



Vector Borne Infections

- A Moving Target

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Disclosure

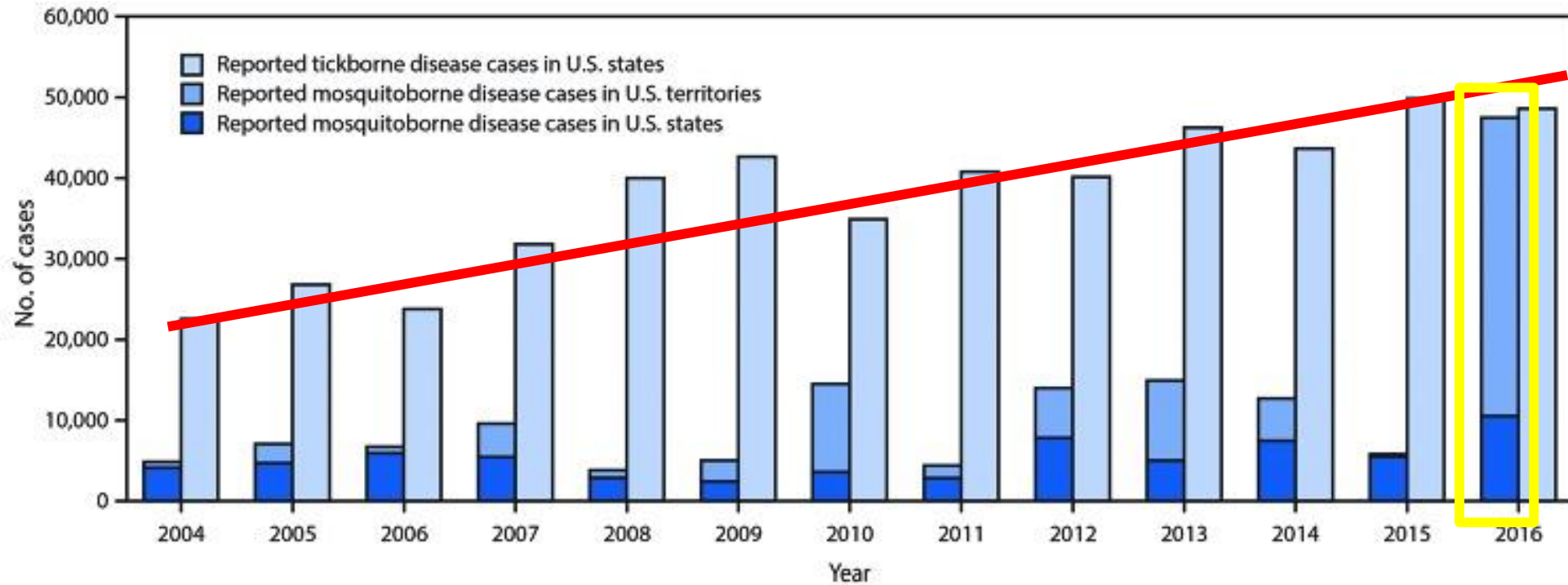
I have no personal or financial relationships with commercial interests relevant to this educational activity.



Outline

- **Tick-borne infections in the US**
- **Mosquito-borne infections in the US**
- **Prevention measures**

Vector-Borne Infections: A Growing Threat



Rosenberg R, et al, MMWR May 2018



Case

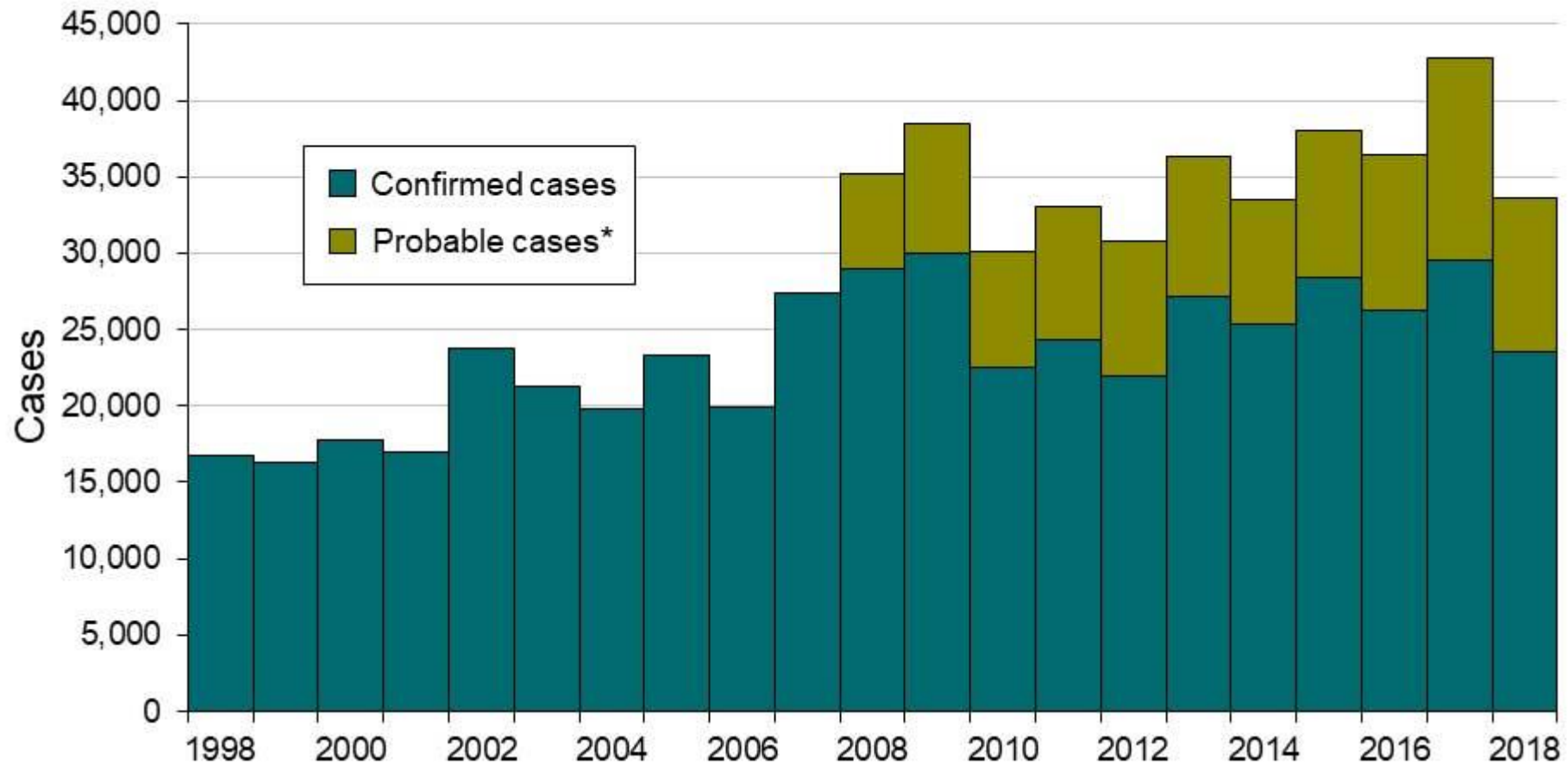
A 15 year old boy presents to clinic with a 1-day h/o rash

He just returned from a 2 week camping trip, but denies tick or mosquito bites

He denies fevers or other constitutional symptoms

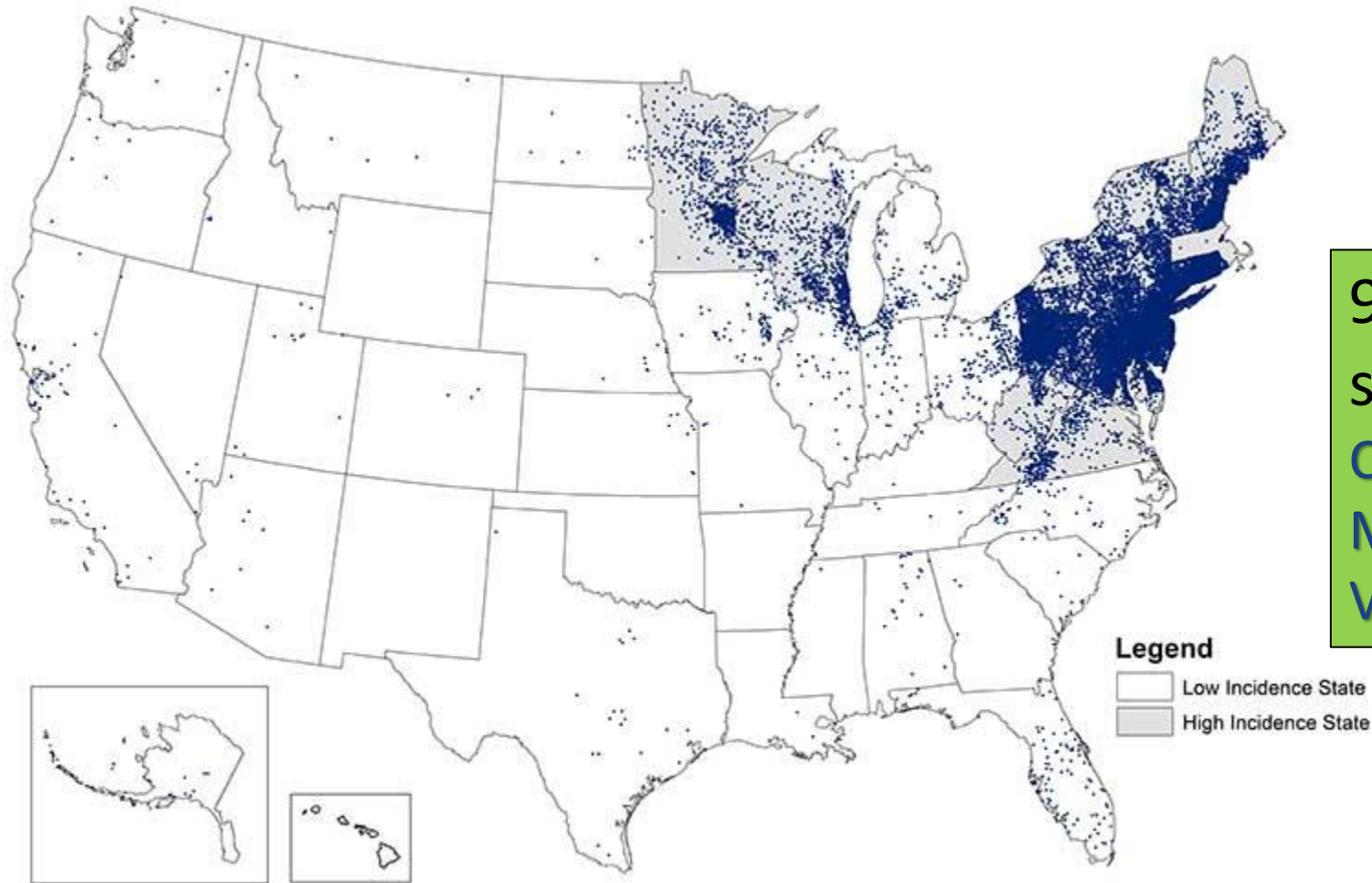
Is this Lyme Disease?

