Tiny Bug, BIG Problem

Lyme and Other Tick-borne Diseases

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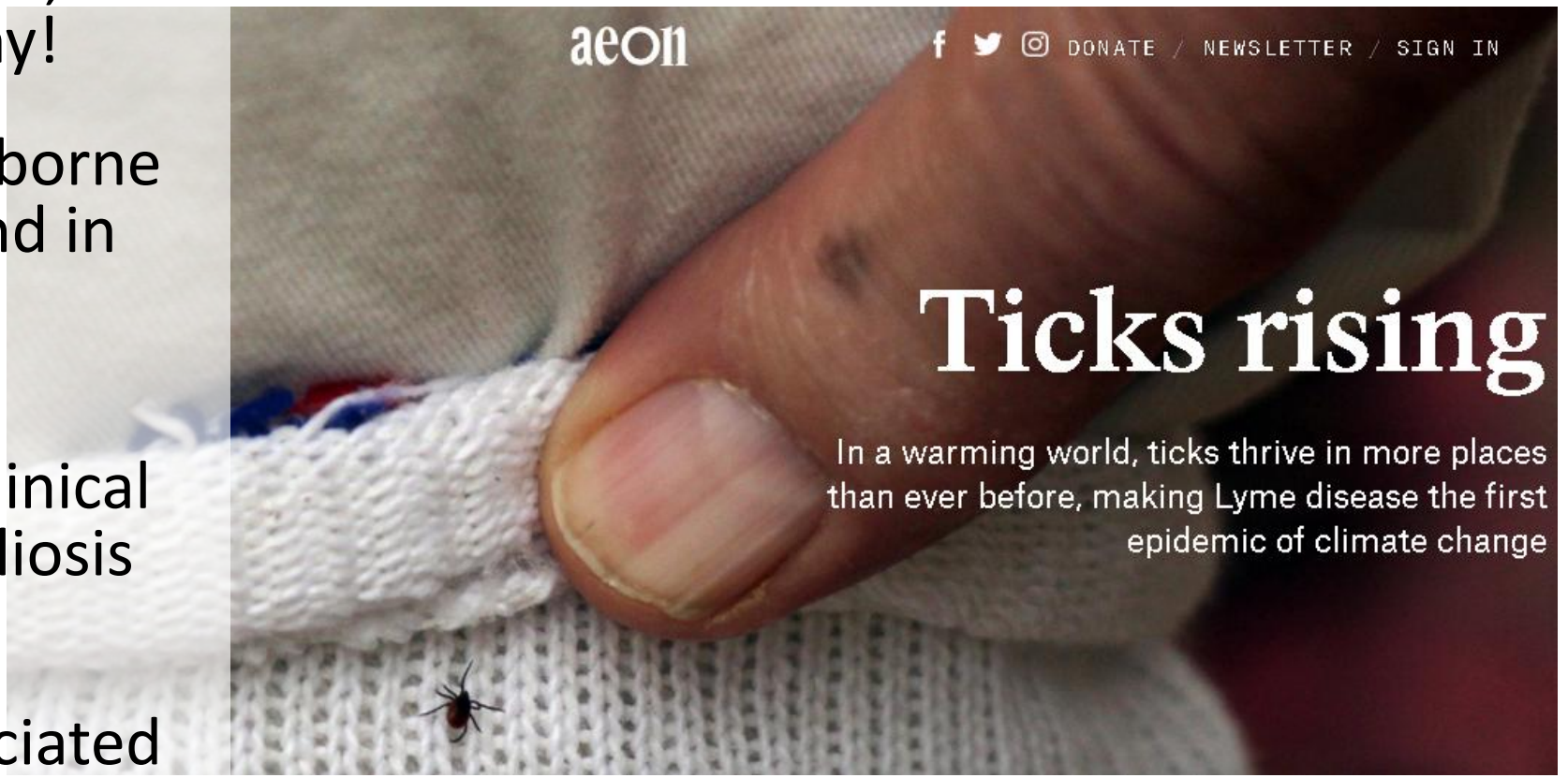
Mom

Overview

- Vectors and hosts: Ticks, and mice, and deer – oh my!
- Health burden of tick-borne diseases worldwide and in the US
- Epidemiological, microbiological, and clinical aspects of Lyme borreliosis (Lyme disease)
- Insights on Lyme-associated chronic illness (Lyme – IACI)



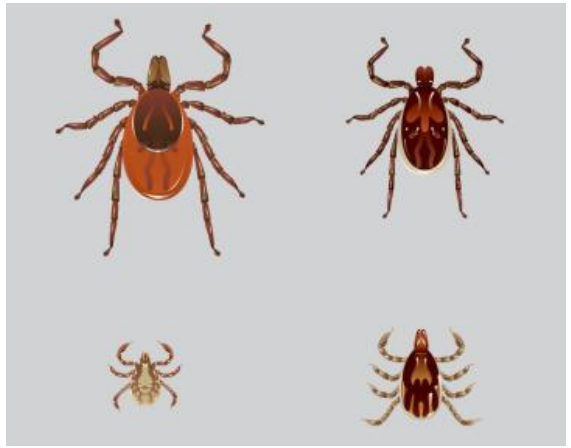
Tick-borne Diseases (TBDs) – Animals are the “hosts” and ticks are the “vectors”

Reservoir host is the white-footed (deer) mouse (*Peromyscus*)

Borrelia burgdorferi (Lyme disease), *B. miyamatoi* (BMD*)* and other “Relapsing Fever” *Borrelia, Anaplasma* (anaplasmosis)*, Ehrlichia* (ehrlichiosis)*, Babesia* (babesiosis), and Powassan virus

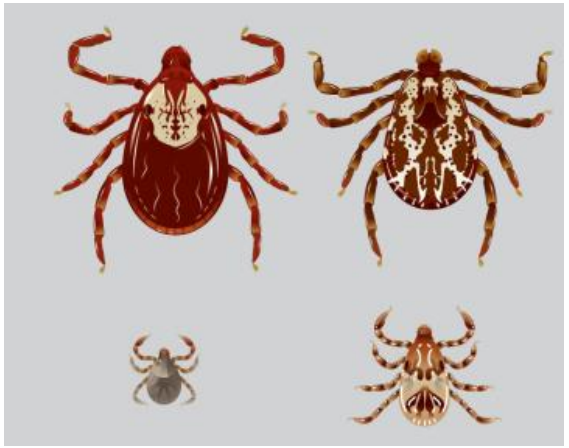
Incidental hosts

Ixodes
Black-legged (deer) tick



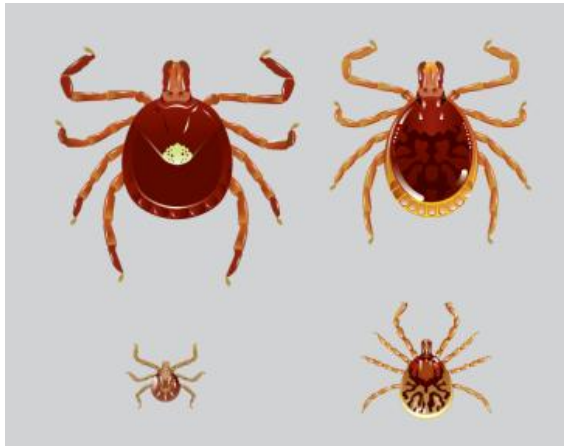
[1]**Lyme disease**
(*Borrelia* spp.)
Anaplasmosis
Babesiosis
Powassan Virus
[2]**BMD** (*Borrelia* spp.)
Ehrlichiosis
Alpha-gal syndrome
Tick paralysis

Dermacentor
Dog tick



RMSF
Tularemia
Powassan Virus
Tick paralysis

Amblyoma
Lone Star tick



Ehrlichiosis
Tularemia
Powassan virus et.al.
RMSF
[2]**STARI** (*Borrelia* spp.)
Alpha-gal syndrome
Tick paralysis

