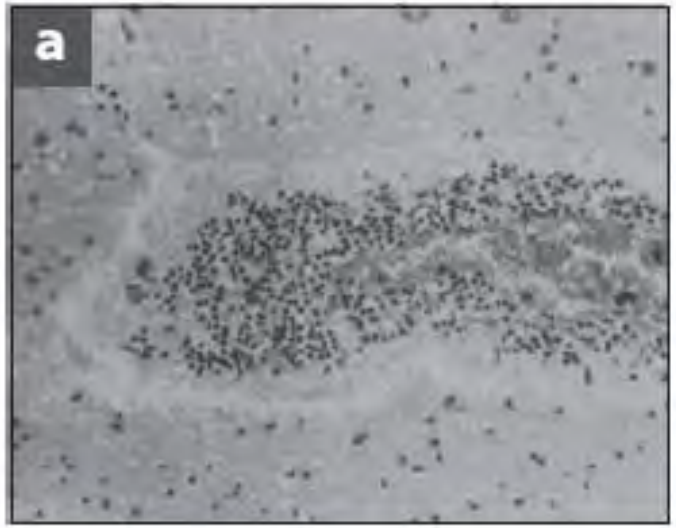


Powassan Virus Neuroinvasive Disease Cases Reported by State, 2006–2015

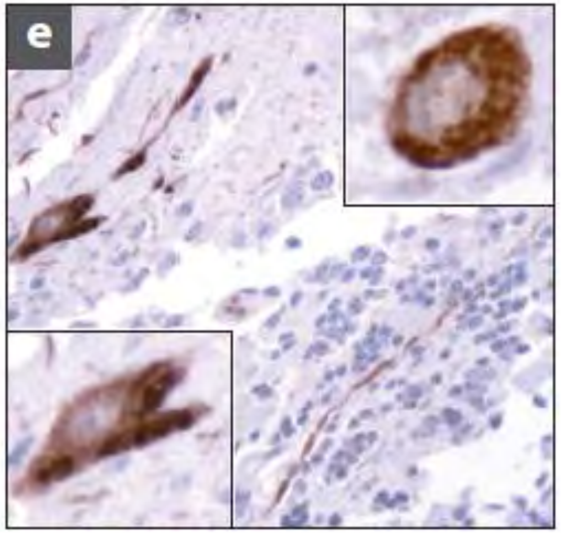


www.cdc.gov/powassan/pdf/powv-by-year_2006-2015.pdf
www.cdc.gov/powassan/pdf/powv-by-state_2006-2015.pdf

Powassan Virus Causes Neurological Damage Both Directly and via Inflammatory Processes



Inflammatory changes within the perivascular and parenchymal portions of the brain



Direct neuronal injury of the Purkinje cells

Tavakoli NP, Wang H, Dupuis M, et al. *N Engl J Med*. 2009 May 4;360(20):2099-107.

Discovery of New Tickborne Viruses Is Ongoing

- **Heartland virus (*Bunyaviridae: Phlebovirus*)**
  - First 2 cases in Missouri, 2009
  - Additional 6 confirmed cases in Tennessee and Missouri, 2012–2013
  - CDC continues to investigate additional cases
  - Few fatalities
  - Lone star tick
    - (*Amblyomma americanum*)
  - Wildlife serologic studies suggest widespread distribution of virus

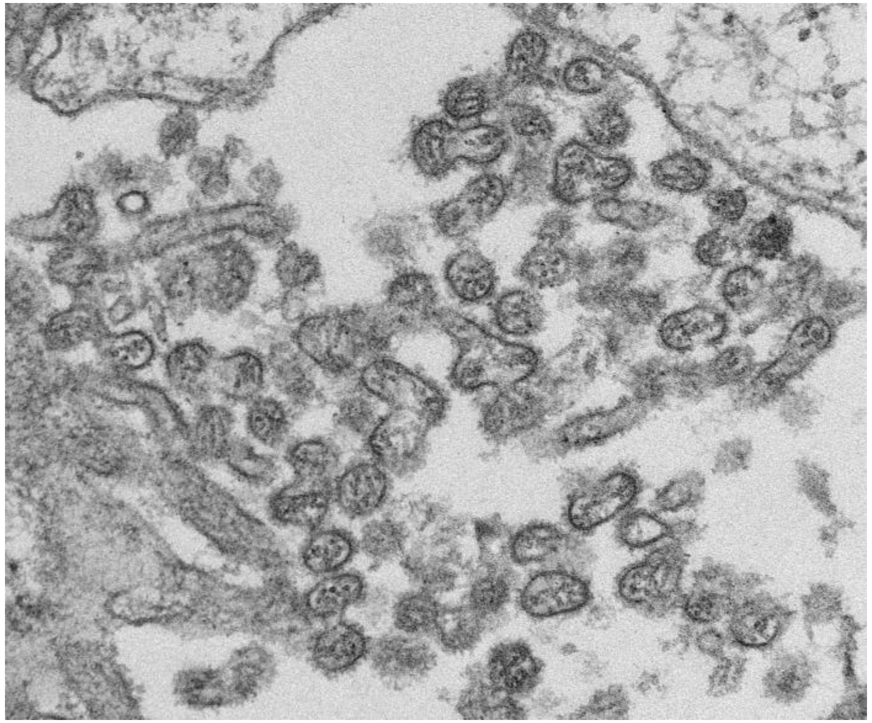
***Amblyomma americanum*, "Lone star tick"**

McMullan LK, Folk SM, Kelly AJ, et al. *N Engl J Med*. 2012 Aug 30;367(9):834-41

Pastula DM, Turabelidze G, Yates KF, et al. *MMWR Morb Mortal Wkly Rep*. 2014 Mar 28;63(12):270-1.