Reported Cases of Lyme Disease, 1996-2018



*Surveillance case definition revised 2008 to include probable cases

Reported Cases of Lyme Disease, 2018

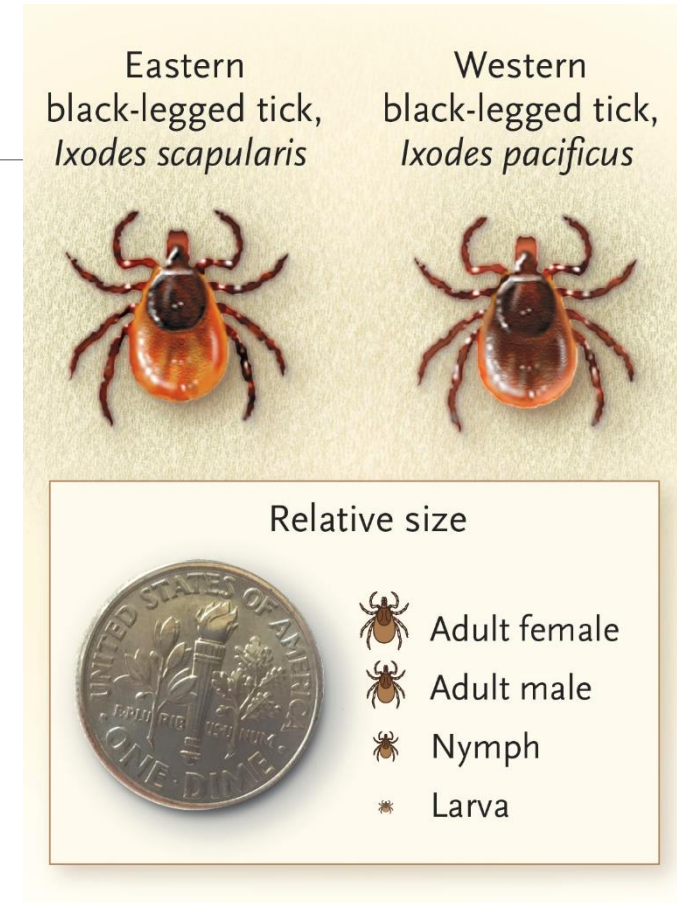


95% of cases from 14 states:

CT, DE, MA, MD, ME, MN, NH, NJ, NY, PA, RI, VT, VA, WI

The Vector

- Deer tick (*Ixodes*)
- Most cases transmitted by nymphs
- Less than 50% of patients with Lyme recall a tick bite
- Attachment of >36 hours required for transmission

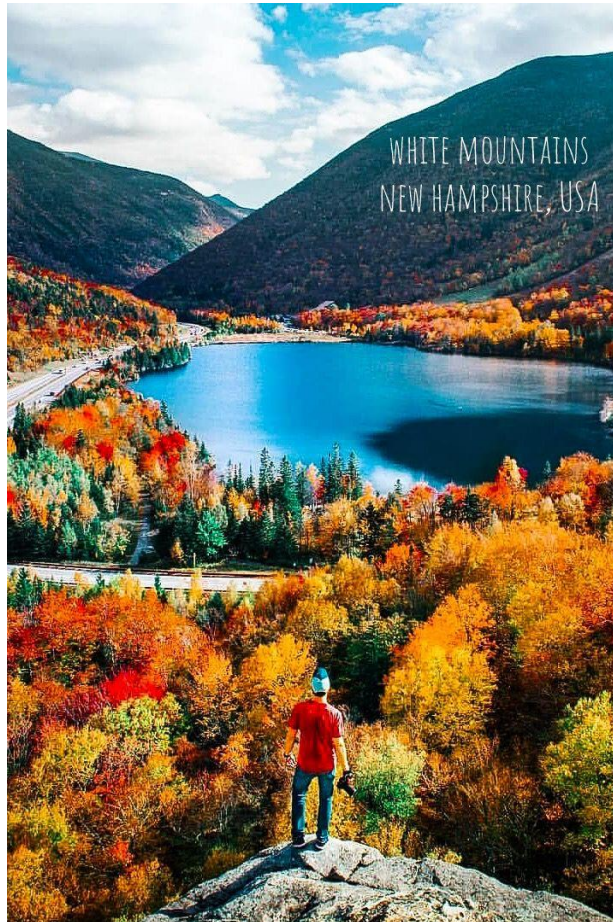


Paules CI et al, NEJM, 2018

Why Should You Care About Lyme?



EXCLUSIVE
JUSTIN BIEBER
BATTLING LYME
DISEASE AND WINNING



Predator Doctors Take Advantage of Patients With 'Chronic Lyme' Scam

| TICKED |

Daniel Summers | Updated Apr. 14, 2017 2:51PM ET / Published Sep. 19, 2014 5:55AM ET



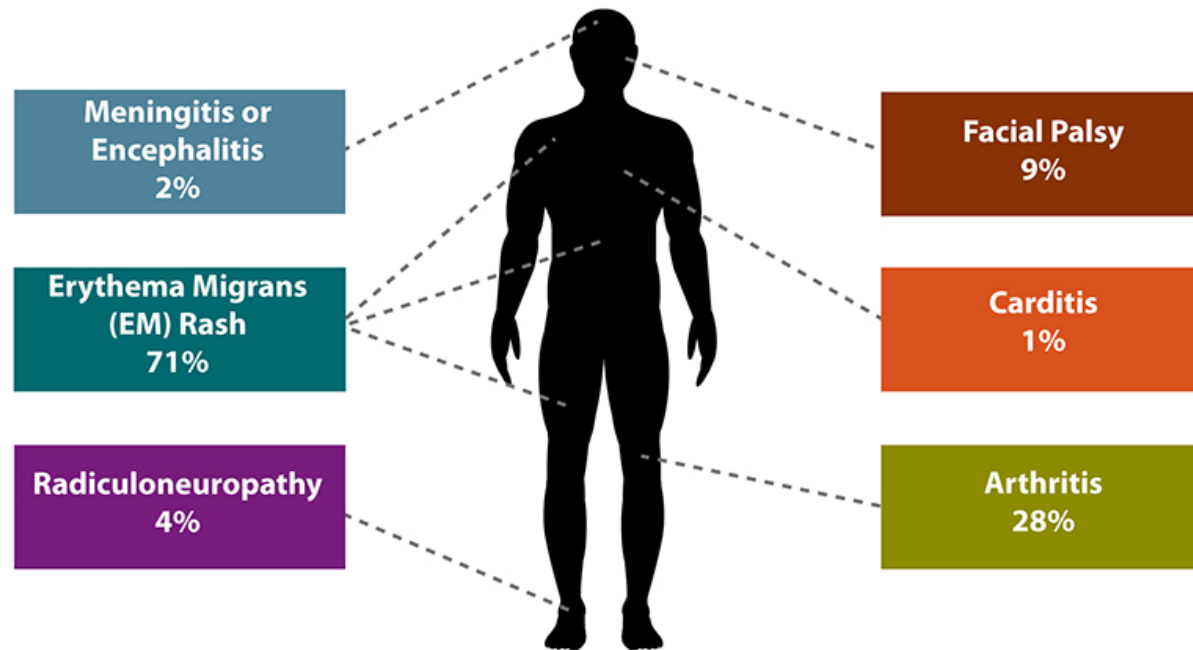
© Elena Scotti/The Daily Beast

Stages of Lyme Disease

Infectious Stage	Onset	Manifestations
Early localized	1-4 weeks	<ul style="list-style-type: none">• Erythema migrans (EM)
Early disseminated	3-8 weeks	<ul style="list-style-type: none">• Single or multiple EM• Neurologic findings• Carditis
Late disseminated	Mo-years	<ul style="list-style-type: none">• Arthritis (migratory)

Clinical Manifestation of Lyme Disease at Diagnosis, 2001-2016

Lyme disease - Relative frequency of clinical features among confirmed cases - United States, 2008 - 2017



*Data on symptoms available for only 61% of 235,037 confirmed cases. Due to the way surveillance data is collected, patients with severe symptoms or later manifestations may be more likely to be included in the above figure, and percentages presented may be higher than what is typically seen in a "real world" setting.

Erythema migrans



- Onset 3-30 days after attachment (median 7 days)
- Expansile lesion \geq 5 cm
- Bull's eye or target appearance
- Painless and nonpruritic
- Identified in **60-80%** of cases
- Variably flu-like symptoms

Atypical Erythema Migrans

Variable	Patients, <i>n</i> (%)
Morphologic characteristics	
Predominant pattern	
Homogeneous	56 (59)
Central erythema	30 (32)
Central clearing	9 (9)
Punctum present	29 (31)
Vesicular or ulcerated	7 (7)
Blue center	2 (2)
Total	95 (100)



Erythema Migrans Mimickers

- Hypersensitivity to tick saliva
- Insect bite
- Nummular eczema
- Granuloma annulare
- Ringworm
- Cellulitis
- **STARI**



Southern Tick Associated Rash Illness (STARI)

Causative agent unknown, no laboratory testing available

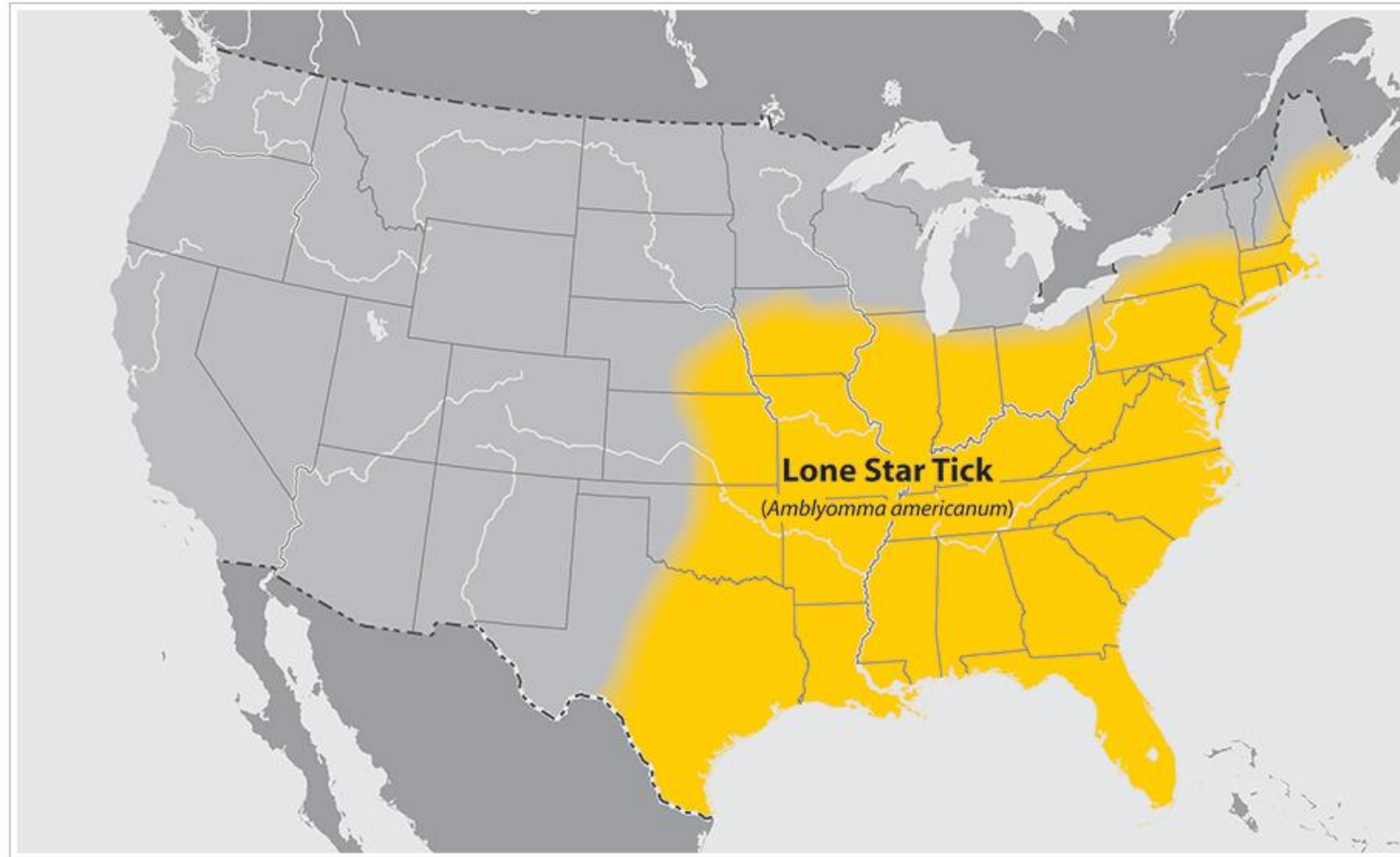
***Borrelia burgdorferi* serology and PCR negative**

Not associated with late sequelae

Treatment ???