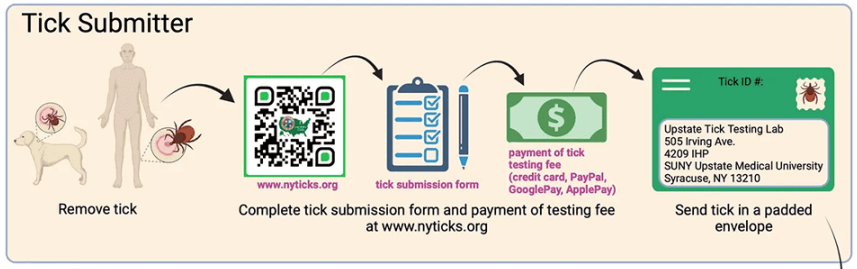
**Haemophysalis*
Longhorned tick

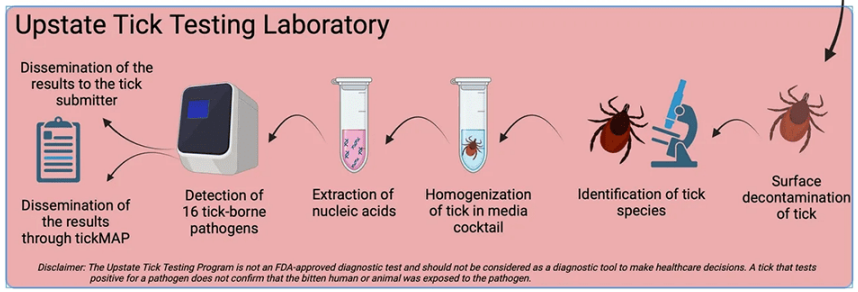
RMSF
Theileriosis
Powassan virus
Blood loss
Heartland virus
Tick paralysis

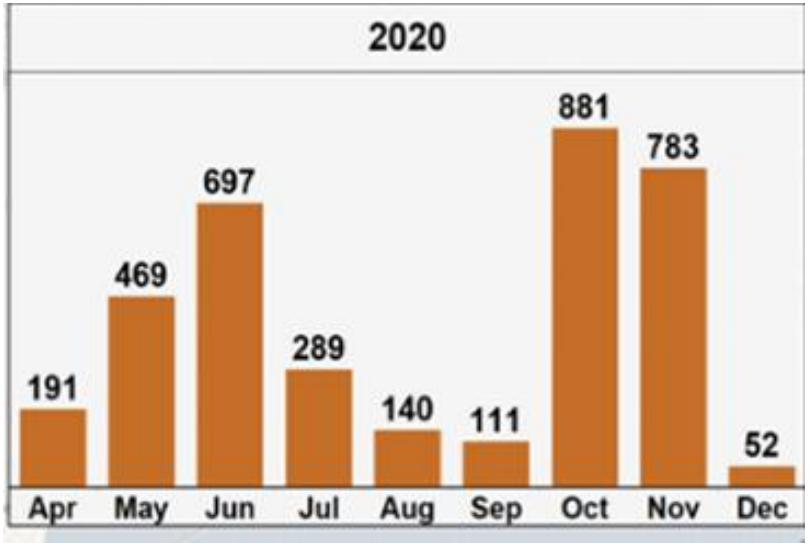
*Carries but doesn't transmit Lyme disease?

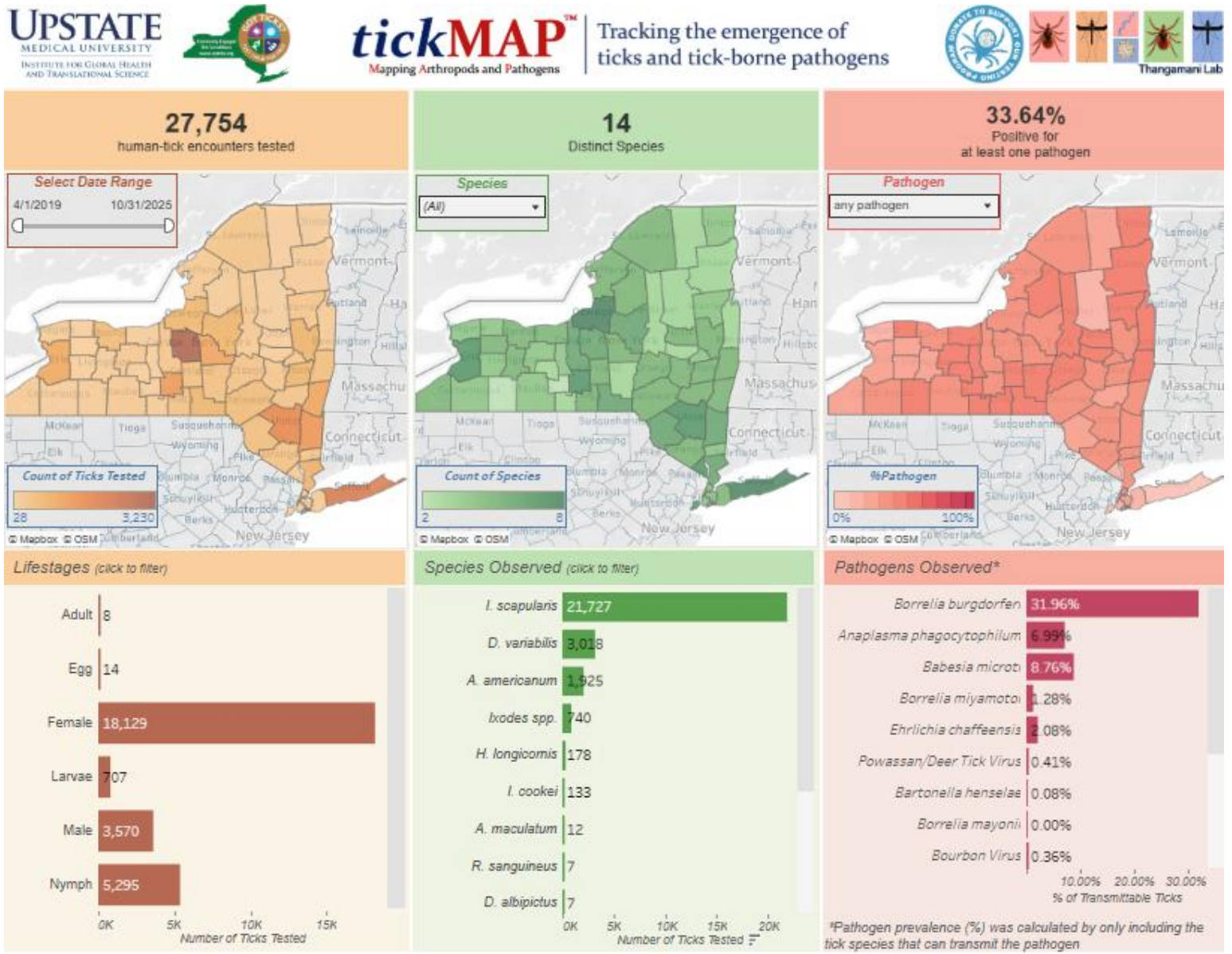
[1]Lyme Borreliosis
[2]Relapsing Fever Borreliosis

https://nyticks.org





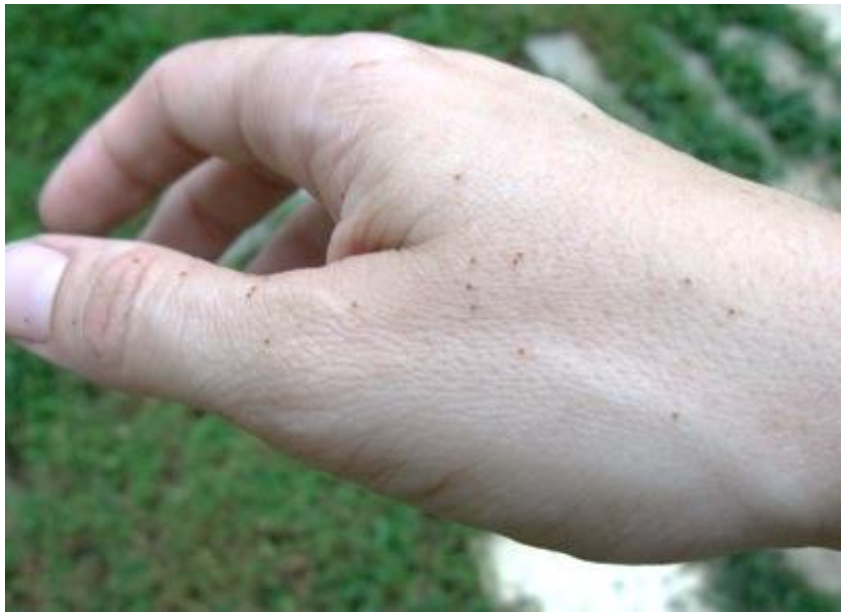




Hart CE, Bhaskar JR, Reynolds E, Hermance M, Earl M, Mahoney M, Martinez A, Petzlova I, Esterly AT, Thangamani S. Community engaged tick surveillance and tickMAP as a public health tool to track the emergence of ticks and tick-borne diseases in New York. PLOS Glob Public Health. 2022 Jun 27;2(6):e0000215