Discovery of Another Virus Likely to Be Tickborne

- **Bourbon virus (*Orthomyxoviridae: Thogotovirus*)**
  - First case in Kansas, 2015
  - Likely tickborne
    - *In vitro* studies support
  - Fatal outcome

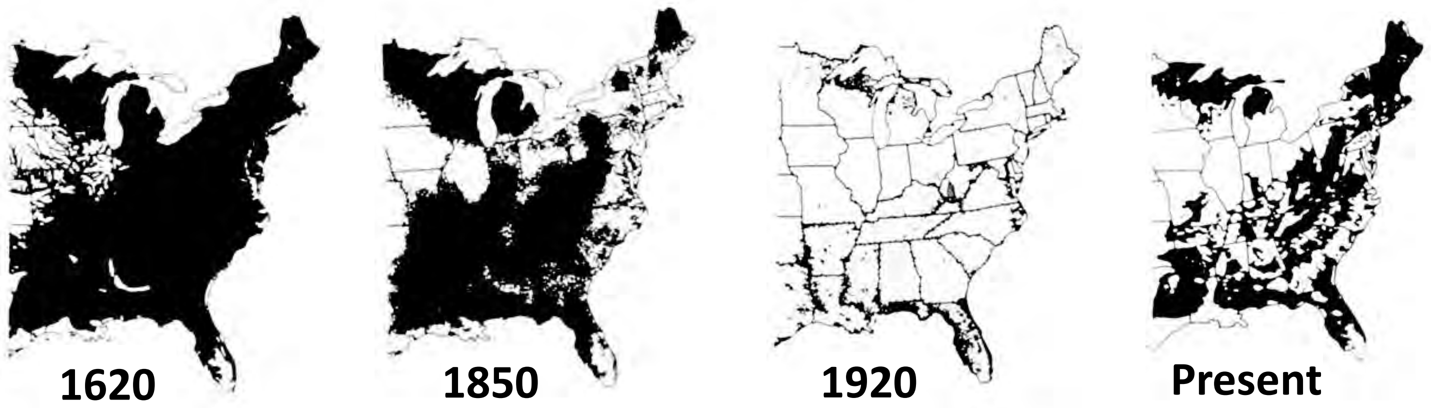


Numerous extracellular Bourbon virus virions with slices through strands of viral nucleocapsids

Kosoy OI, Lambert AJ, Hawkinson DJ, et al. *Emerg Infect Dis*. 2015 May;21(5):760-4.

Knowledge Gaps and Unmet Needs

- As new viruses emerge, so do questions and concerns
- What determines human risk and likelihood of emergence as human threat? How best to intervene?

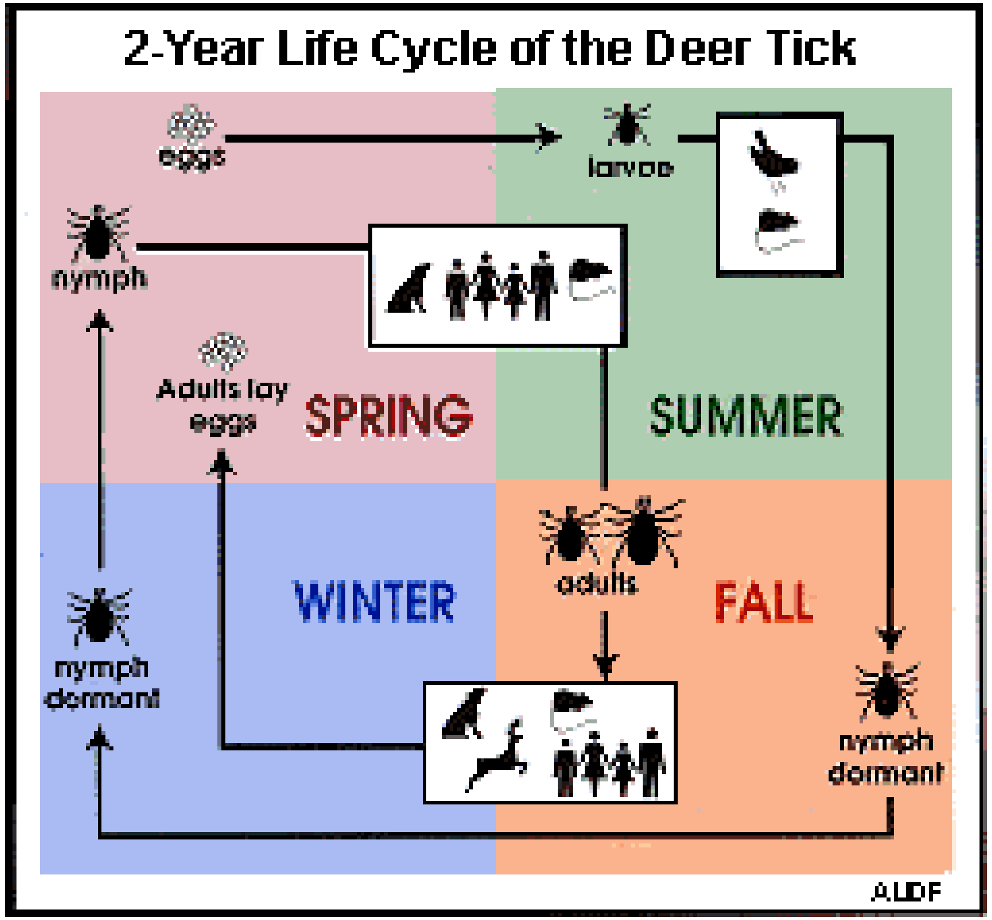


Forest cover in the U.S., East of the Mississippi, from colonization to the present

Reforestation Drives Emergence

Ecology: How Do Tickborne Arboviruses Perpetuate in Nature?