Differentiating Lyme From STARI



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



Case Revisited

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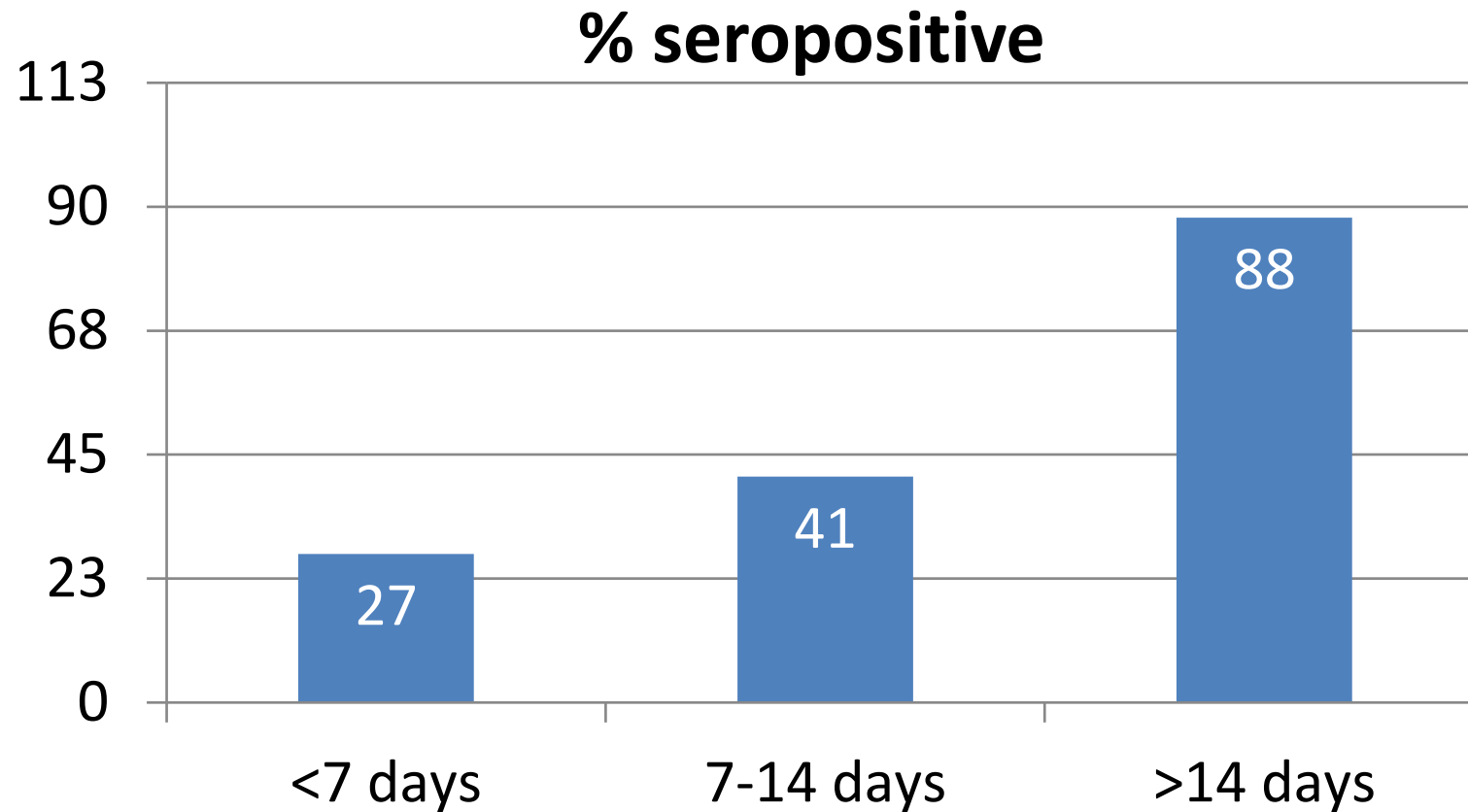
He denies fevers or other constitutional symptoms

Is this Lyme Disease?

If NJ: YES

If MS: Probably not

Serology Following Onset of Rash



Diagnosis of Early Localized Lyme Disease

False negative serologic tests common

EM considered sufficient for diagnosis, reporting*, and **treatment**



*Reporting of clinically diagnosed cases varies by state

Therapy for Lyme Disease

Indication	Treatment	Duration
Erythema migrans	Doxycycline	10-21 days
	Amoxicillin	14-21 days
	Cefuroxime axetil	14-21 days

Early Disseminated Lyme Disease

Onset 2 weeks to 3 months after bite in **untreated** patients

Clinical manifestations

- Multiple EM lesions (with fevers)
- Neurologic (15%)-aseptic meningitis, cranial nerve palsy
- Carditis (1%)—esp. conduction block



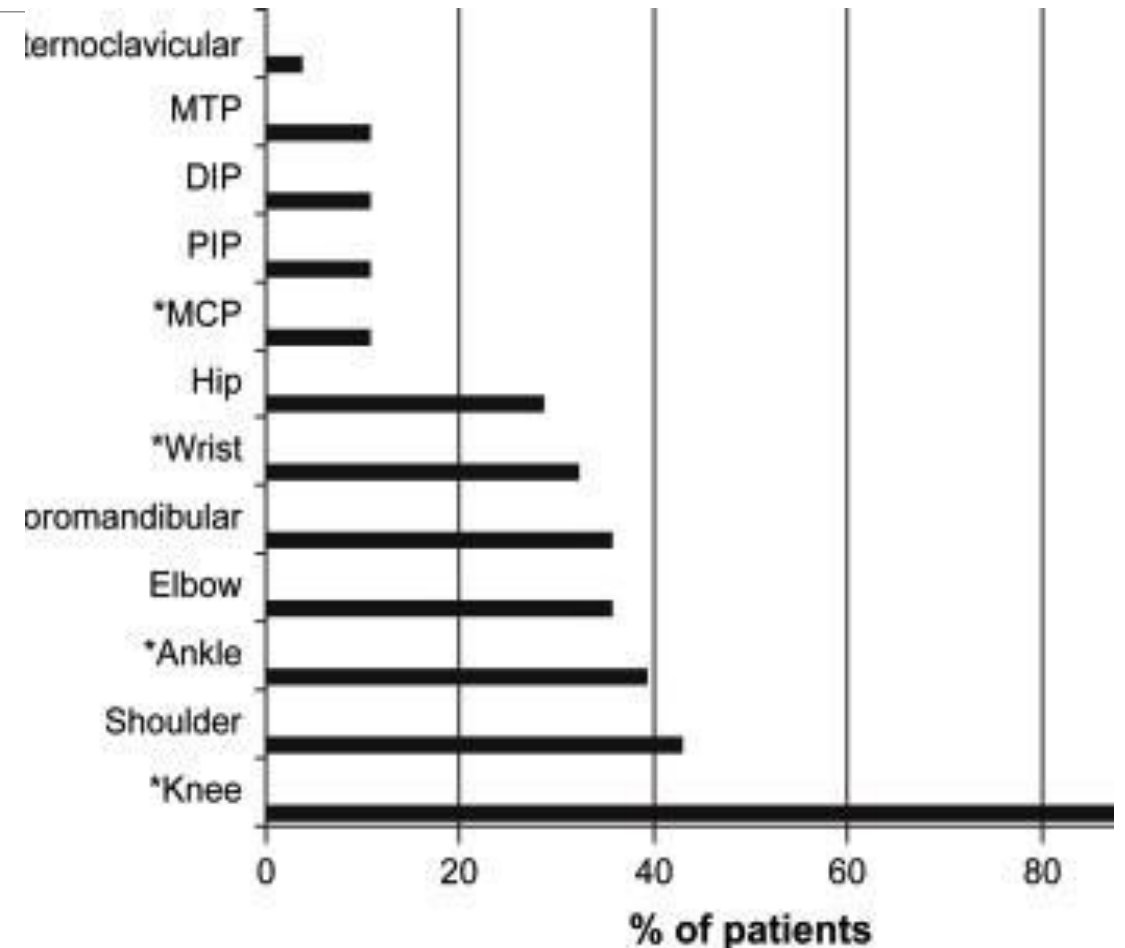
Late Disseminated Disease

Occurs months to years after infection

Mono or oligoarticular Arthritis

- 60% of untreated patients
- Migratory (10% persistent)

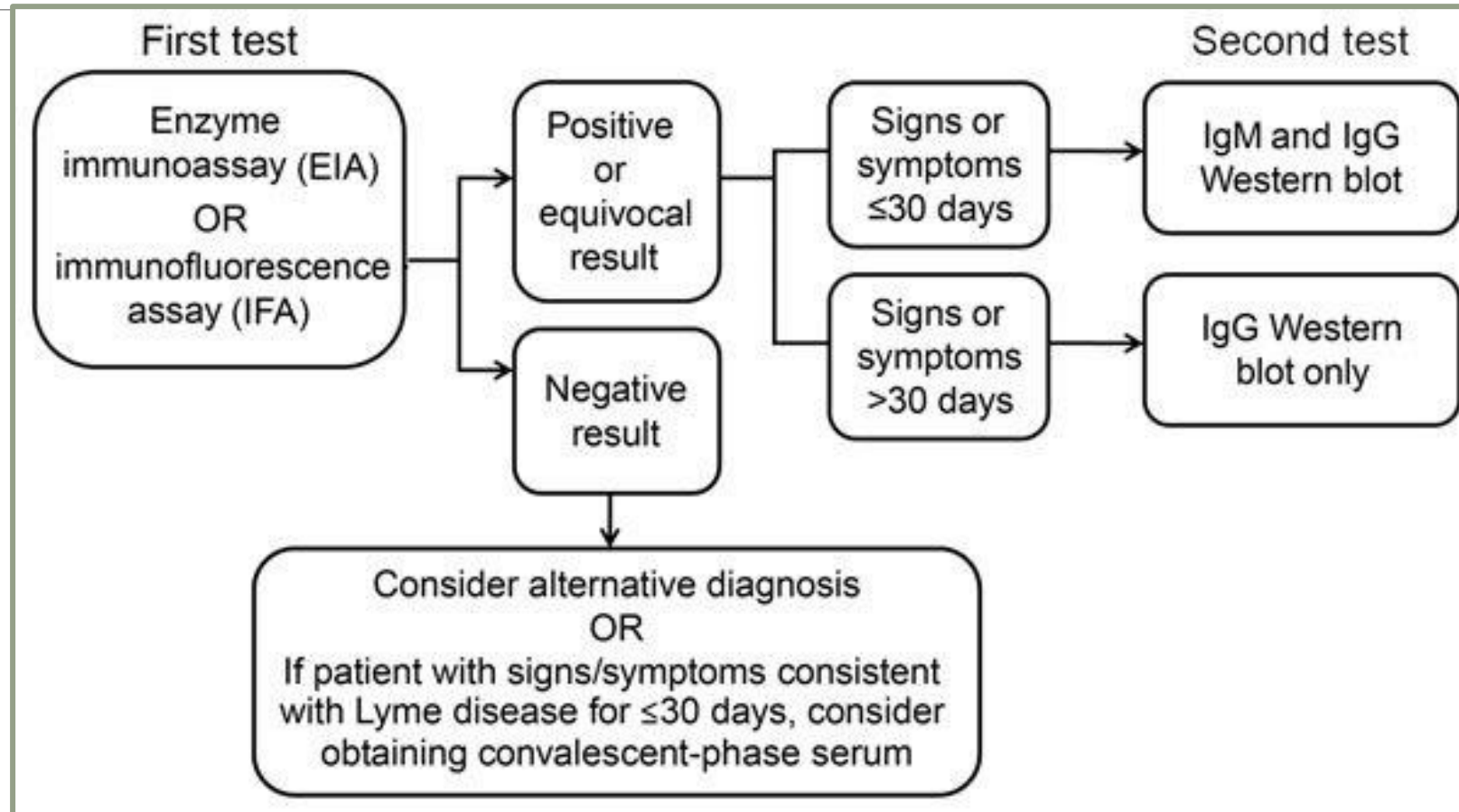
Neurologic manifestations rare!