Ixodes scapularis

Larval stage



Female Adult

Nymph stage

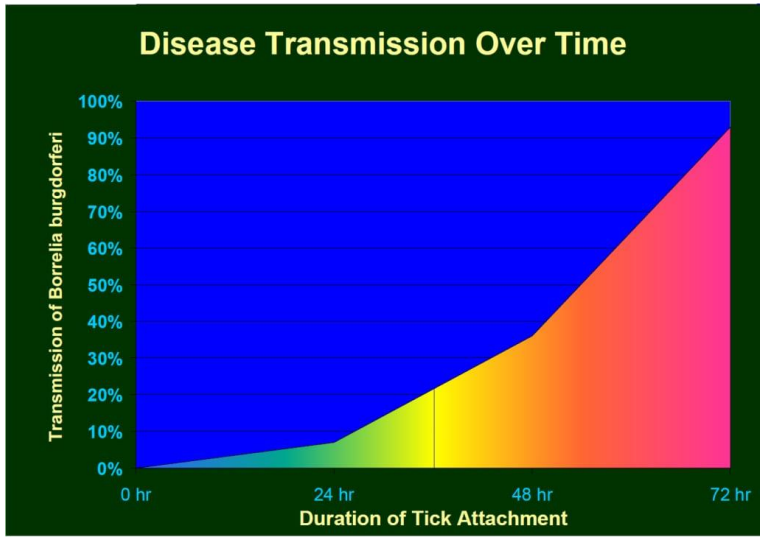
Engorged Female Adult

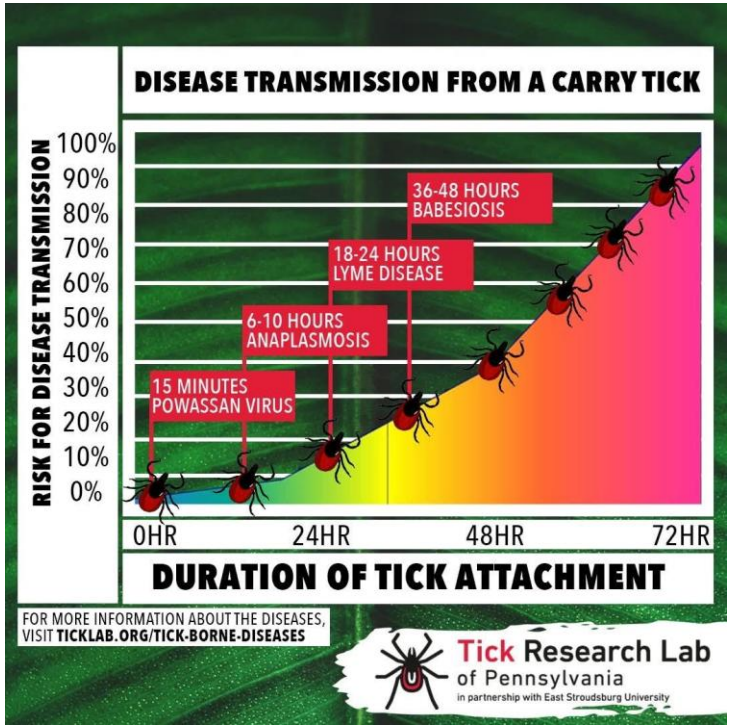
How long before a tick makes you sick??

No one really knows….

- Ticks may carry no pathogens, or may carry multiple pathogens.
- Different tick stages may take longer or shorter to transmit pathogens
- Assumption that ticks must be attached for > 48 hours is based on limited research done with mice and nymph stage ticks ONLY
- Bottom Line: The longer the tick is attached, the higher the risk!

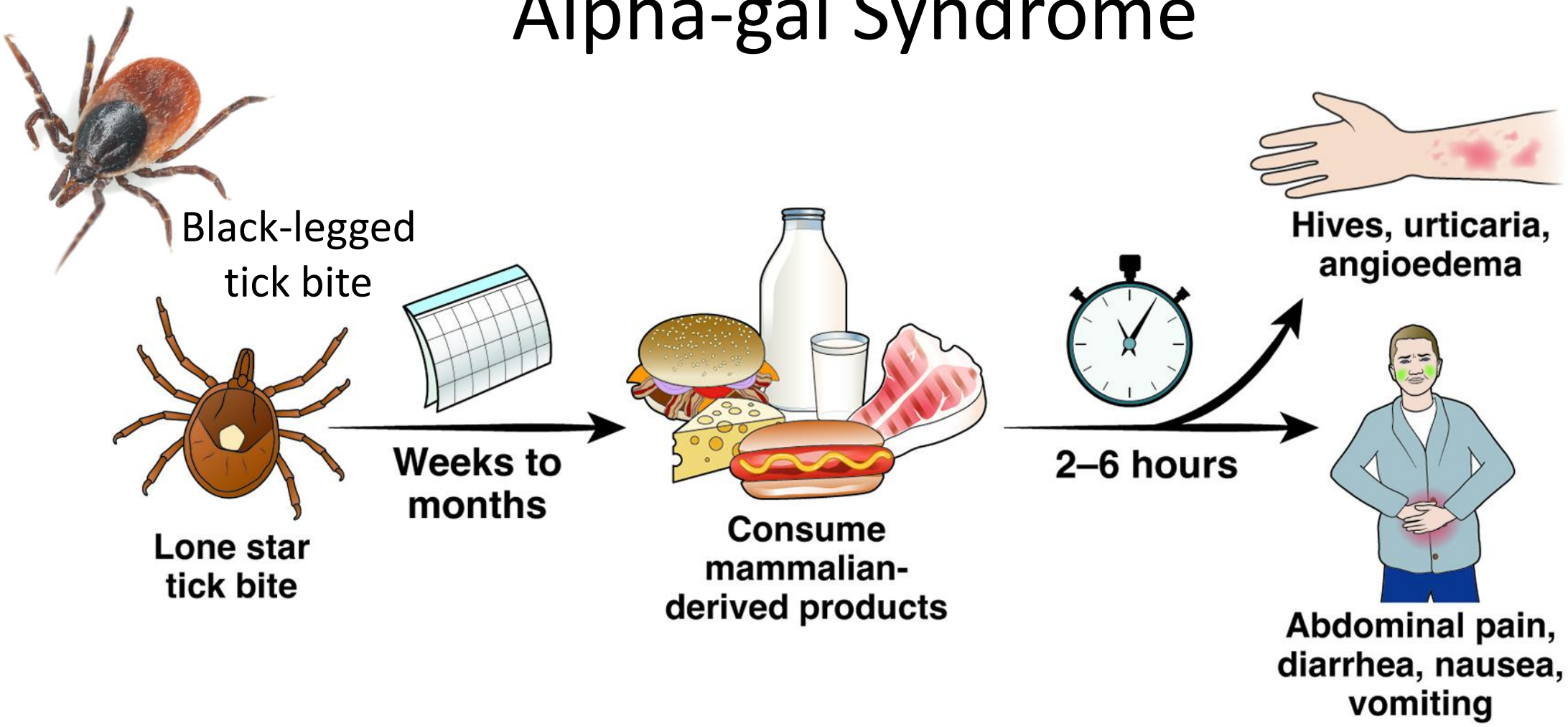
Lyme disease





New TBD on the Block:

Alpha-gal Syndrome

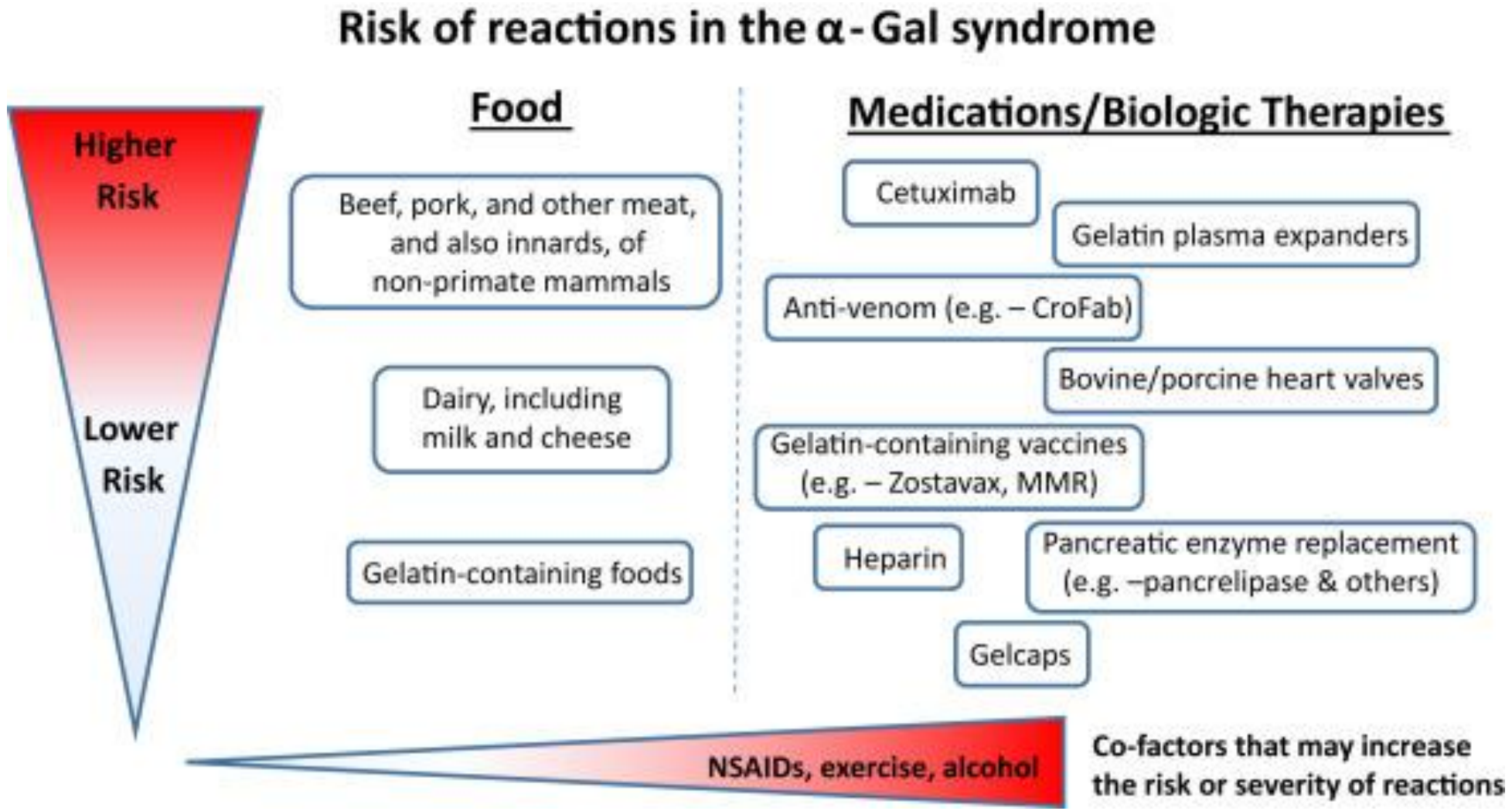


Allergic reaction to α-galactose

"Alpha-gal that is contained in glycolipids is suspected to be the triggering antigen, and the slow gut absorption of lipid accounts for the delay in reaction. Some patients have only one symptom such as hives or gastrointestinal distress, but most report multiple symptoms."

Houchens, Nathan & Hartley, Sarah & Commins, Scott & Claar, Dru & Saint, Sanjay. (2021). Clinical Problem-Solving: Hunting for a Diagnosis. New England Journal of Medicine. 384. 462-467. 10.1056/NEJMcps2017588.

Allergy to Mammalian Meat

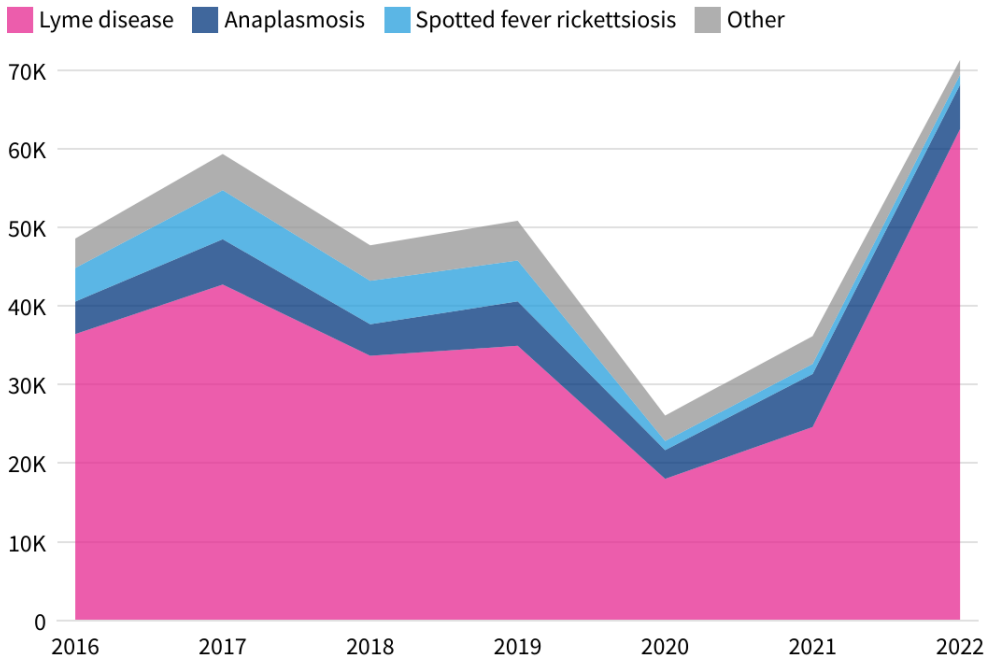



Ticks
SUCK!!!

Lyme disease is the most common tick-borne AND vector-borne disease in the US

Lyme disease accounted for 74% of all reported tickborne diseases from 2016–2022, and of 88% of all cases in 2022.

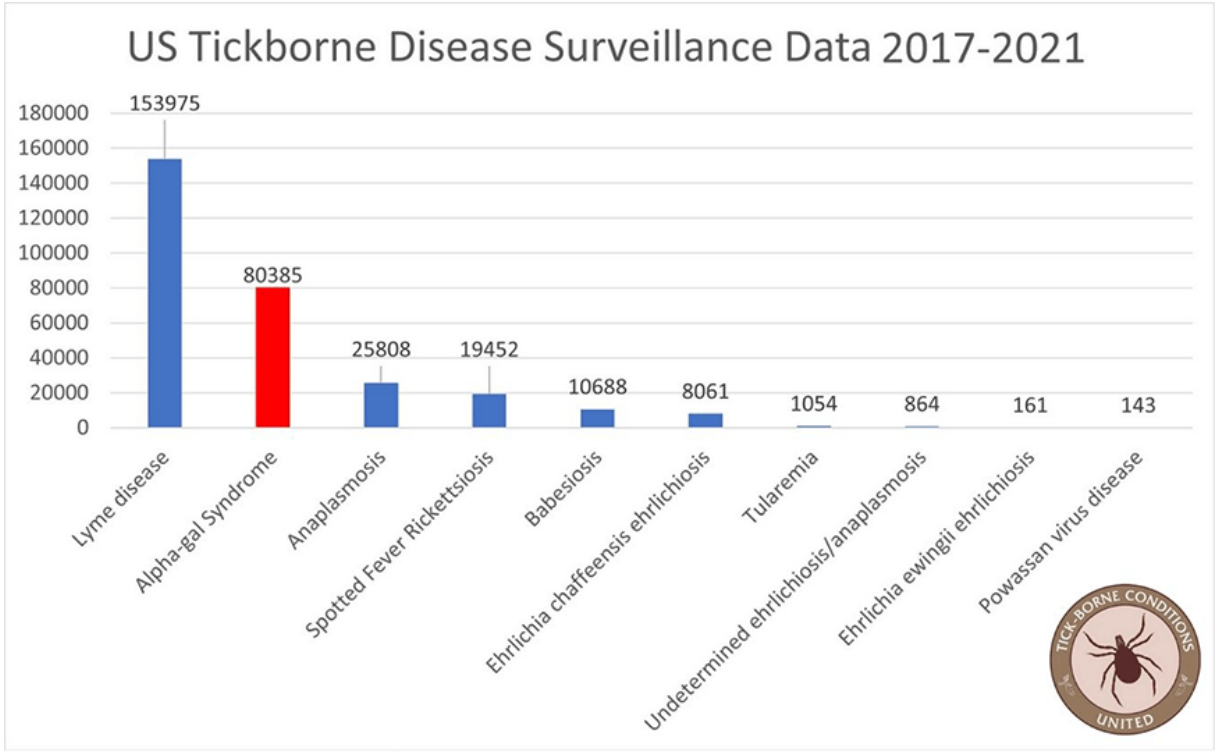
Cases of reported tickborne diseases, 2016–2022