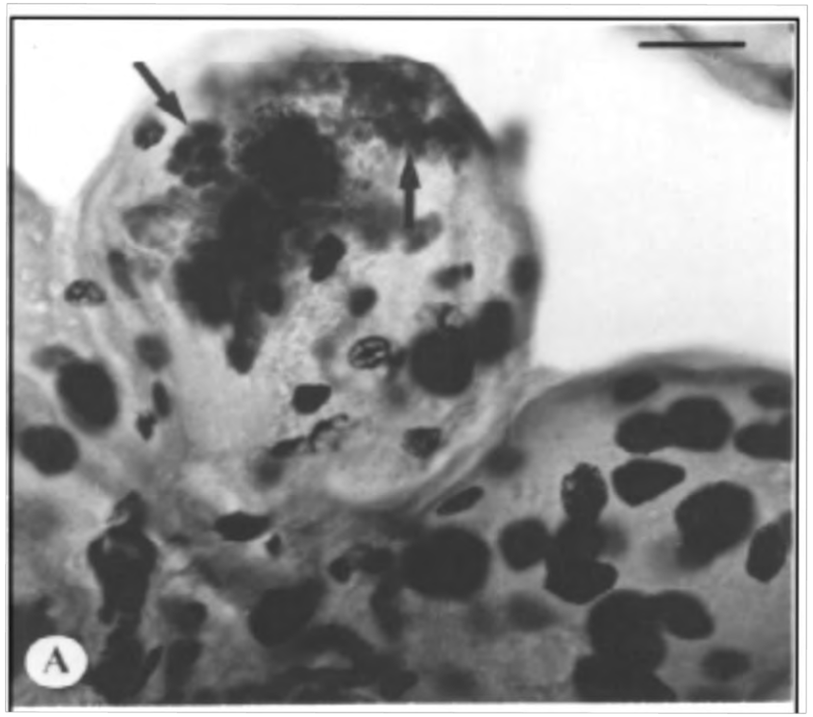
- Modeling and experimental studies show multiple transmission routes required
- Model parameters obtainable and transmission cycles can be studied
- Niche complexity



Nonaka E, Ebel GD, Wearing HJ. *PLoS One*. 2010 Jul 23;5(7):e11745.
Nuttall PA, Labuda M. *Adv Virus Res*. 2003;60:233-72.
Davis S, Bent SJ. *J Theor Biol*. 2011 Jan 21;269(1):96-103.

How Do Ticks, Hosts, and Pathogens Interact?

- **What factors influence tick vector competence at the molecular level?**
- **Most work covers tick salivary secretions**
  - Hundreds of protein and non-protein molecules
    - Affect hemostasis, inflammation, i.e., host immune response to tick feeding
    - Effect of pathogens poorly understood

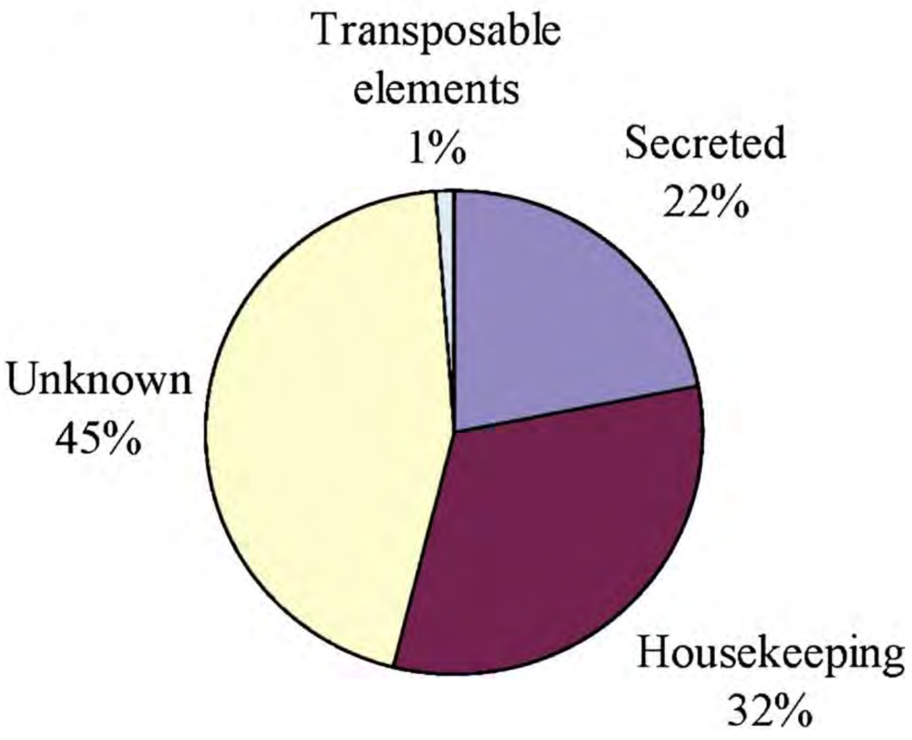


***Ehrlichia microti*. Polyhedral clusters of rickettsiae (arrows) within hypertrophied salivary acinus**

Telford SR 3rd, Armstrong PM, Katavolos P, et al. *Emerg Infect Dis.* 1997 Apr-Jun;3(2):165-70.

Figuring Out Function of Tick Genes

- **Tick genome sequence**
  - Extremely large
  - Most genes duplicated
  - Metagenomics also contributes to key phenotypes



Distribution of assembled contigs from cDNA library from the salivary glands of adult female *Hyalomma marginatum rufipes* ticks

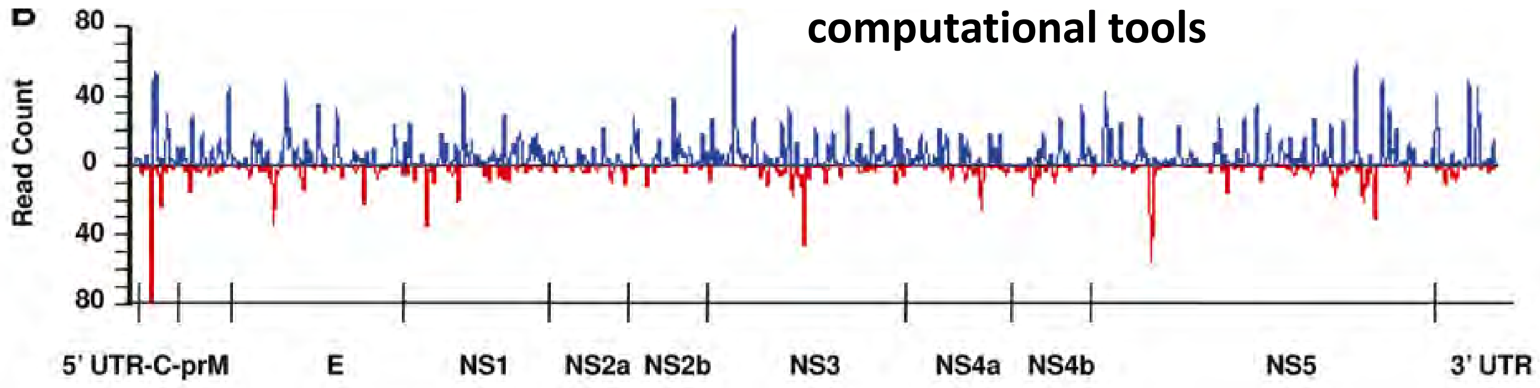
Francischetti IM, Anderson JM, Manoukis N, et al. *J Proteomics*. 2011 Nov 18;74(12):2892-908.