Serologic Diagnosis of Lyme Disease



Two-Step Testing for Lyme Disease



NEW FDA-Approved Testing Algorithm

July 2019 FDA approved “modified 2-tier test”

2 EIA test (concurrently or sequentially)

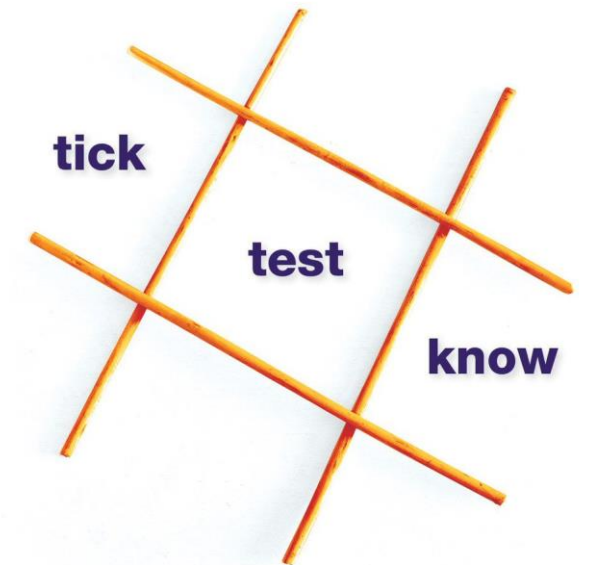
Approved as 2nd tests

- ZEUS ELISAs (VLsE1, IgG, IgM, IgG/IgM)

Both EIA need to be positive for diagnosis

Advantage: less labor intensive, less subjective

The **GAME CHANGER** in early
Lyme disease detection



Pitfalls in Laboratory Testing

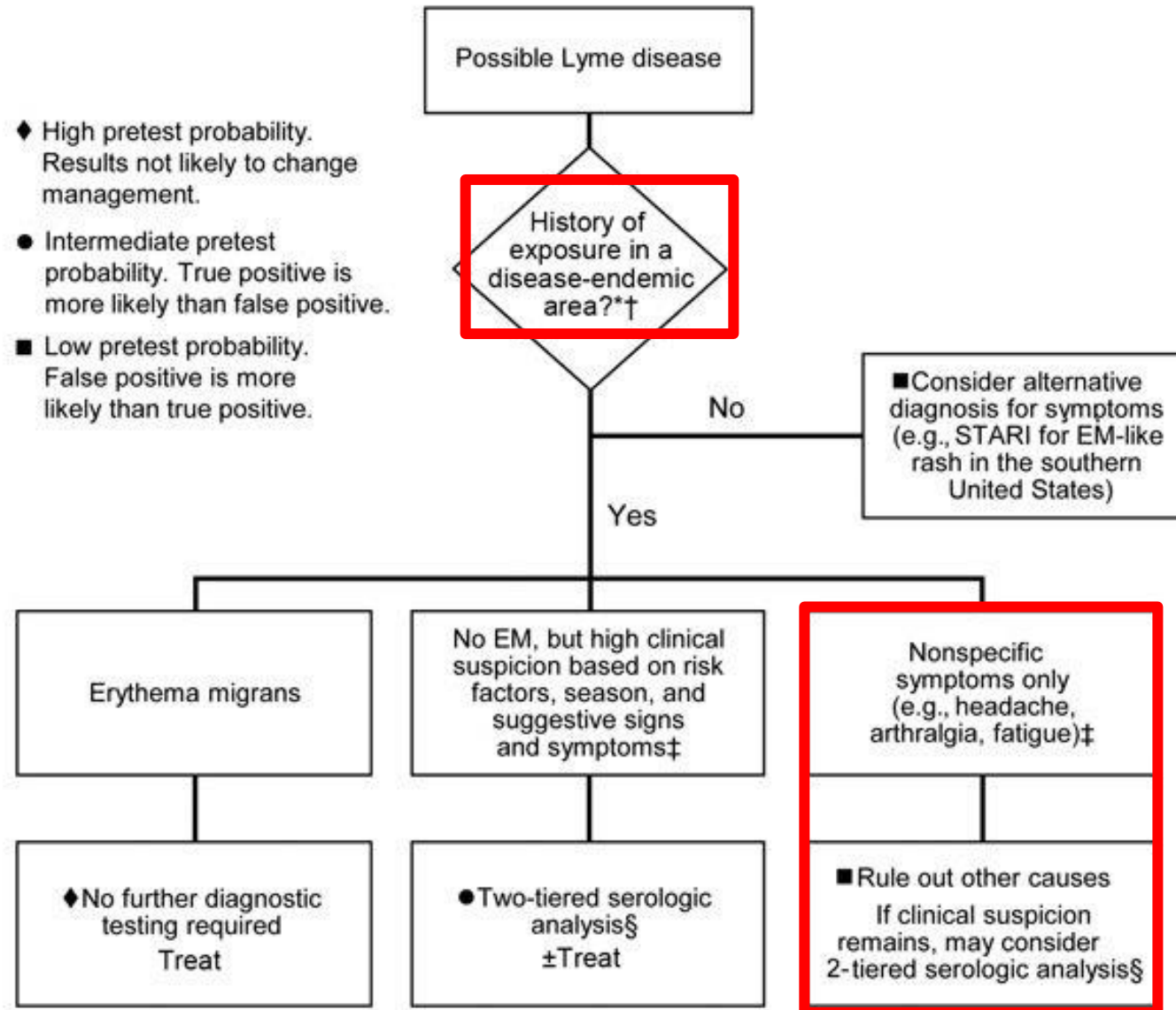
Early infection, often seronegative

After >1 month of symptoms, IgG should be positive and an isolated IgM response likely a false positive

Antibodies stay positive for life...don't retest or re-treat based on persistently elevated or rising titers

Likelihood of a false positive goes up if pre-test probability is low

When NOT to test for Lyme Disease



Clinician Beware!

Laboratory tests that are not recommended



Some laboratories offer Lyme disease testing using assays whose accuracy and clinical usefulness have not been adequately established. Examples of unvalidated tests include:

- Capture assays for antigens in urine
- Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- “Reverse Western blots”
- In-house criteria for interpretation of immunoblots
- Measurements of antibodies in joint fluid (synovial fluid)
- IgM or IgG tests without a previous ELISA/EIA/IFA

Compatible with Tests that Require Urine

Urine Collection Kit

The Urine Collection Kit is compatible with all tick-borne disease tests that require urine samples. These tests are particularly useful during the acute phase of a tick-borne disease infection before antibodies are present as well as for seronegative patients, patients with vague symptoms of long duration, and previously-treated patients with recurring symptoms.

✓ Borrelia

Deposit ¹
\$20.00

ADD THIS KIT TO CART

[Kit Details ›](#)

Compatible with Tests that Require Whole Blood Serum

Blood Collection Kit

The Blood Collection Kit is compatible with most of the tick-borne disease tests and panels. The panels are usually the most comprehensive available for testing for Borreliosis/Lyme disease as well as co-infection(s) with other tick-borne illnesses.

✓ Borrelia

Deposit ¹
\$20.00

ADD THIS KIT TO CART

[Kit Details ›](#)

Case Revisited

Treated with a 14 day course of doxycycline

4 weeks later he returns c/o fatigue, low-grade fevers, and dark urine

PE notable for scleral icterus, mild RUQ pain

Rash has resolved

Labs:

WBC=8.7

H/H=7.2/23

Alk phos=135

Bilirubin=6.2



Mom asks, "Is this Chronic Lyme Disease?"

“Chronic” Lyme Disease



Post-Lyme Disease Syndrome

Persistent symptoms >2 months after appropriate treatment

- Arthralgias, myalgias, fatigue, headaches, dizziness, paresthesia

Occurs in 10-15% of cases

Frequency decreases over time

- 6 months-6%
- 12 months-4%

Etiology--? Immunologic; NOT due to latent infection—No improvement with prolonged antibiotic therapy

Treatment is supportive care

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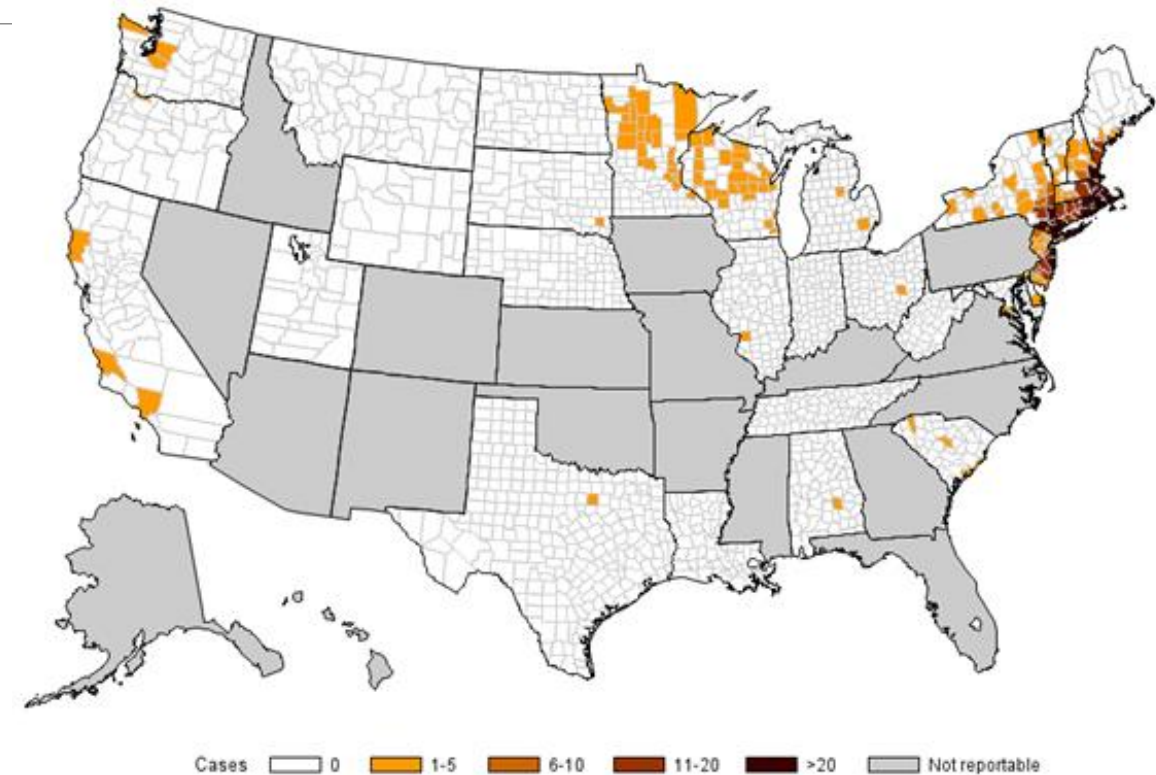
Babesiosis