Data unavailable for Babesiosis in 2022. Due to the COVID-19 pandemic, data from some jurisdictions in 2019 and 2020 are incomplete. Criteria for Lyme disease cases changed in 2022, resulting in increased reporting. "Other" category includes babesiosis, Ehrlichia chaffeensis ehrlichiosis, tularemia, undetermined ehrlichiosis/anaplasmosis, Ehrlichia ewingii ehrlichiosis, and Powassan virus disease

Source: Centers for Disease Control

USAFACTS

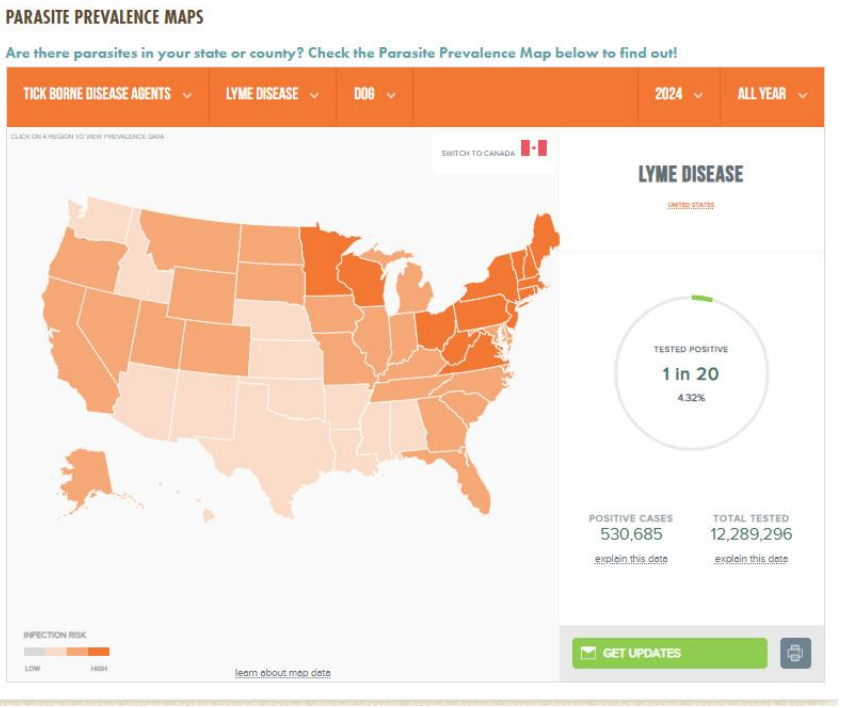


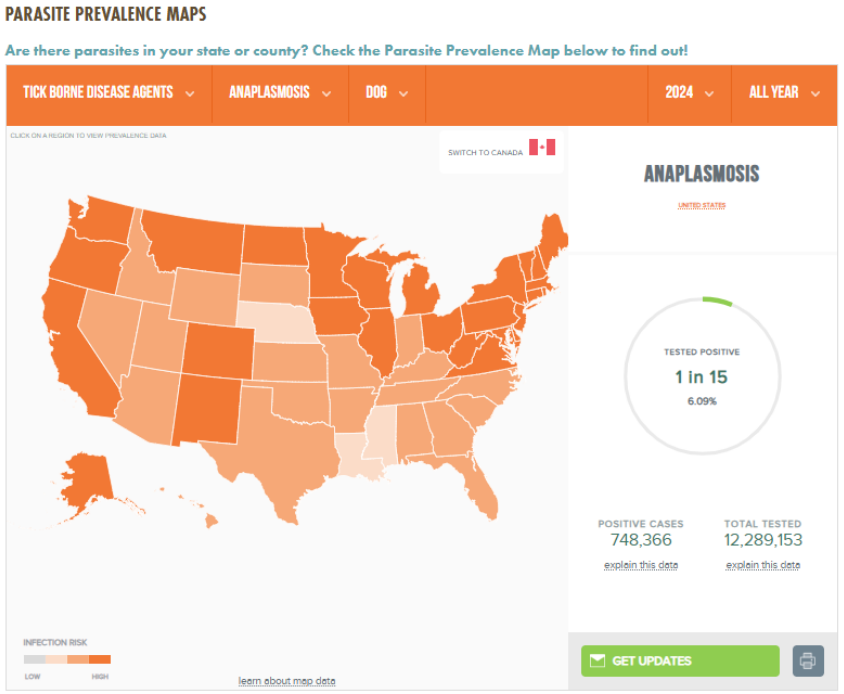
Centers for Disease Control and Prevention. (2024, July 15). Tickborne disease surveillance data summary. Centers for Disease Control and Prevention. https://www.cdc.gov/ticks/data-research/facts-stats/tickborne-disease-surveillance-data-summary.html

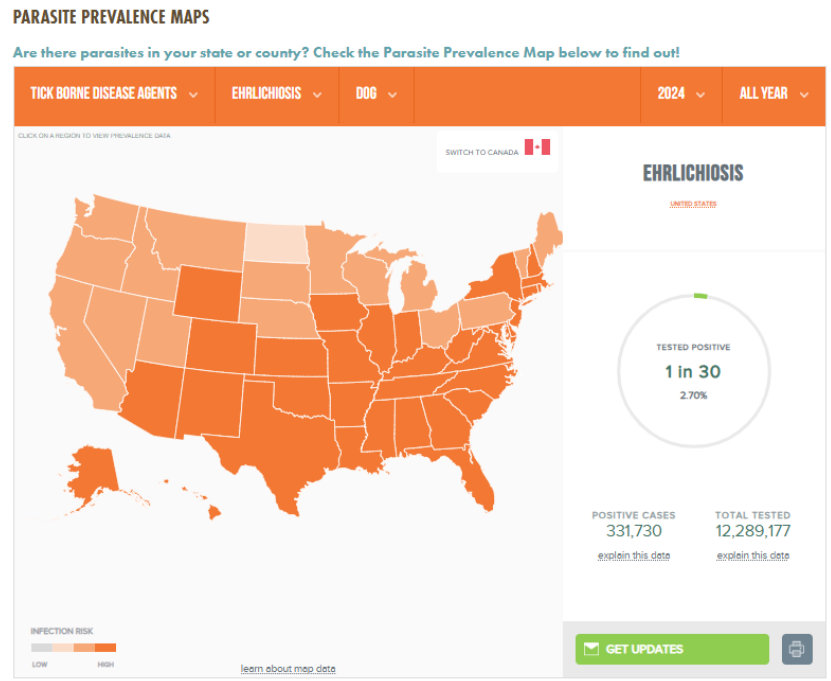
Thompson, J. M., Carpenter, A., Kersh, G. J., Wachs, T., Commins, S. P., & Salzer, J. S. (2023). Geographic distribution of suspected alpha-gal syndrome cases—United States, January 2017–December 2022. Morbidity and Mortality Weekly Report, 72(30), 815–820. https://www.cdc.gov/mmwr/volumes/72/wr/mm7230a2.htm

CAPC Surveillance (Dogs)