Exciting Time to Study Tickborne Diseases

In vitro and in vivo systems to study tick-borne viruses

Ecology of ticks and their hosts

New sequencing and computational tools



Barriers to Rapid Advances in Tickborne Virus Research

- **Technical**
  - Containment and regulatory restrictions
  - System complexity
  - Long tick life cycle
    - One tick lifecycle per grant or funding cycle
- **Environmental**
  - Tickborne viruses emerge slowly relative to mosquito-borne viruses
  - Significance, impact, innovation
- **Few researchers active**

Note tick in tweezers

Summary

- Tick borne viruses are emerging health concerns
- Interesting, relevant and feasible questions present opportunities to the field
- Difficult technical and environmental barriers currently impede progress

Advances in Diagnosing Tickborne Diseases

Bobbi S. Pritt, MD, MSc, DTM&H

Director, Clinical Parasitology Laboratory

Co-Director, Vector-borne Diseases Laboratory Services

Professor of Pathology and Laboratory Medicine

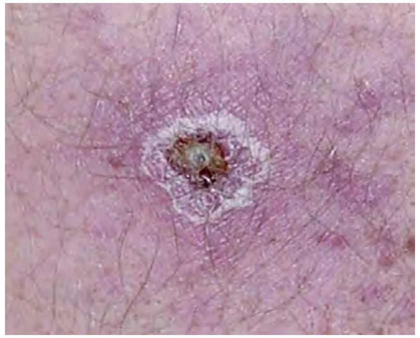
Division of Clinical Microbiology, Mayo Clinic

Primary Methods for Diagnosis of Tickborne Diseases

- **Clinical evaluation**
- **Tickborne diseases must be considered in differential diagnosis**
  - Order correct laboratory tests
  - Begin empirical antimicrobial therapy if indicated
  - Especially if rickettsiosis, ehrlichiosis, or anaplasmosis is suspected
    - Infections may be rapidly fatal
    - Need to be treated quickly, often before test results are available

Rash of Rocky Mountain spotted fever

Eschar of *Rickettsia parkeri* rickettsiosis



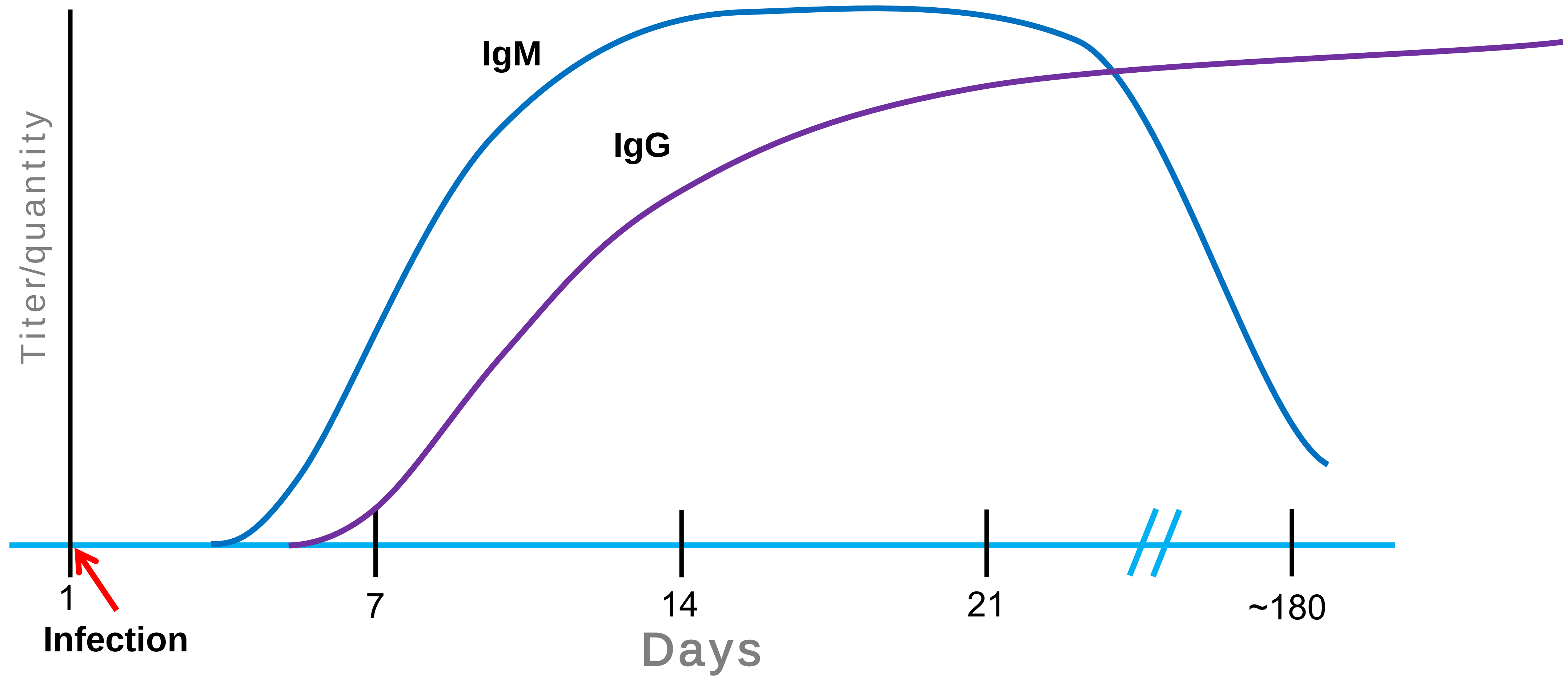
Biggs HM, Behravesh CB, Bradley KK, et al. *MMWR Recomm Rep.* 2016 May 13;65(2):1-44.
Tickborne Diseases of the United States. 2016. CDC, Atlanta, GA.
www.cdc.gov/ticks/diseases/