Can occur in isolation or as a co-infection

Intra-erythrocytic parasite

Spread by Ixodes ticks

Transmission can also be through blood transfusion



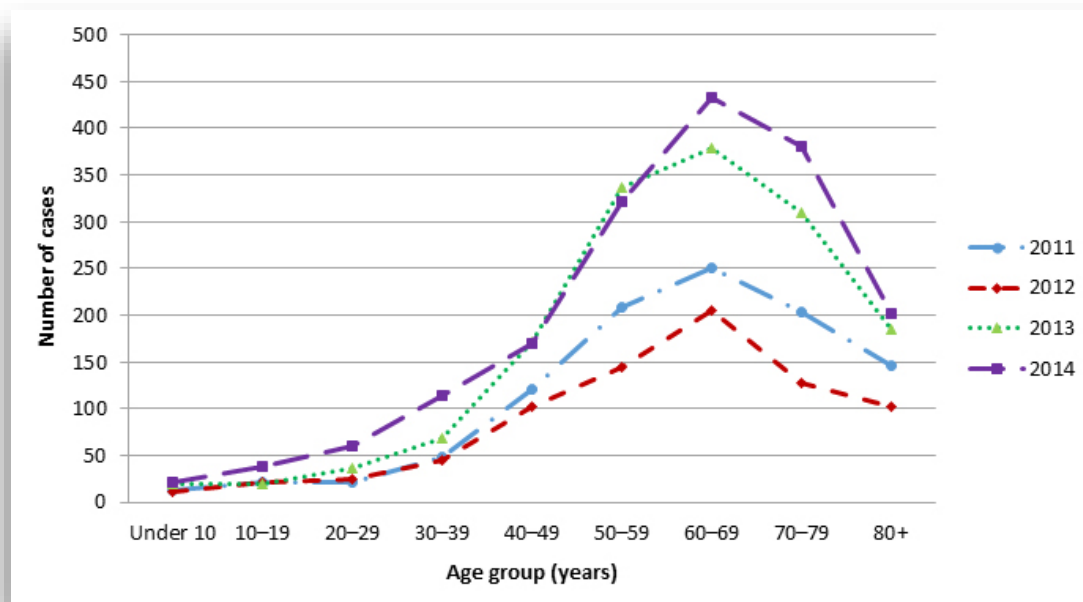
Reported cases of Babesiosis, 2014

Babesiosis

25-50% of infections asymptomatic

Remainder range from a mild febrile illness to fulminant infection

Signs and symptoms related to hemolysis



Risk factors for severe disease

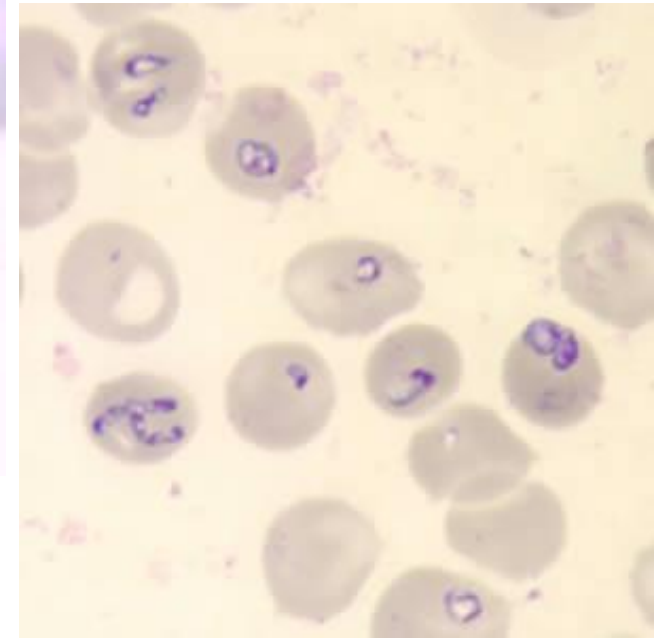
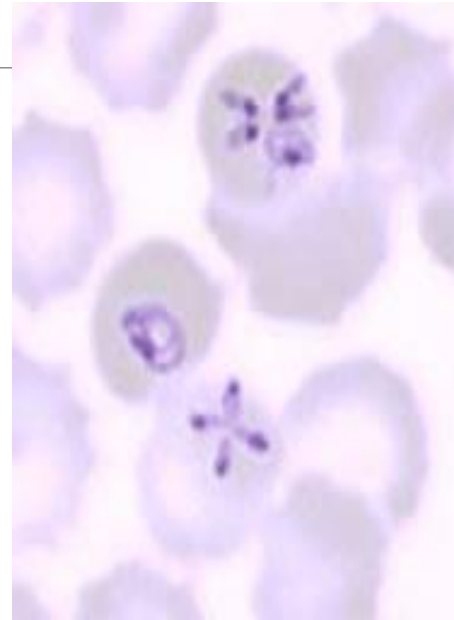
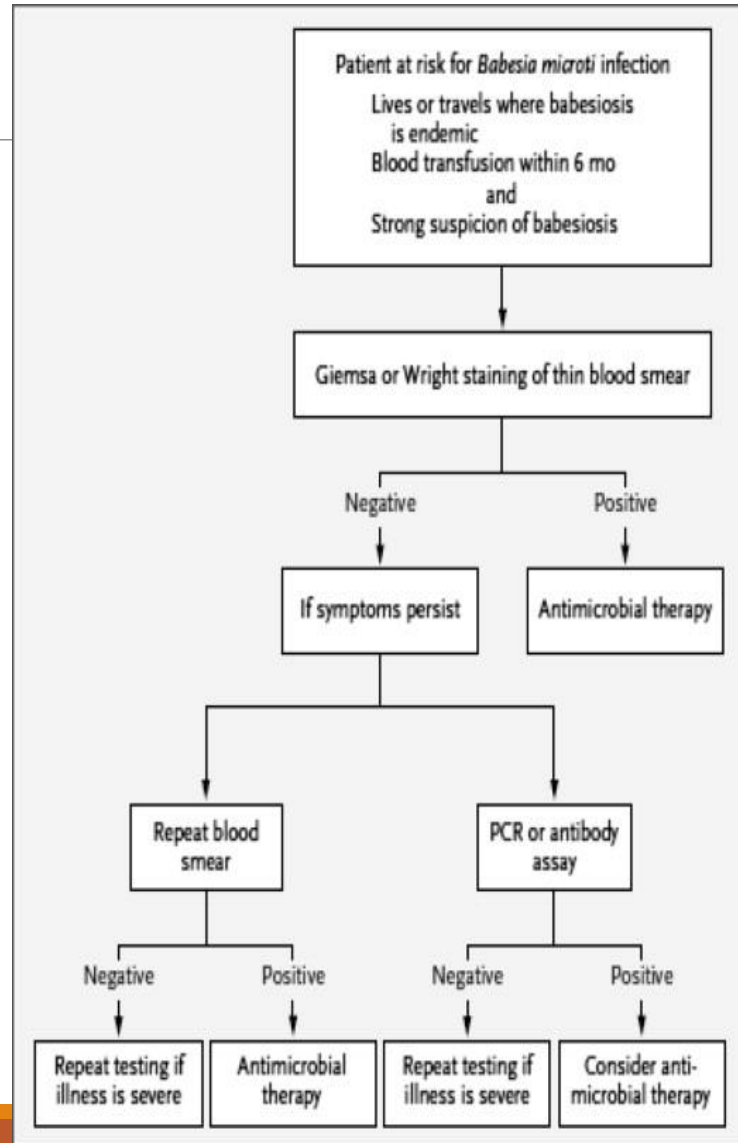
Advanced age

Asplenia

Immunocompromise

Chronic health conditions

Evaluation for *Babesia*



Babesia parasites in red blood cells on a stained blood smear. (CDC Photo: DPDx)



But Wait...
There's
MORE!

Human Ehrlichioses, cases Reported - 2016

Anaplasmosis (HGA)



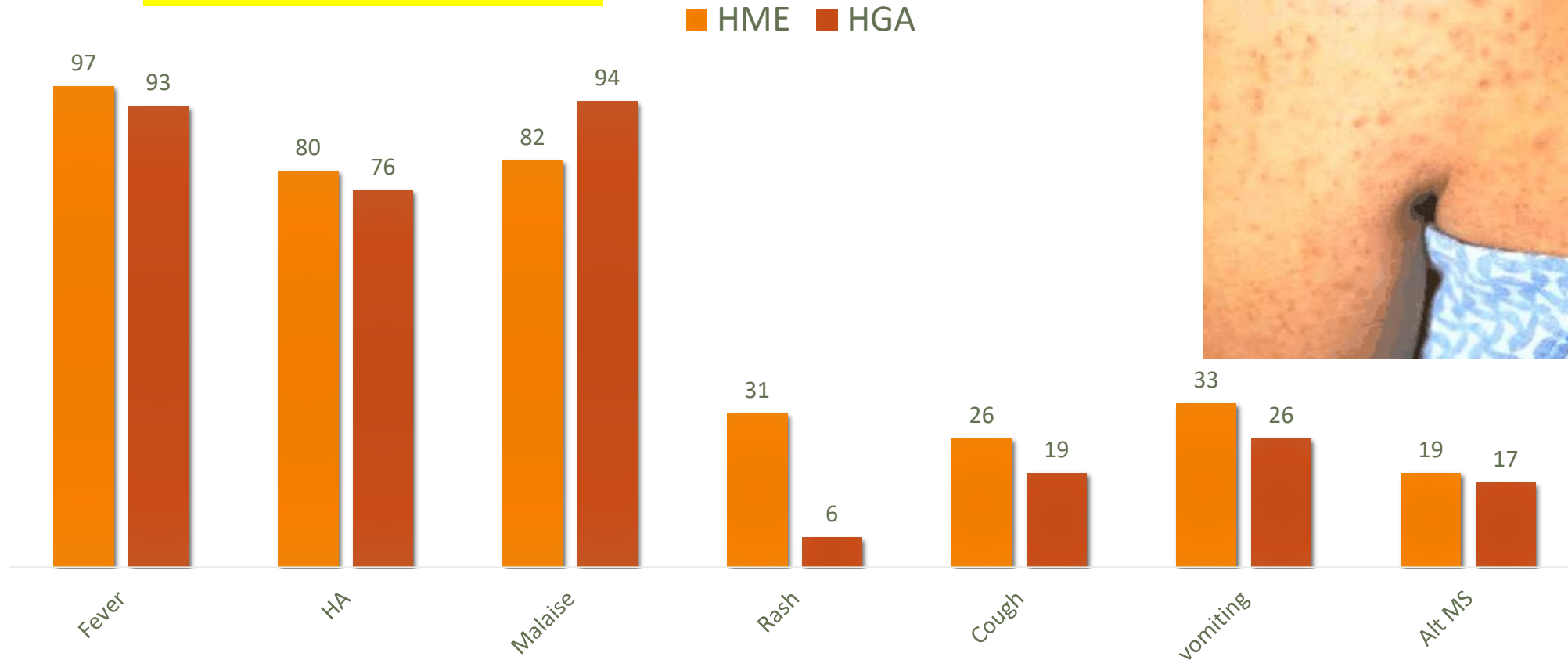
Ehrlichiosis (HME)



<https://www.cdc.gov/ticks/tickbornediseases/overview.html>

Signs & Symptoms of HME & HGA

Flu-like presentation



© Richard Jacobs, MD

Laboratory Findings Suggestive of HME/HGA

Laboratory clues:

- Leukopenia
- Thrombocytopenia
- Elevated Transaminases

Buffy coat smear (<20-50%)



Diagnosis and Treatment of HME and HGA

Serology

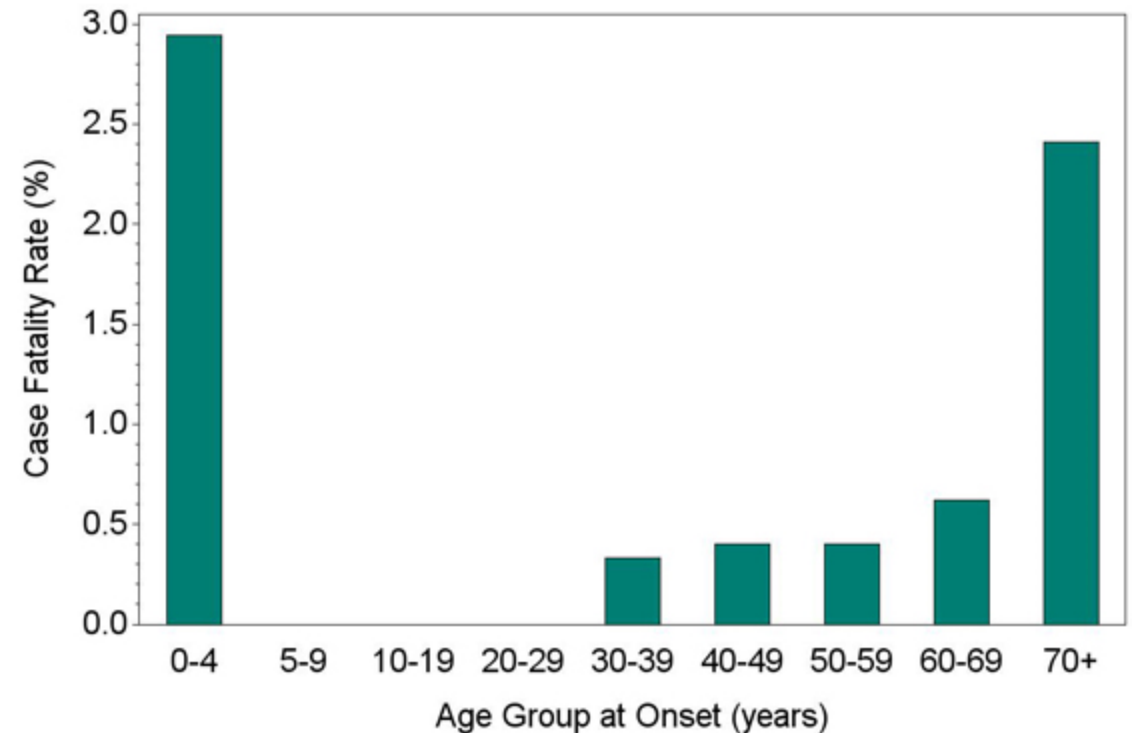
- Acute serology: **~30%**
- Con serology (weeks later): ~90%

Whole blood PCR (pre-abx) ~70-90%

Treat *regardless* of test results if clinically consistent

Treatment delay increases mortality

Doxycycline for 7-14 days



**Case Fatality Rate of Ehrlichia chaffeensis
by Age Group, 2008-2013**

Doxycycline Use in Children

ORIGINAL
ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS



No Visible Dental Staining in Children Treated with Doxycycline for Suspected Rocky Mountain Spotted Fever

Suzanne R. Todd, DVM¹, F. Scott Dahlgren, MSPH¹, Marc S. Traeger, MD², Eugenio D. Beltrán-Aguilar, DMD, DrPH³, Donald W. Marianos, DDS¹, Charlene Hamilton, MPH⁴, Jennifer H. McQuiston, DVM¹, and Joanna J. Regan, MD¹

Objective To evaluate whether cosmetically relevant dental effects occurred among children who had received doxycycline for treatment of suspected Rocky Mountain spotted fever (RMSF).