https://www.petsandparasites.org/parasite-prevalence-maps/#/







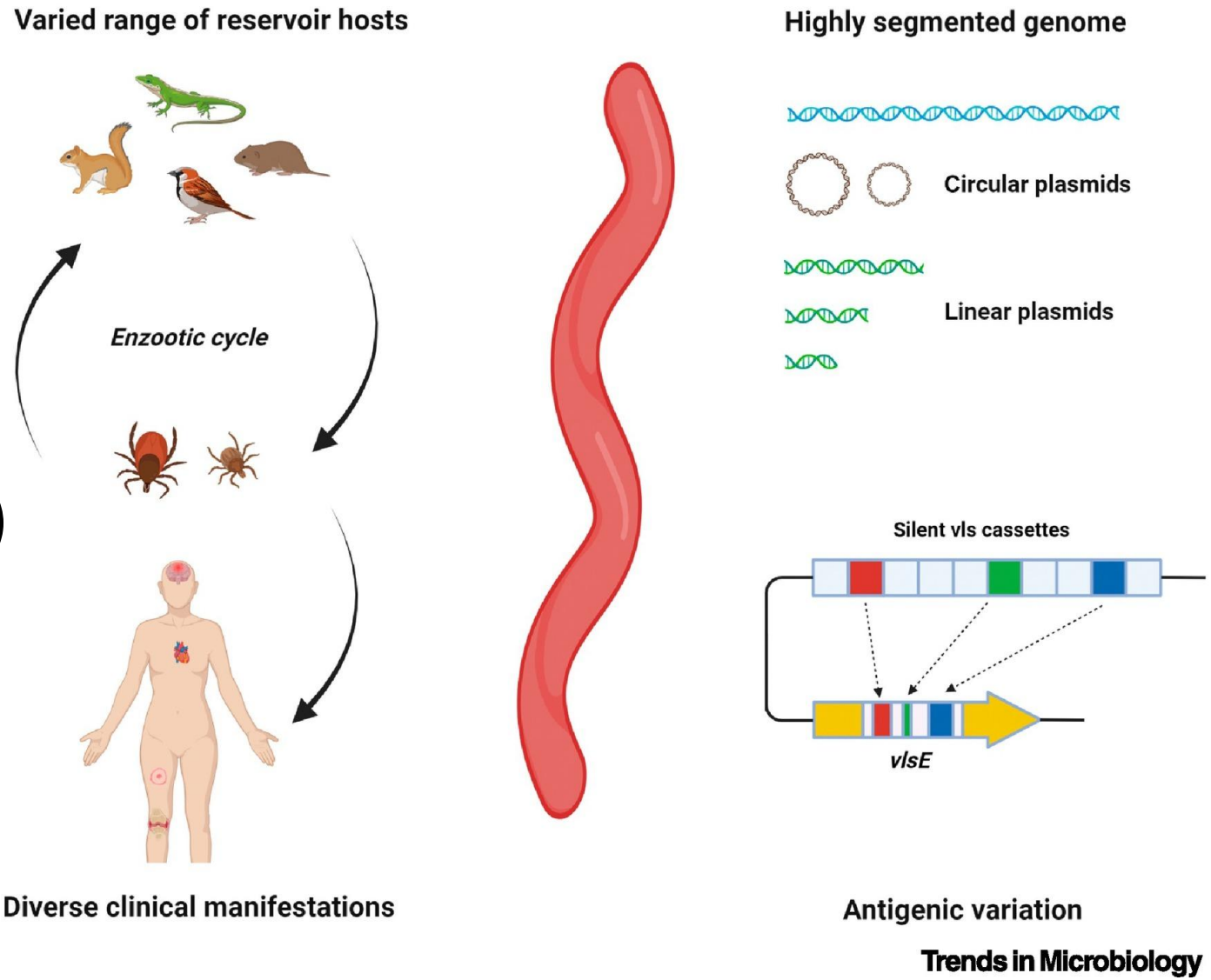
Lyme disease – Lyme borreliosis

Lyme borreliosis

- *Borreliella burgdorferi* (US)
- *B. afzelii* (Europe)
- *B. garinii* (Europe)

Relapsing fever borreliosis (US)

- *Borrelia miyamatoi* (BMD)
- *B. hermsii*
- *B. parkeri*
- *B. turicatae* (STARI)



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Lyme Disease Pathogenesis

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Abstract

Lyme disease *Borrelia* are obligately parasitic, tick-transmitted, invasive, persistent bacterial pathogens that cause disease in humans and non-reservoir vertebrates primarily through the induction of inflammation. During transmission from the infected tick, the bacteria undergo significant changes in gene expression, resulting in adaptation to the mammalian environment. The organisms multiply and spread locally and induce inflammatory responses that, in humans, result in clinical signs and symptoms. *Borrelia* virulence involves a multiplicity of mechanisms for dissemination and colonization of multiple tissues and evasion of host immune responses. Most of the tissue damage, which is seen in non-reservoir hosts, appears to result from host inflammatory reactions, despite the low numbers of bacteria in affected sites. This host response to the Lyme disease *Borrelia* can cause neurologic, cardiovascular, arthritic, and dermatologic manifestations during the disseminated and persistent stages of infection. The mechanisms by which a paucity of organisms (in comparison to many other infectious diseases) can cause varied and in some cases profound inflammation and symptoms remains mysterious but are the subjects of diverse ongoing investigations. In this review, we provide an overview of virulence mechanisms and determinants for which roles have been demonstrated *in vivo*, primarily in mouse models of infection.

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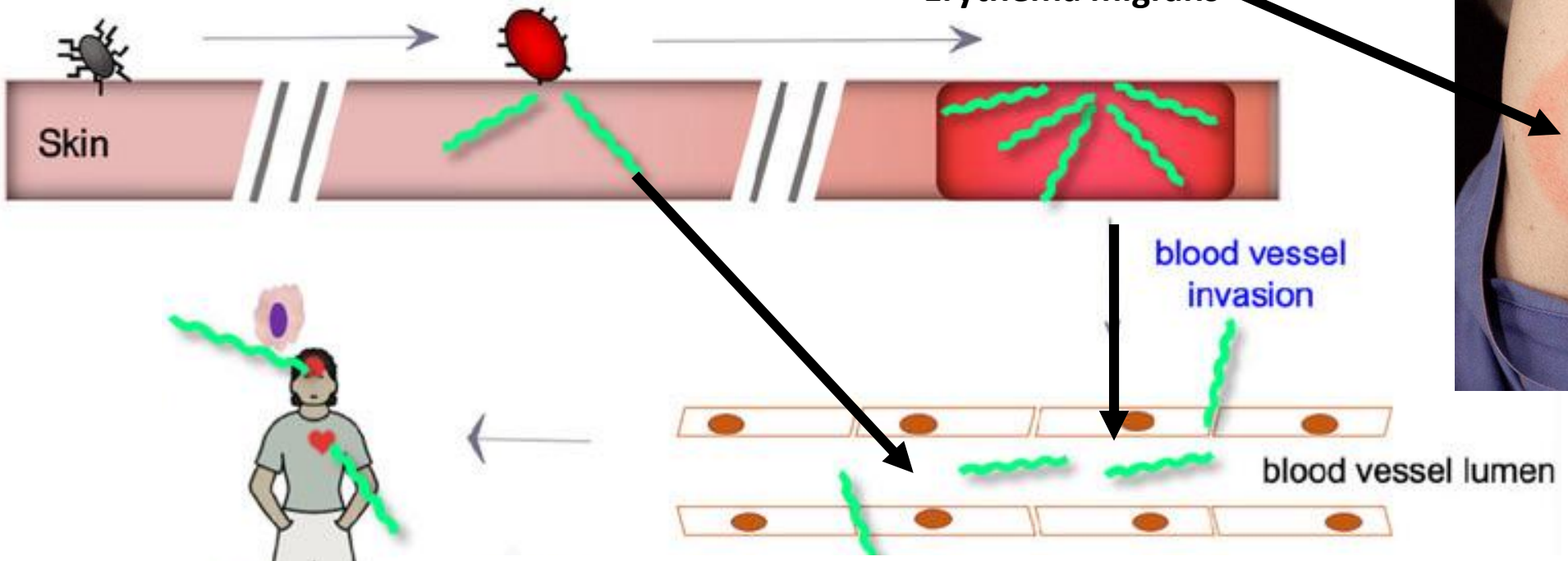
- Lyme disease Borrelia are obligately parasitic, tick-transmitted, **invasive, persistent bacterial pathogens** that cause disease in humans and non-reservoir vertebrates primarily through the induction of inflammation.
- During transmission from the infected tick, the **bacteria undergo significant changes in gene expression**, resulting in adaptation to the mammalian environment.
- The organisms multiply and spread locally and induce inflammatory responses that, in humans, result in clinical signs and symptoms. ***Borrelia* virulence involves a multiplicity of mechanisms for dissemination and colonization of multiple tissues and evasion of host immune responses**.
- Most of the tissue damage, which is seen in non-reservoir hosts, appears to result from host inflammatory reactions, despite the low numbers of bacteria in affected sites. This host response to the Lyme disease ***Borrelia* can cause neurologic, cardiovascular, arthritic, and dermatologic manifestations** during the disseminated and persistent stages of infection.
- **The mechanisms by which a small number of organisms … can cause varied and in some cases profound inflammation and symptoms remains mysterious but are the subjects of diverse ongoing investigations.**

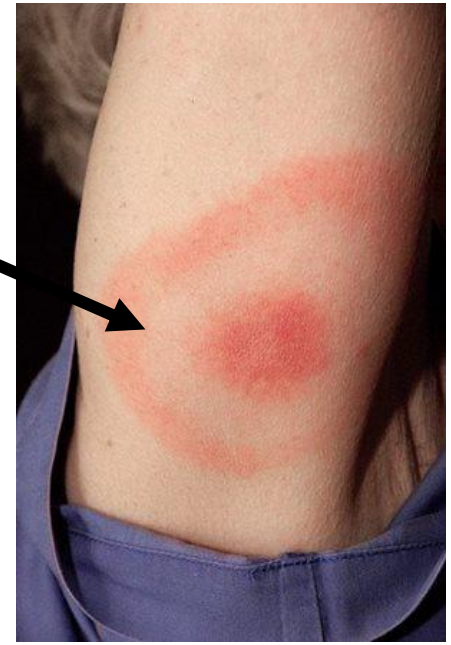
Multiple Mechanisms for Bacterial Dissemination and Colonization