Indirect Laboratory Methods: Serology

- **Principle:**
  - Detection of the host's immune response to organisms
  - IgM or IgG class host antibodies in serum
- **Uses:**
  - Method of choice for diagnosing many tickborne diseases
    - *Rickettsia, Ehrlichia* and *Anaplasma* species, tickborne viruses
  - Testing for tickborne viruses uses laboratory-developed methods
    - Available primarily through state public health laboratories or CDC
  - Not primary diagnostic choice for babesiosis
  - Sensitivity varies by the time that the specimen is obtained during the course of infection

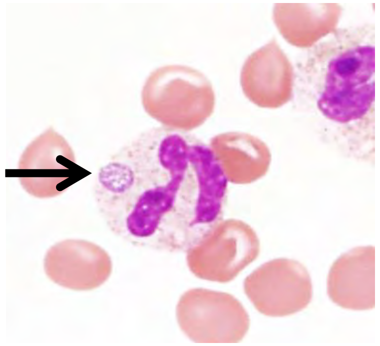
Biggs HM, Behravesh CB, Bradley KK, et al. *MMWR Recomm Rep.* 2016 May 13;65(2):1-44.
Tickborne Diseases of the United states. 2016. CDC, Atlanta, GA.
www.cdc.gov/ticks/diseases/

Serology: IgM and IgG Patterns

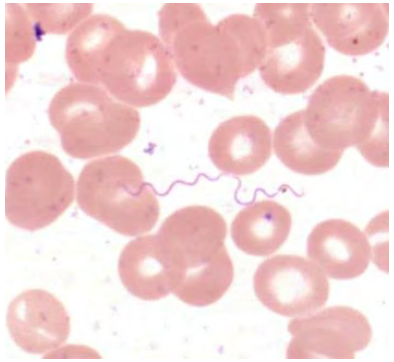


Direct Laboratory Methods for Diagnosis of Tickborne Diseases

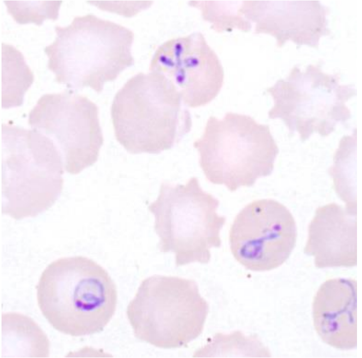
- **Microscopy**



Anaplasma phagocytophilum morula



Relapsing fever *Borrelia* spp. spirochetes

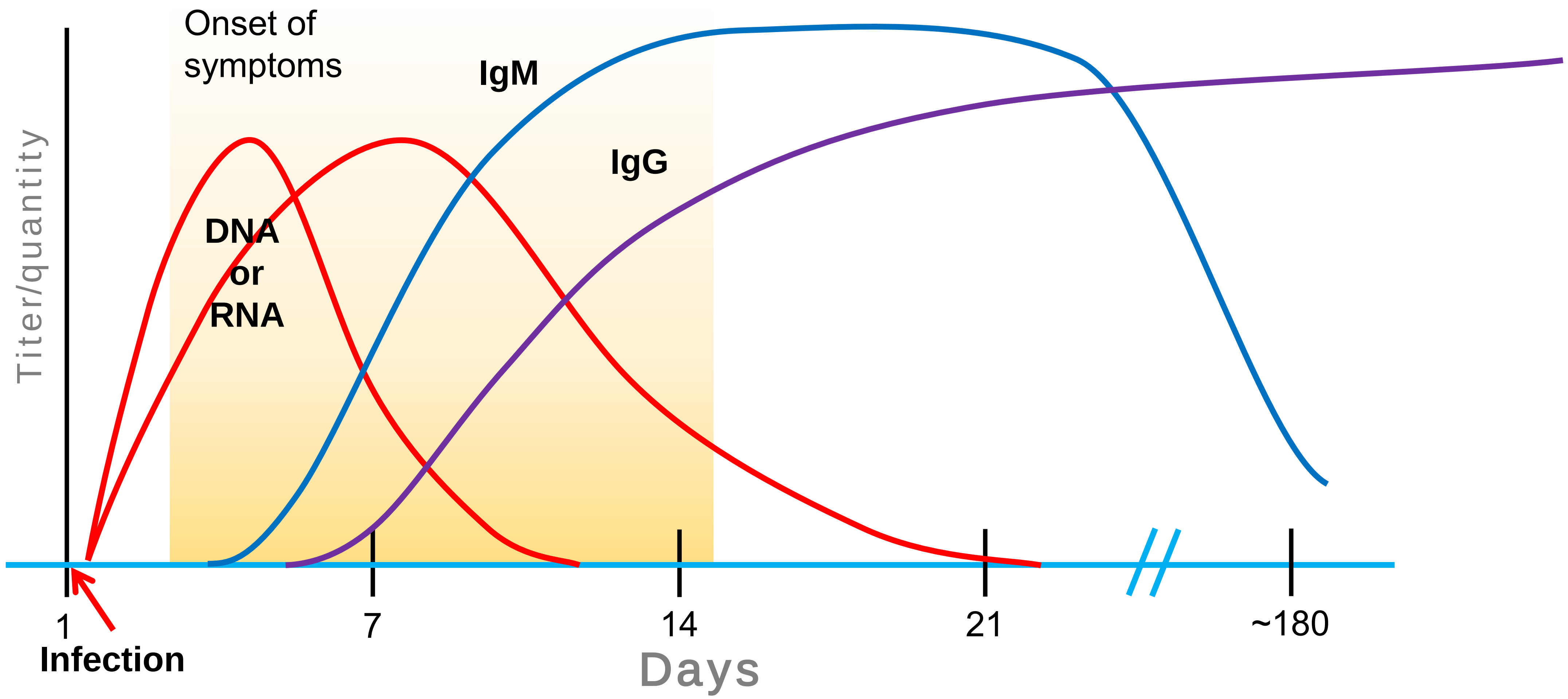


Babesia spp. parasites within red blood cells

- **Nucleic acid amplification tests (e.g., polymerase chain reaction)**
- **Culture not routinely used, except for tularemia**

Biggs HM, Behravesh CB, Bradley KK, et al. *MMWR Recomm Rep.* 2016 May 13;65(2):1-44.
Tickborne Diseases of the United states. 2016. CDC, Atlanta, GA.
www.cdc.gov/ticks/diseases/

Direct Methods - General Pattern



Nucleic Acid Amplification Tests – What Can They Do?