Study design Children who lived on an American Indian reservation with high incidence of RMSF were classified as exposed or unexposed to doxycycline, based on medical and pharmacy record abstraction. Licensed, trained dentists examined each child's teeth and evaluated visible staining patterns and enamel hypoplasia. Objective tooth color was evaluated with a spectrophotometer.

Results Fifty-eight children who received an average of 1.8 courses of doxycycline before 8 years of age and who now had exposed permanent teeth erupted were compared with 213 children who had never received doxycycline. No tetracycline-like staining was observed in any of the exposed children's teeth (0/58, 95% CI 0%-5%), and no significant difference in tooth shade ($P = .20$) or hypoplasia ($P = 1.0$) was found between the 2 groups.

Conclusions This study failed to demonstrate dental staining, enamel hypoplasia, or tooth color differences among children who received short-term courses of doxycycline at <8 years of age. Healthcare provider confidence in use of doxycycline for suspected RMSF in children may be improved by modifying the drug's label. (*J Pediatr* 2015;166:1246-51).

Tetracycline-class antibiotics (tetracyclines) once were used widely to treat a variety of infections in children, but studies



Doxycycline
saves lives!

A good reason to smile:
New research shows NO evidence
of tooth staining from short courses
of doxycycline.

Doxycycline is the best treatment
for suspected rickettsial infections
in patients of all ages.



Click to learn more.

Other Co-Infections

THE CHECKUP

With a Tick Boom, It's Not Just Lyme Disease You Have to Fear



No vaccine. No treatment. And this rare tick-borne disease can be transmitted within minutes

Christopher Sil

Lindy Washburn, The Journal News

Published 6:46 a.m. ET Aug. 8, 2019 | Updated 8:40 a.m. ET Aug. 8, 2019

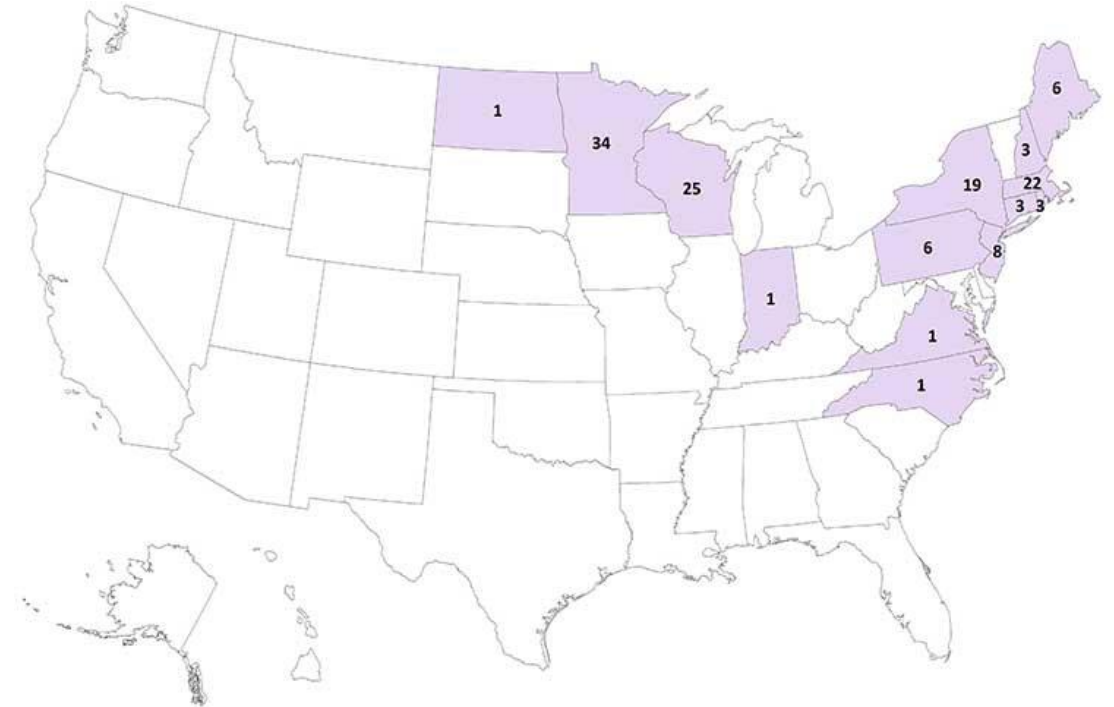
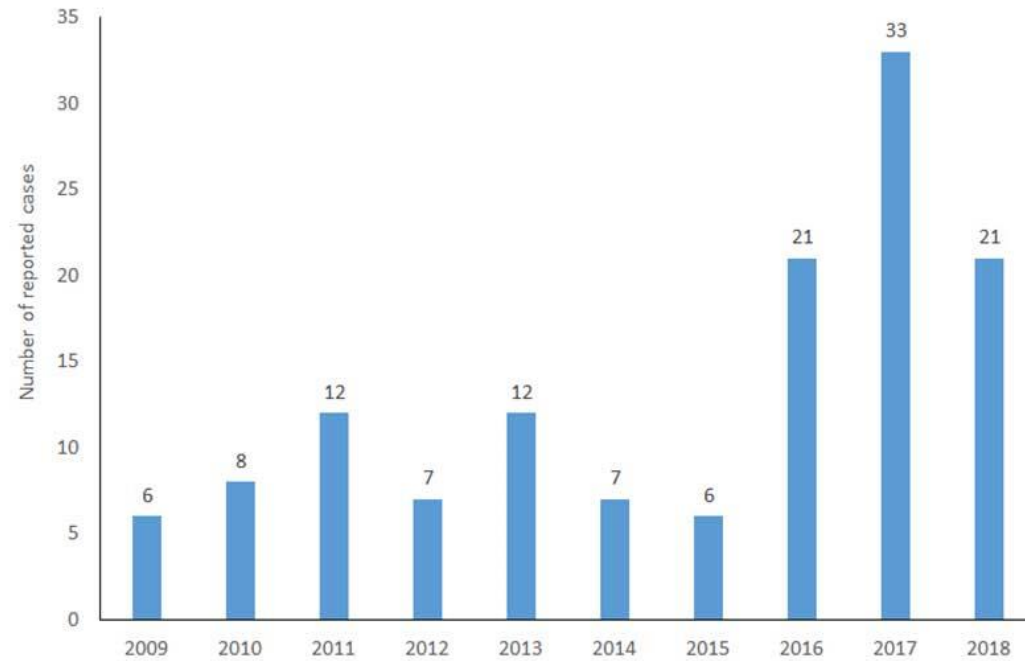
Kay Hagan, Former North Carolina Senator, Dies at 66

A Democrat, she served one term after defeating Elizabeth Dole. She was found to have a tick-borne virus in 2016.



Powassan Virus Neuro-invasive Disease

Powassan virus neuroinvasive disease cases reported by year, 2009-2018



RMSF: The Vector



- American dog tick
- Tick attachment ≥ 6 hours required for transmission
- Symptom onset 7 days (range, 2-14 days) after tick bite



ABOUT THIS MAP: This map is not meant to represent risks for a specific tick-borne disease, because disease transmission is influenced by multiple factors beyond mere tick presence. This map has been designed to answer the question "What ticks should I be concerned about at a regional scale?" Please consult a local public health authority or USDA Agricultural Extension Office to determine more specific information at the state, county, or municipal level. Background data for this map is from the US National Atlas.

National Center for Emerging and Zoonotic Infectious Diseases
Division of Vector-Borne Diseases



Spotted Fever Rickettsioses Cases - 2016

Reported to CDC, U.S., 2016



- **RMSF**
- ***R. parkeri***
- **Pacific Coast tick fever**
- **Rickettsial pox**

<https://www.cdc.gov/ticks/tickbornediseases/overview.html>

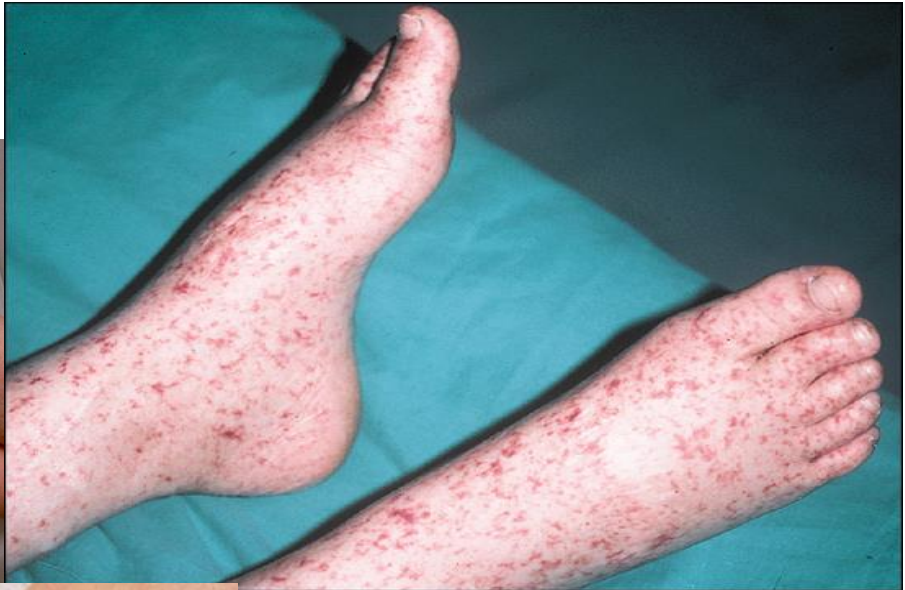
RMSF: A Diagnostic Challenge

Classic triad

- **Fever-98-100%**
- **Rash-80-95%**
- **Headache 60-90%**

Days from onset	Signs and symptoms (untreated)
1-2	<ul style="list-style-type: none">• Fever• Headache, myalgias, malaise (flu-like)
2-4	<ul style="list-style-type: none">• Rash• Abdominal pain, n/v• Cough• Edema
5-7	<ul style="list-style-type: none">• High grade fever• Rash becomes petechial
7-9	<ul style="list-style-type: none">• Purpura fulminans• Sepsis, AKI, ARDS• Meningoencephalitis, coma

Progression of Rash



Laboratory Features of RMSF

Characteristic	Value (median and interquartile range)
Platelets/mm ³	128,000 (72,000-228,000)
<150,000/mm ³	59%
<100,000/mm ³	41%
Sodium, mEq/dL	133 (129-137)
<135 mEq/dL	52%
Alanine transaminase, U/L	55 (36-78)
Aspartate transaminase, U/L	83 (44-125)

Diagnostic Testing and Treatment of SFR Diseases

Test	SFGR
Acute Serology	15%
Convalescent serology	>90%
Skin biopsy	70-90%
Whole blood PCR	NA

Most patients are seronegative at presentation

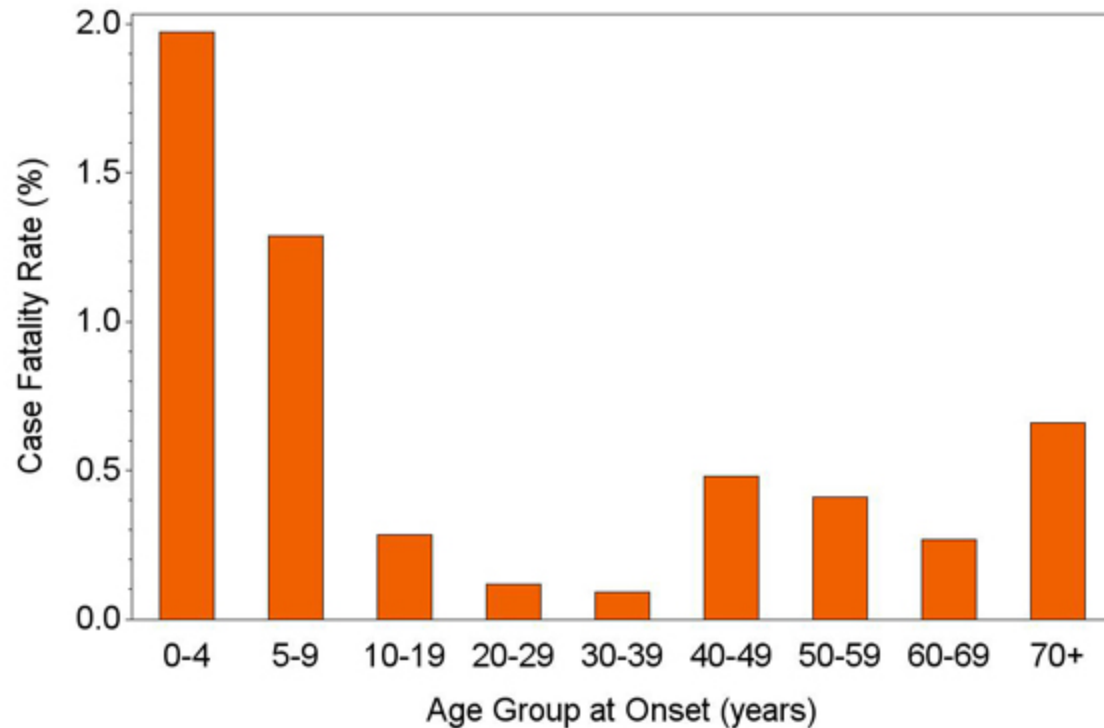
Convalescent serology allow RETROSPECTIVE diagnosis

Treat first, confirm diagnosis later!