Tick attaches to host and injects tick **salivary proteins** that **suppress the immune response,** modulate blood coagulation, protect Bb

Spirochetes inoculated into host during tick feeding

Spirochetes replicate and spread in skin:
Erythema migrans





Spirochetes penetrate endothelial layer, invade connective-tissue rich areas including the synovium, cardiac membranes and meninges, causing inflammation resulting in **arthritis, carditis, encephalopathy, neuropathy**

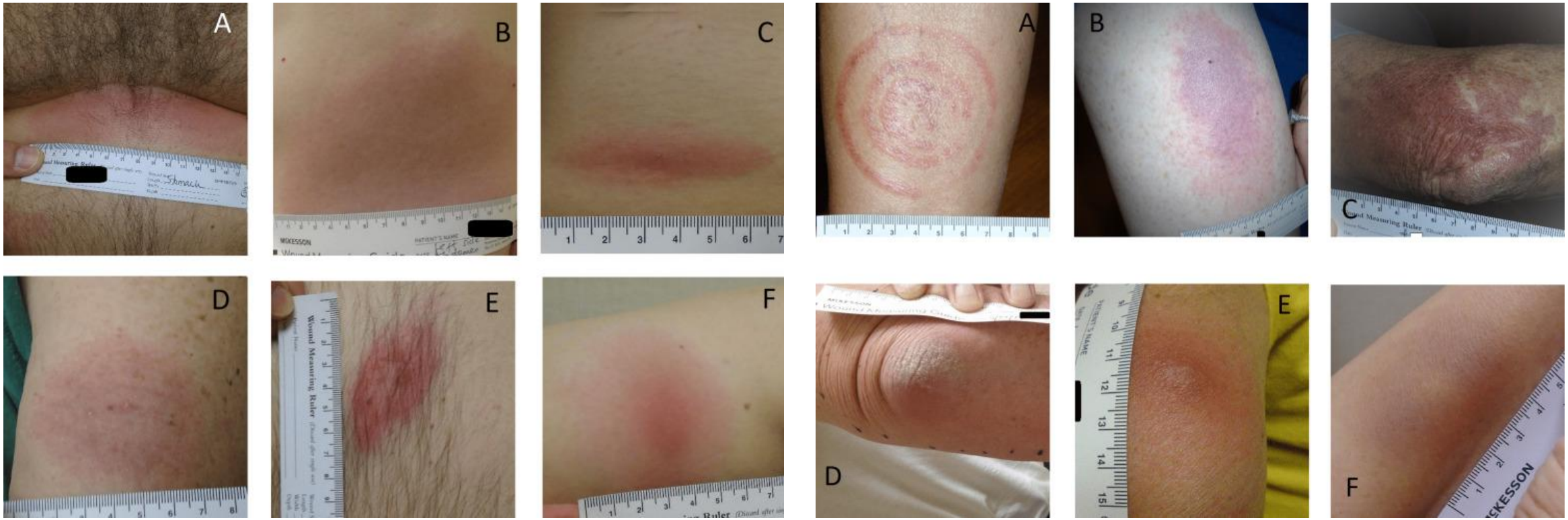
Lyme disease is difficult to diagnose

Misdiagnosis and delayed diagnosis can make Lyme disease more difficult to treat and lead to prolonged and debilitating illness

- ***The rash is not always present or easily recognized***
- ***Diagnostic tests cannot yet accurately identify the earliest stage of Lyme disease when making the diagnosis is crucial.***
- Early symptoms can be mistaken for a summer flu
- Lyme disease can involve several parts of the body, including joints, connective tissue, heart, brain, and nerves, and produce different symptoms at different times.
- Antibody testing done after early treatment may be negative and never turn positive for some cases
- *Borrelia burgdorferi* can evade our protective immune system and trigger immune system dysfunction.
- No reliable blood test is presently available to measure treatment success, necessitating close clinical follow up and improved physician education.

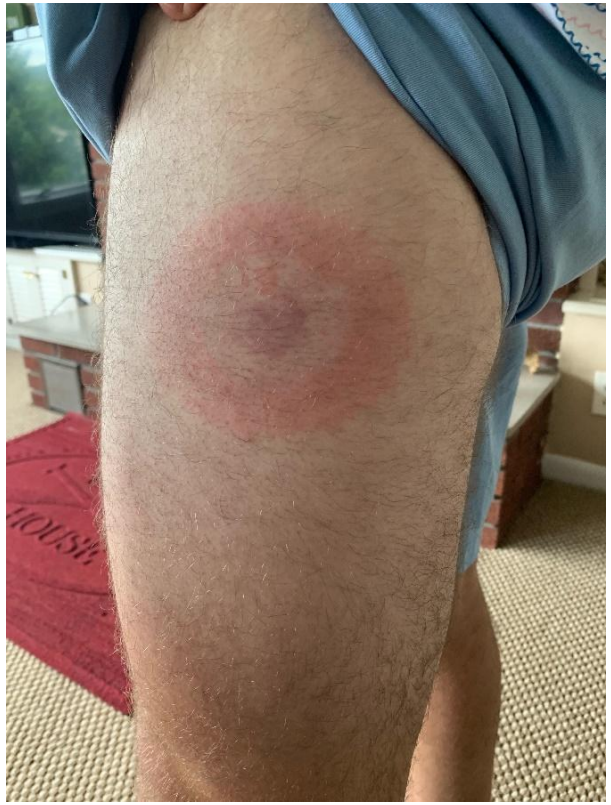
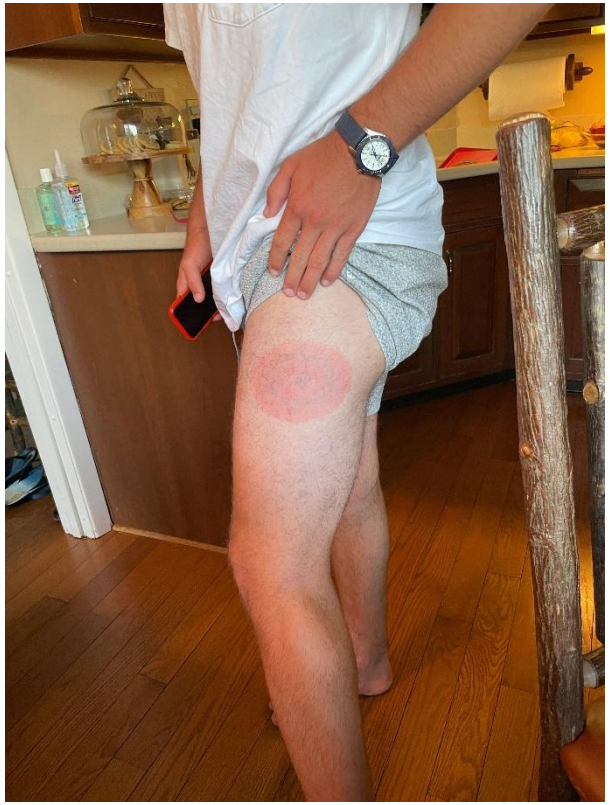
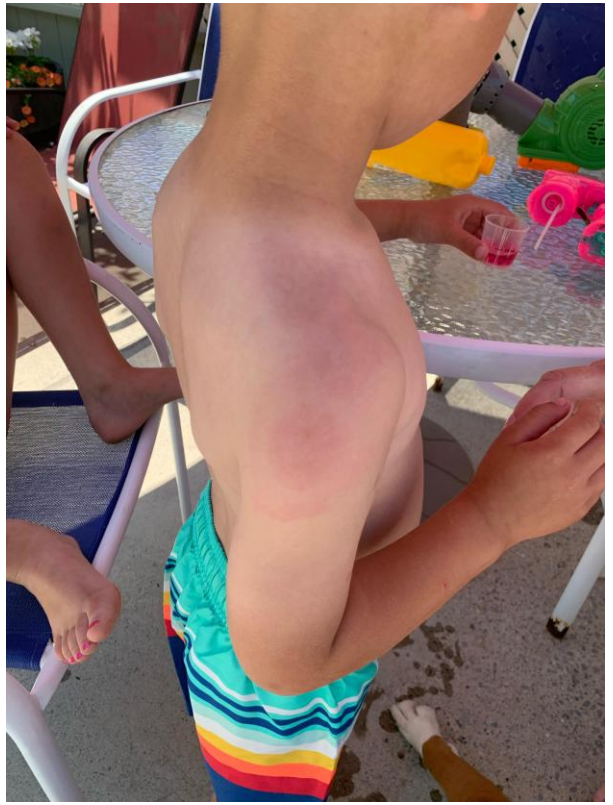
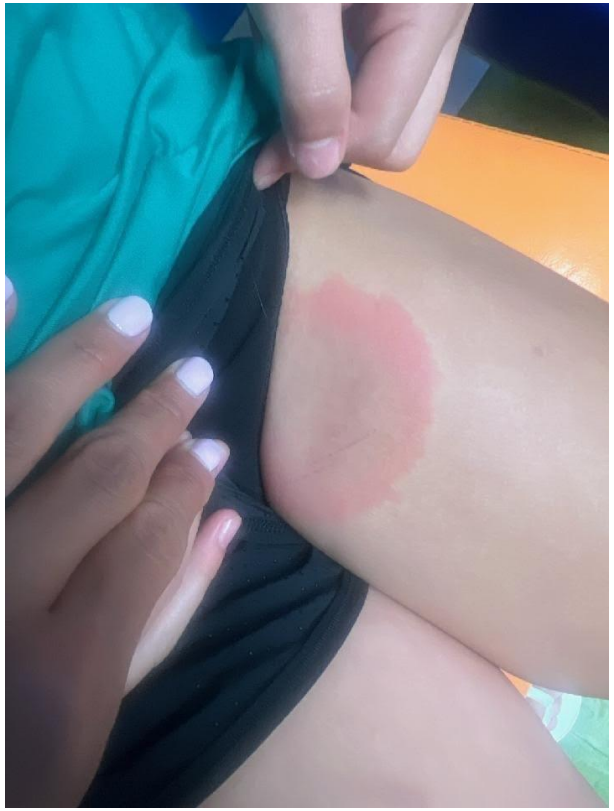
https://www.hopkinslyme.org/lyme-disease/diagnosis-of-lyme-disease/