- **One of the earliest methods for detecting some organisms**
- **Insensitive if nucleic acid is no longer detectable by the time the patient presents for evaluation**
- **Especially useful for *Anaplasma phagocytophilum*, *Ehrlichia* species and *Babesia* species (whole blood specimens)**
  - These organisms are usually present in high amounts during the symptomatic stage of infection
- **Variety of nucleic acid amplification methods available**
  - None are FDA-approved/cleared

Biggs HM, Behravesh CB, Bradley KK, et al. *MMWR Recomm Rep.* 2016 May 13;65(2):1-44.
Tickborne Diseases of the United states. 2016. CDC, Atlanta, GA.
www.cdc.gov/ticks/diseases/

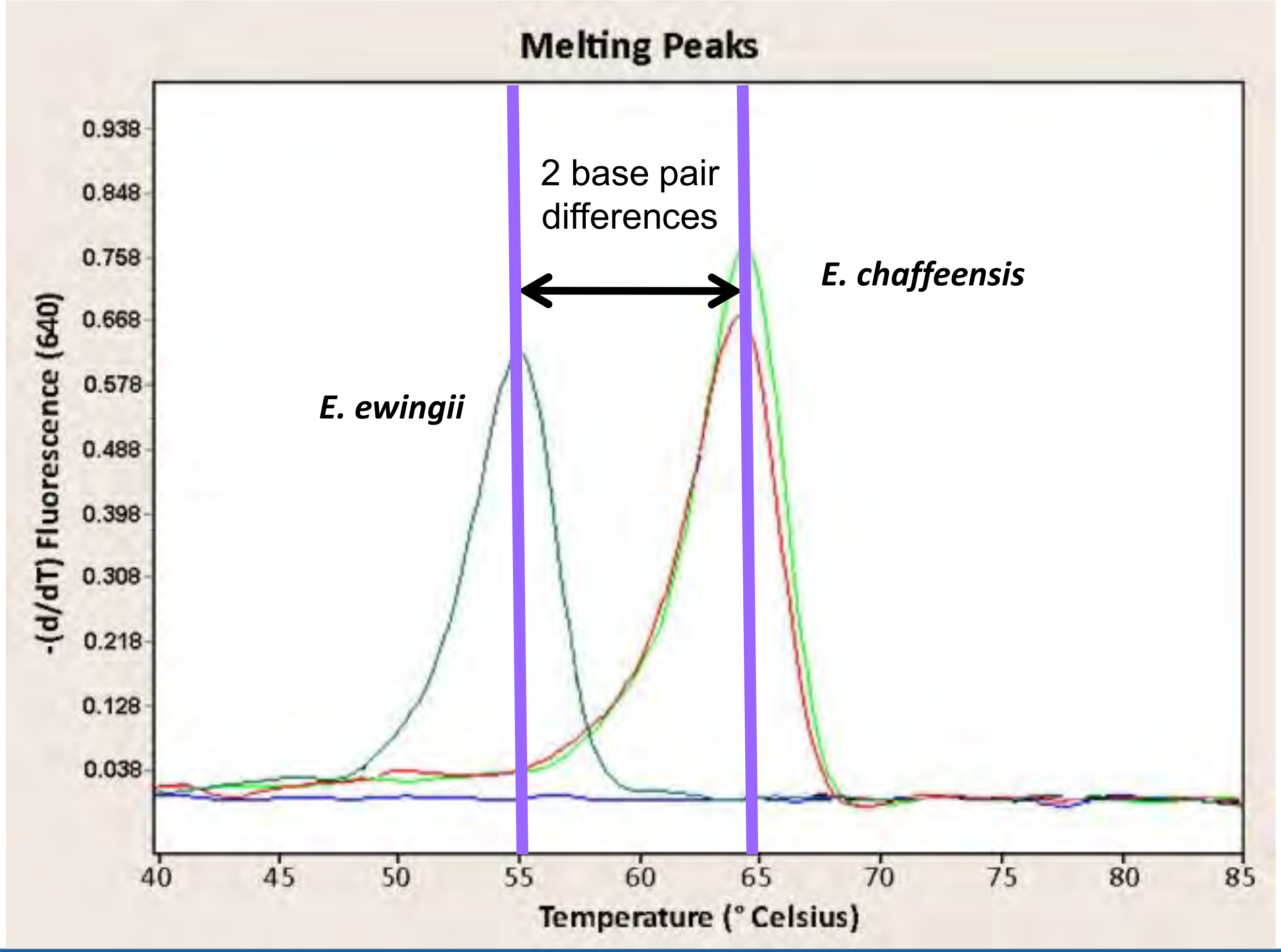
Polymerase Chain Reaction

- **Fluorescent probes are used to detect DNA as it is amplified**
  - Can be highly sensitive and specific
  - Semiquantitative detection
- **Melting curve analysis**
  - Uses nonspecific DNA-binding dyes or specific probes
  - Additional benefit of detecting mutations (and even new organisms)

Biggs HM, Behravesh CB, Bradley KK, et al. *MMWR Recomm Rep.* 2016 May 13;65(2):1-44.
Tickborne Diseases of the United states. 2016. CDC, Atlanta, GA.
www.cdc.gov/ticks/diseases/

Example: Melting Temperature Analysis with Fluorescence Resonance Energy Transfer (FRET) Hybridization Probes

Real-time PCR targeting *groEL* (gene encoding the heat shock operon) of *Ehrlichia* spp.