Treatment for ALL AGES is doxycycline

Fatal Cases of SFR

Case Fatality Rate of Spotted Fever Rickettsiosis by Age Group, 2008-13



Children <10 years account for 6% of cases, but 22% of RMSF deaths

National survey, 2012

- 80% of providers would rx doxycycline to patients ≥ 8 years
- 35% would give to patients <8 years

Average time to death of untreated RMSF is 8 days

EMPIRIC treatment with doxycycline can be life-saving

Not all Tick-borne Disease is Infectious...



Tick-Associated Meat Allergy

Galactose-alpha 1,3-galactose (alpha gal) present in both tick saliva and red meat

Human IgE production stimulated by meat consumption

Symptoms:

- **Hives or skin rash**
- **Nausea, stomach cramps, indigestion, vomiting, diarrhea**
- **Stuffy/runny nose, sneezing**
- **Bronchospasm**
- **Anaphylaxis**



Diagnosis of Alpha-Gal Allergy

**IgE Alpha Gal
immunoassay,
or.....**



Treatment Alpha-Gal Allergy



Summary



Tick borne diseases are **COMMON**

Lyme is most common, but regional

Coinfections can occur

Consider Ehrlichioses & Rickettsioses

- Nonspecific febrile illness
- Spring/summer/fall
- Potential tick exposure
- Rash may be a clue (but often absent)

Don't wait for lab confirmation

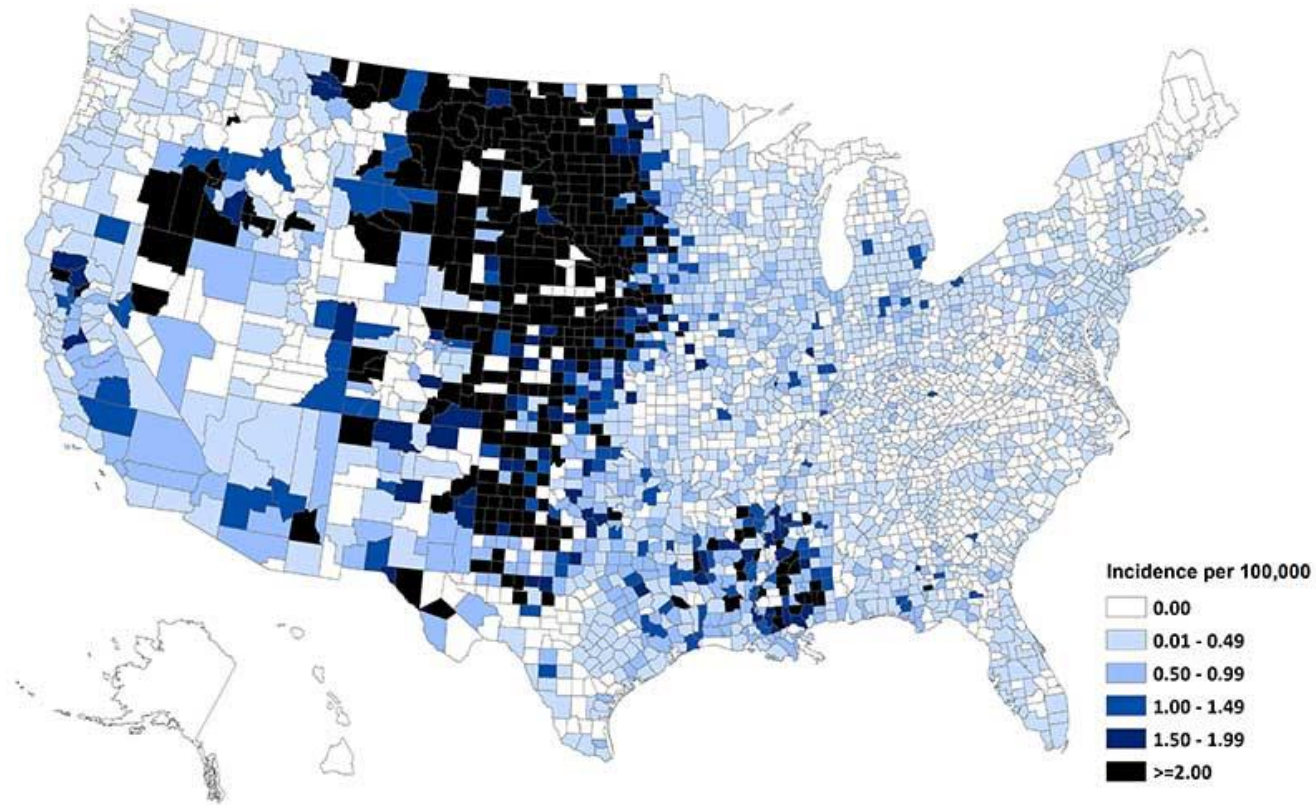
Early treatment may be LIFE saving

Doxycycline for all ages

Mosquito-borne Infections in the US

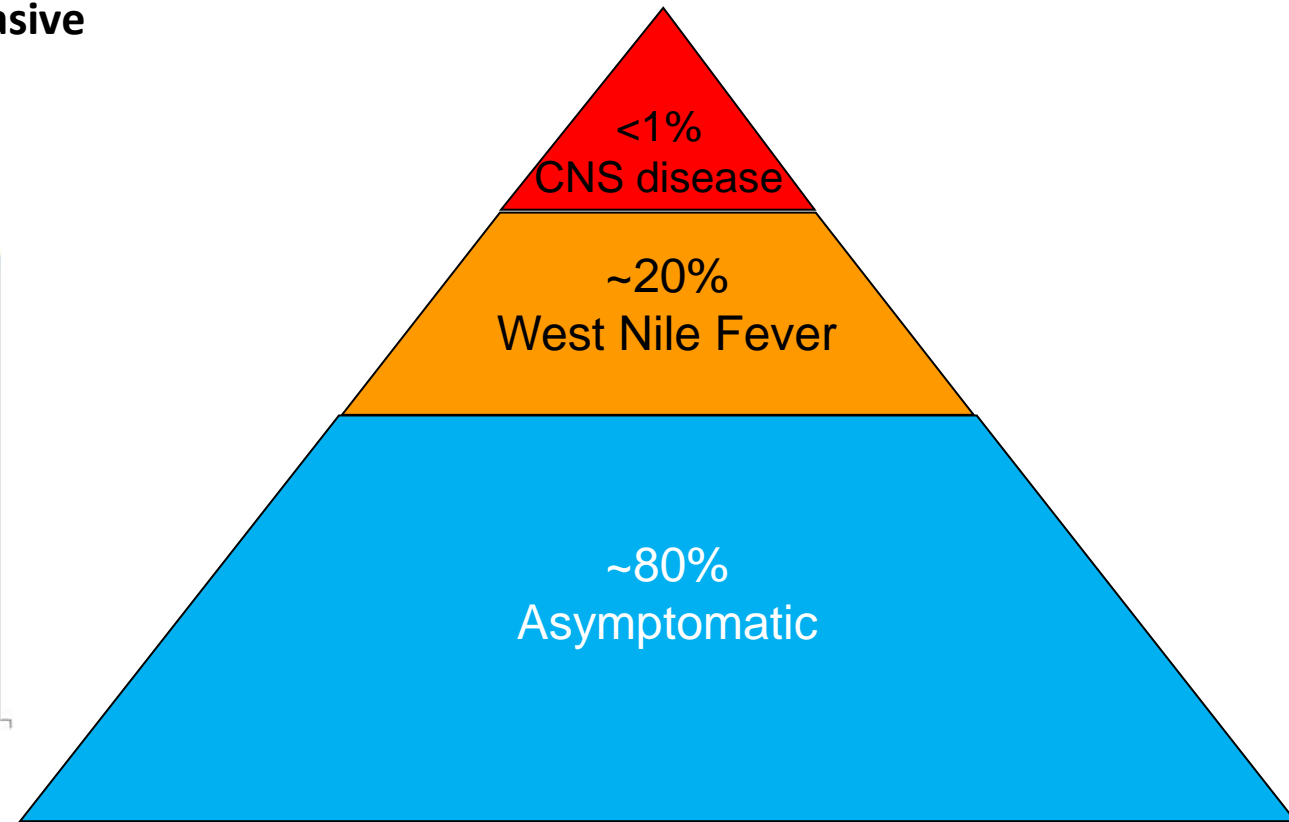
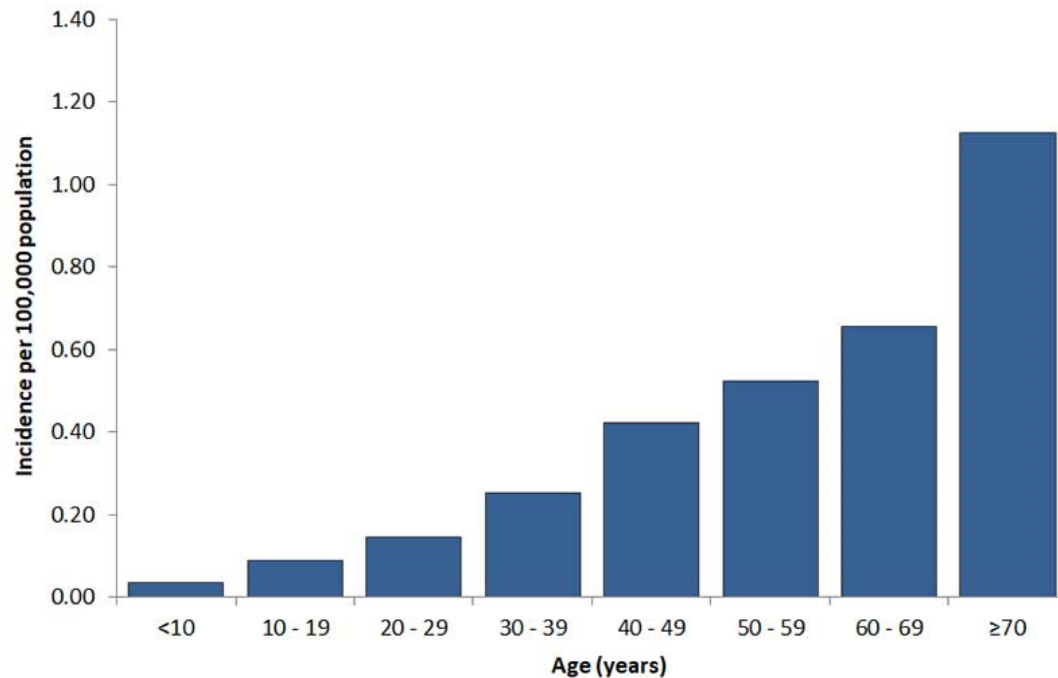


West Nile Virus Infections, 1999-2018



WNV Human Infection

Average annual incidence of West Nile virus neuroinvasive disease reported to CDC by age group, 1999-2018



West Nile Fever

Outcome	Total Patients, n (%) [95% CI]
Symptom [†]	
Fatigue	94 (96 [90-99])
Fever	79 (81 [72-87])
Headache	70 (71 [62-79])
Muscle pain or aches	61 (62 [52-71])
Muscle weakness	60 (61 [51-70])
Rash	56 (57 [47-66])
Neck pain or stiffness	54 (55 [45-65])
Difficulty concentrating	52 (53 [43-63])
Joint pain or aches	36 (37 [28-47])



West Nile Virus Neurologic Disease

Meningitis

Encephalitis

Acute flaccid paralysis

- Symmetric or asymmetric
- Polio-like illness
- Progression to respiratory failure requiring mechanical ventilation

Correspondence



A Poliomyelitis-like Syndrome from West Nile Virus Infection

To the Editor: Muscle weakness is an important predictor of death in West Nile virus encephalitis.^{1,2} Yet this important finding lacks a well-defined pathological basis. In monkey models, West Nile virus causes poliomyelitis.³



MMWR

Morbidity and Mortality Weekly Report

Weekly

September 20, 2002 / Vol. 51 / No. 37

Acute Flaccid Paralysis Syndrome Associated with West Nile Virus Infection — Mississippi and Louisiana, July–August 2002

West Nile virus (WNV) infection can cause severe, potentially fatal neurologic illnesses including encephalitis and

probable on the basis of the presence of virus specific Ig antibody in serum.