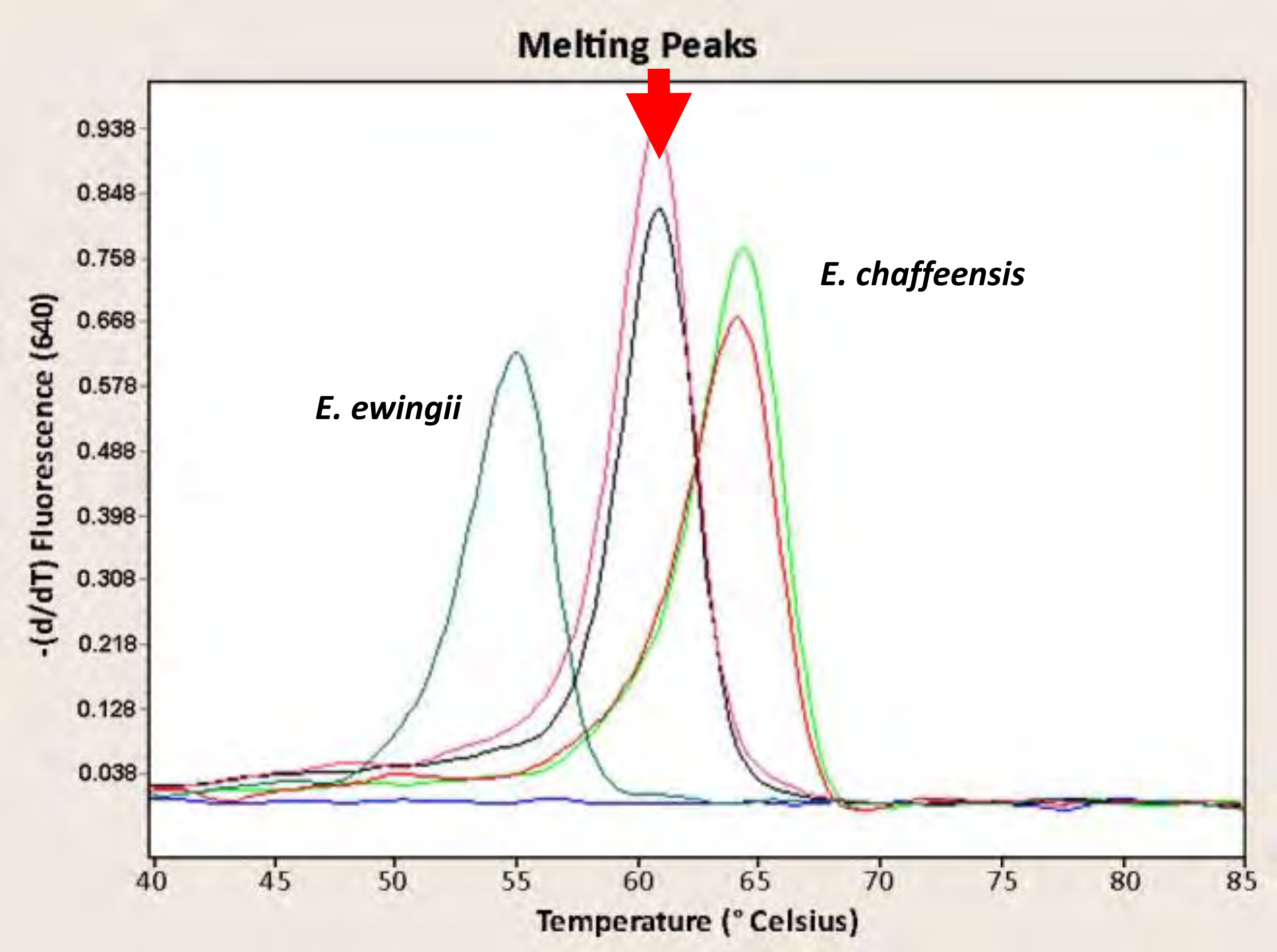
Previous name:
***Ehrlichia muris*-like agent (EMLA)**

New accepted name:
Ehrlichia muris eauclairensis

Pritt BS, Sloan LM, Johnson DK, et al. *N Engl J Med*. 2011 Aug 4;365(5):422-9.
Pritt et al. *Int J Syst Evol Microbiol.* In Press

Example: Melting Temperature Analysis with Fluorescence Resonance Energy Transfer (FRET) Hybridization Probes

Real-time PCR targeting *groEL* (gene encoding the heat shock operon) of *Ehrlichia* spp.



Previous name:
***Ehrlichia muris*-like agent (EMLA)**

New accepted name:
Ehrlichia muris eauclairensis

This same method allowed for detection of *Borrelia mayonii*

Pritt BS, Sloan LM, Johnson DK, et al. *N Engl J Med*. 2011 Aug 4;365(5):422-9.
Pritt et al. *Int J Syst Evol Microbiol.* In Press