Treatment of WNV



No anti-viral agents

Supportive care

Exclude other treatable pathogens or syndromes

Imported Arboviruses



Chikungunya Virus

“That which bends up” due to severe joint pains

Symptoms

- **Fever**
- **Polyarthralgia (may last months to years)**
- **Headache**
- **Maculopapular rash (variable)**

Prior to 2013, NO cases detected in the Americas

As of 2017: >1.7 million cases reported

Zika Virus: Methods of Transmission

Mosquito bite (*Aedes* spp)

Maternal-Child Transmission

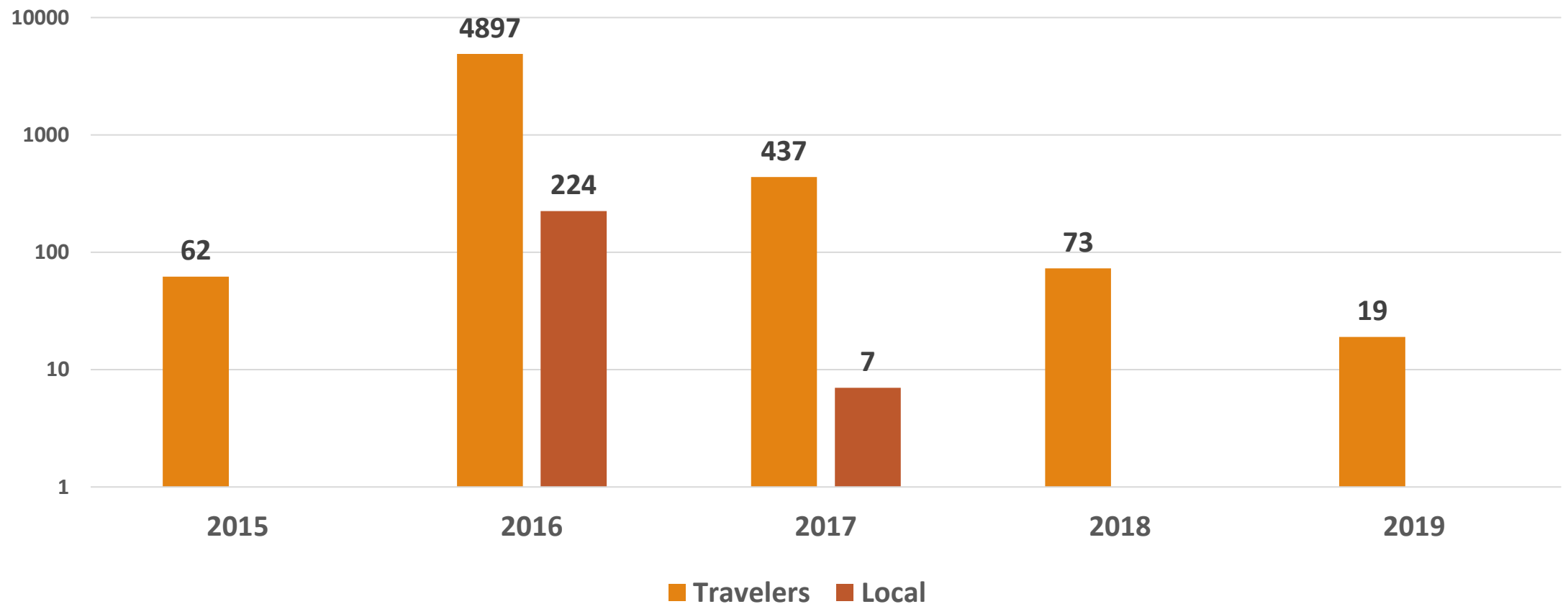
Sexual transmission

Blood transfusion

- **Screening of donations 8/2016**



Zika Virus Infections in the US (Log Scale)



Summary: Mosquito-borne Infections

West Nile virus infection is the most common mosquito borne disease in the US

Range from asymptomatic infection to neuroinvasive disease

- Imported infections include Chikungunya and Zika virus

Treatment is supportive care



Vectors are Inescapable

Mosquitos

- Rural and urban areas
- Standing water (tires, tree holes, indoor pots)
- Bite through clothes

Ticks

- Widespread in environment
- Pets as reservoirs



Behavioral Interventions

Cover up

Screen windows/doors

Shower after outdoor activities

Buddy Check



EPA-Registered Repellents

DEET –500 products

Picaridin—40 products

IR 3535—45 products

Oil of Lemon Eucalyptus—10 products

Catnip Oil—4 products

BLOUD—1 product

Oil of Citronella-3 products



Any Volunteers?



TABLE 1. PROTECTION TIMES OF INSECT REPELLENTS.*

PRODUCT	ACTIVE INGREDIENT AND CONCENTRATION	COMPLETE-PROTECTION TIME		CATEGORY OF PROTECTION†
		MEAN	RANGE	
		min		
OFF! Deep Woods (SC Johnson)	DEET, 23.8%	301.5±37.6	200–360	A
Sawyer Controlled Release (Sawyer)	DEET, 20%	234.4±31.8	180–325	B
OFF! Skintastic (SC Johnson)	DEET, 6.65%	112.4±20.3	90–170	C
Bite Blocker for Kids (HOMS)	Soybean oil, 2%	94.6±42.0	16–195	D
OFF! Skintastic for Kids (SC Johnson)	DEET, 4.75%	88.4±21.4	45–120	D
Skin-So-Soft Bug Guard Plus (Avon)	IR3535, 7.5%	22.9±11.2	10–60	E‡
Natrapel (Tender)	Citronella, 10%	19.7±10.6	7–60	E‡
Herbal Armor (microencapsulated) (All Terrain)	Citronella, 12%; peppermint oil, 2.5%; cedar oil, 2%; lemongrass oil, 1%; geranium oil, 0.05%	18.9±13.3	1–55	E§
Green Ban for People (Mulgum Hollow Farm)	Citronella, 10%; peppermint oil, 2%	14.0±11.3	1–45	E
Buzz Away (Quantum)	Citronella, 5%	13.5±7.5	5–30	E
Skin-So-Soft Bug Guard (Avon)	Citronella, 0.1%	10.3±7.9	1–30	E
Skin-So-Soft Bath Oil (Avon)	Uncertain¶	9.6±8.8	1–30	E
Skin-So-Soft Moisturizing Suncare (Avon)	Citronella, 0.05%	2.8±3.4	1–15	F
Gone Original Wristband (Solar Glooooooow)	DEET, 9.5%	0.3±0.2	0.17–1.33	G
Repello Wristband (Repello Products)	DEET, 9.5%	0.2±0.08	0.17–0.63	H
Gone Plus Repelling Wristband (Solar Glooooooow)	Citronella, 25%	0.2±0.09	0.17–0.48	H

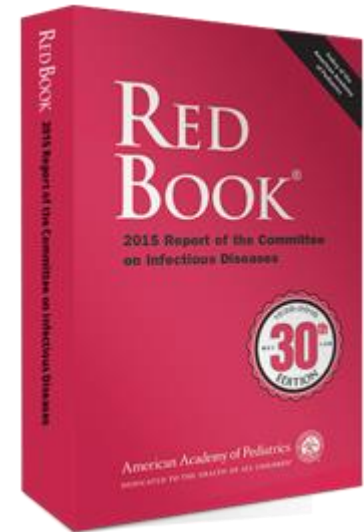
DEET (*N,N*-diethyl-3-methylbenzamide)

Is it effective?

- Available since 1957, the “Gold Standard”
- Active against **both** mosquitoes and ticks

Is it safe in children?

- **Yes!**
- EPA: no age or concentration restriction
- CDC and AAP : Safe for use on children **over the age of 2 months**, recommends **≤30%** DEET



Increased Concentration, Increased Duration

100% DEET= 12 hours

34.5% DEET (SR) = 12 hours

30% DEET= up to 8 hours

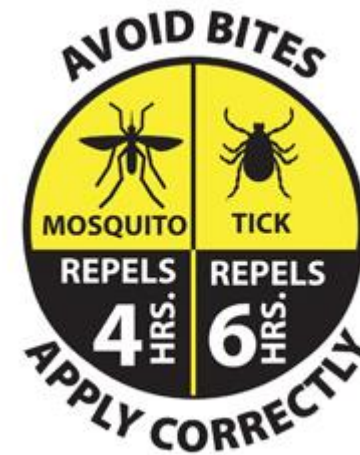
25% DEET= up to 6+ hours

15% DEET= up to 4+ hours

10% DEET= up to 2+ hours

5% DEET= 90 min

Minimal incremental prolonged protection above 50%





WRONG!



RIGHT!

Insecticides

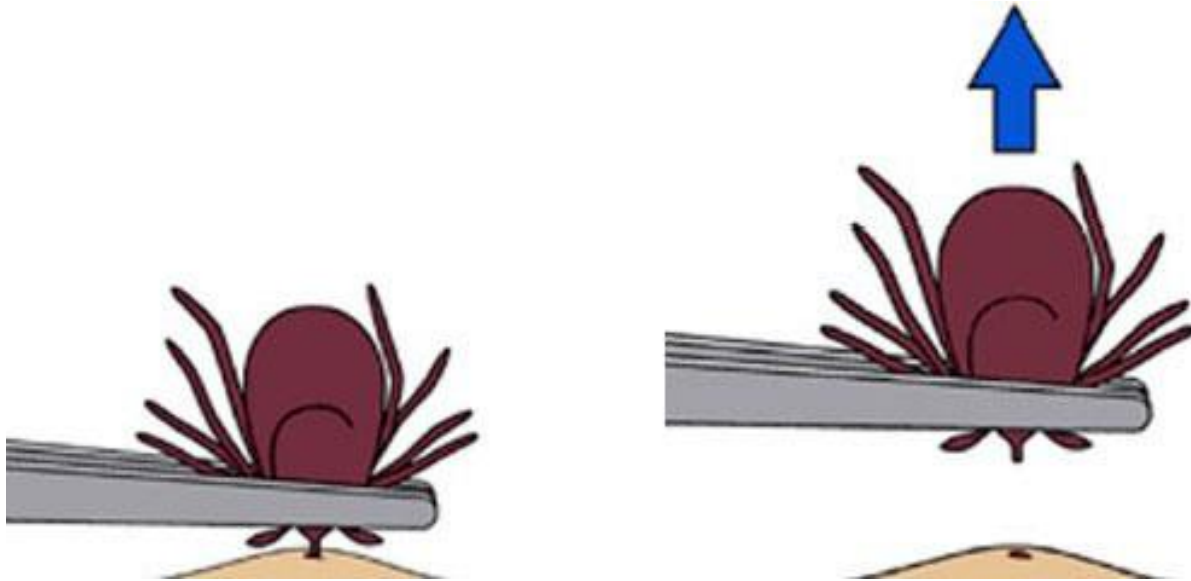
Repellents *REPEL* insects

Insecticides (Permethrin) *KILL* them

- Apply to clothes, shoes, bed nets, camping gear
- Permethrin-treated clothing EPA approved (including children and pregnant women)
- Avoid use on skin
- Avoid use on fabric that young children may chew or suck



Tick Removal



Clean thoroughly with soap and water, alcohol, or an iodine scrub

What NOT to do...

- Burn it (gasoline, kerosene)
- Smother it (petroleum jelly)
- Poison it (fingernail polish)
- Annihilate it (lit matches)
- Crush it

Summary

Behavioral interventions

- Air conditioners or screens
- Cover up
- Shower and buddy check

Repellents active against BOTH ticks and mosquitos (>20%)

- DEET
- Picaridin
- IR3535

Insecticides



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Questions?