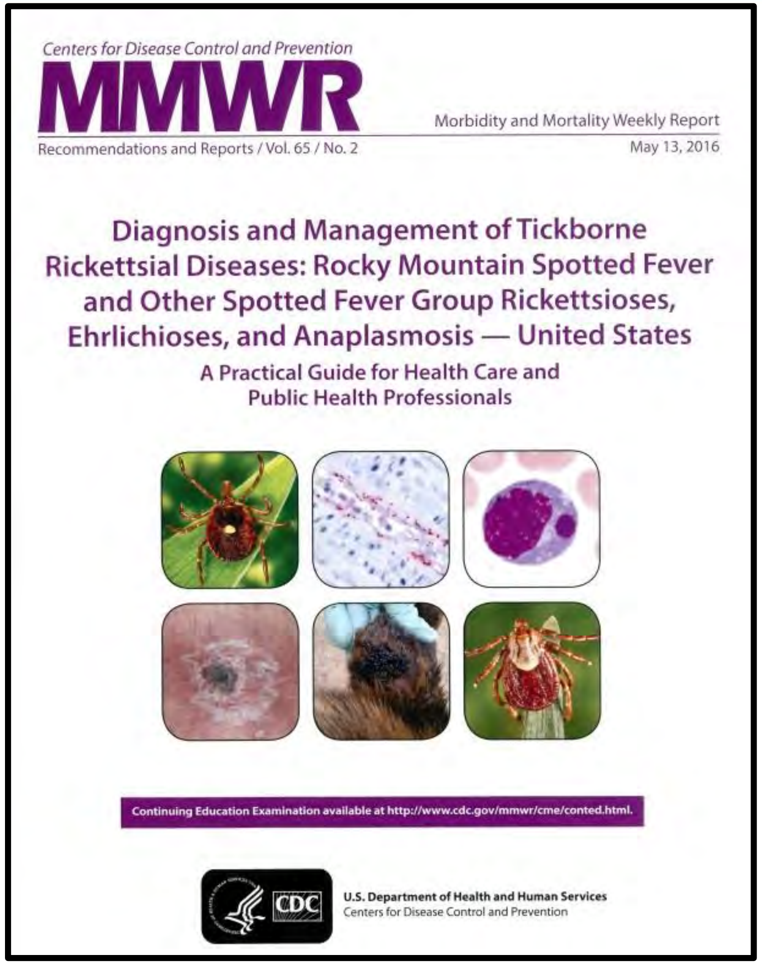
Beyond Singleplex PCR

- **Multiplex molecular panels**
  - Specific primers/probes to detect multiple bacterial, viral, and parasitic pathogens in a single test
    - Panels for tickborne disease under development
  - Only detects targeted organisms, non-targeted organisms will be missed
- **Broad range sequencing**
  - Targeted gene amplification with subsequent sequence identification
    - Common targets: 16S rRNA gene (bacteria), internal transcribed spacer (ITS) region (fungi)
    - No equivalent for viruses; instead, groups of closely related viruses can be targeted (e.g. flavivirus)

Next Steps in Testing

- **Metagenomics**
  - Amplification all nucleic acid in a specimen: bacterial, fungal, viral, parasitic and human
  - Extensive pre- and post-processing steps used to select for targets of interest and remove nonrelevant nucleic acid
  - Currently very expensive and time consuming; this is bound to change in the future!

Recommended Reading



Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 65 / No. 2

May 13, 2016

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.

CDC

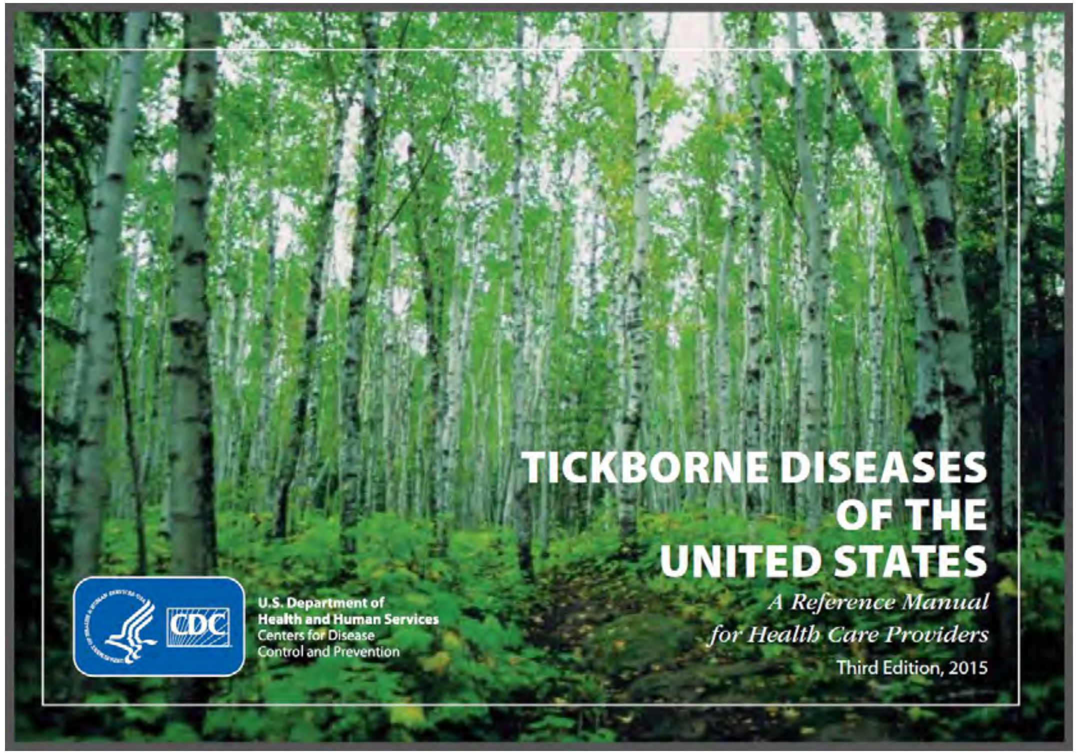
U.S. Department of Health and Human Services

Centers for Disease Control and Prevention

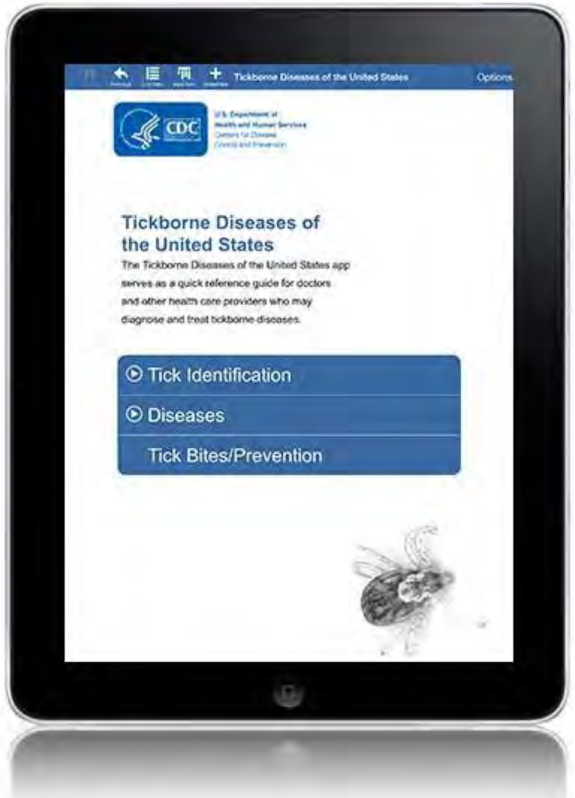
Thank you

Biggs HM, Behravesh CB, Bradley KK, et al. MMWR Recomm Rep. 2016 May 13;65(2):1-44.

Resources for Tickborne Diseases



cdc.gov/lyme/resources/tickbornediseases.pdf



cdc.gov/mobile/applications/
mobileframework/tickborne-diseases.html

www.cdc.gov/ticks

CDC PUBLIC HEALTH GRAND ROUNDS

Emerging Tickborne Diseases

March 21, 2017

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