Variability of EM and non-EM rashes

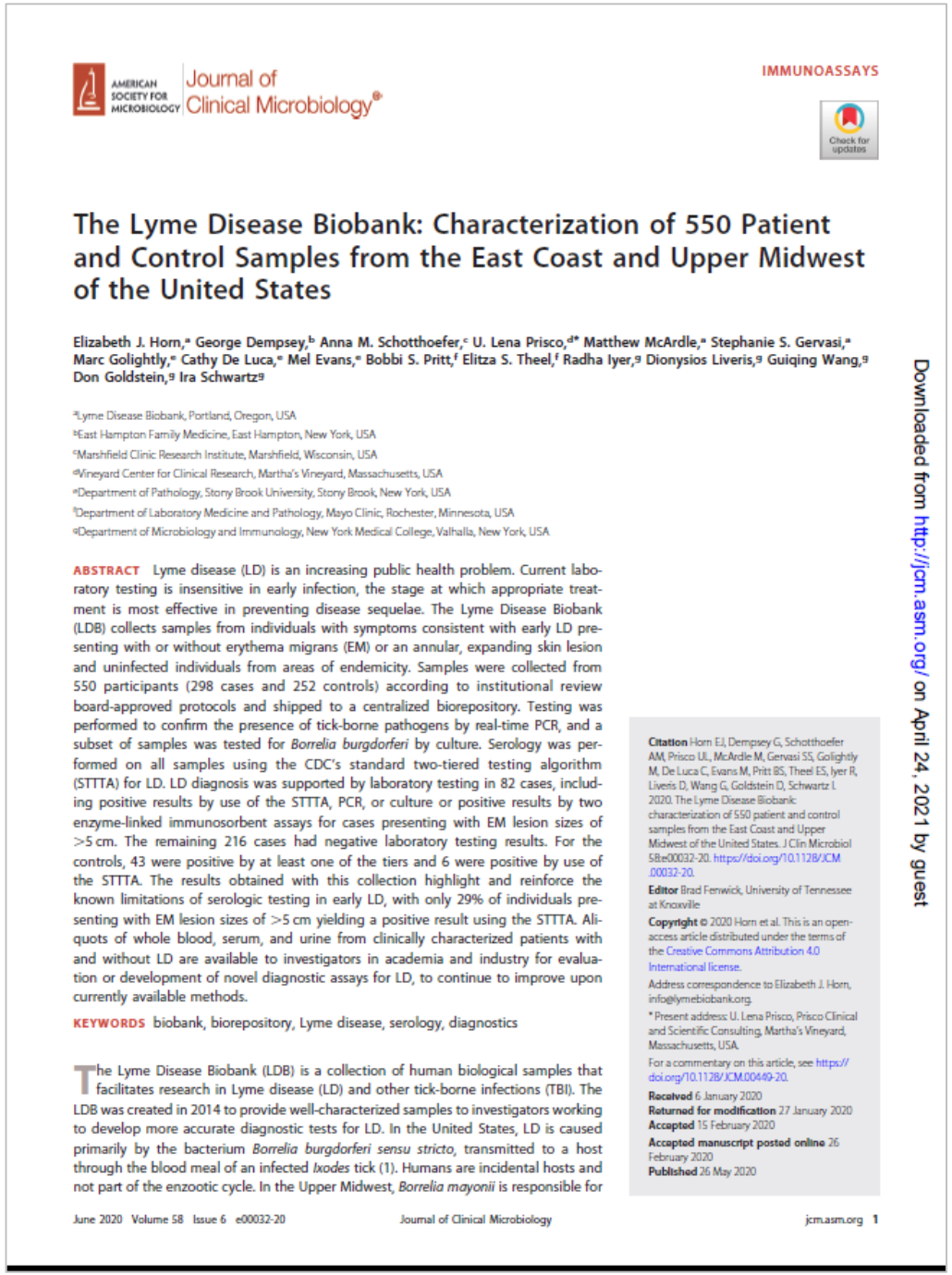


Schotthoefer AM, Green CB, Dempsey G, Horn EJ. The Spectrum of Erythema Migrans in Early Lyme Disease: Can We Improve Its Recognition? Cureus. 2022 Oct 25;14(10):e30673. doi: 10.7759/cureus.30673.

So who gets the antibiotic??

(All pictures used with permission)



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IMMUNOASSAYS

The Lyme Disease Biobank: Characterization of 550 Patient and Control Samples from the East Coast and Upper Midwest of the United States

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[g]Department of Microbiology and Immunology, New York Medical College, Valhalla, New York, USA

ABSTRACT Lyme disease (LD) is an increasing public health problem. Current laboratory testing is insensitive in early infection, the stage at which appropriate treatment is most effective in preventing disease sequelae. The Lyme Disease Biobank (LDB) collects samples from individuals with symptoms consistent with early LD presenting with or without erythema migrans (EM) or an annular, expanding skin lesion and uninfected individuals from areas of endemicity. Samples were collected from 550 participants (298 cases and 252 controls) according to institutional review board-approved protocols and shipped to a centralized biorepository. Testing was performed to confirm the presence of tick-borne pathogens by real-time PCR, and a subset of samples was tested for *Borrelia burgdorferi* by culture. Serology was performed on all samples using the CDC's standard two-tiered testing algorithm (STTTA) for LD. LD diagnosis was supported by laboratory testing in 82 cases, including positive results by use of the STTTA, PCR, or culture or positive results by two enzyme-linked immunosorbent assays for cases presenting with EM lesion sizes of >5 cm. The remaining 216 cases had negative laboratory testing results. For the controls, 43 were positive by at least one of the tiers and 6 were positive by use of the STTTA. The results obtained with this collection highlight and reinforce the known limitations of serologic testing in early LD, with only 29% of individuals presenting with EM lesion sizes of >5 cm yielding a positive result using the STTTA. Aliquots of whole blood, serum, and urine from clinically characterized patients with and without LD are available to investigators in academia and industry for evaluation or development of novel diagnostic assays for LD, to continue to improve upon currently available methods.

KEYWORDS biobank, biorepository, Lyme disease, serology, diagnostics

The Lyme Disease Biobank (LDB) is a collection of human biological samples that facilitates research in Lyme disease (LD) and other tick-borne infections (TBI). The LDB was created in 2014 to provide well-characterized samples to investigators working to develop more accurate diagnostic tests for LD. In the United States, LD is caused primarily by the bacterium *Borrelia burgdorferi sensu stricto*, transmitted to a host through the blood meal of an infected *Ixodes* tick (1). Humans are incidental hosts and not part of the enzootic cycle. In the Upper Midwest, *Borrelia mayonii* is responsible for

Citation Horn EJ, Dempsey G, Schotthoefer AM, Prisco UL, McArdle M, Gervasi SS, Golightly M, De Luca C, Evans M, Pritt BS, Theel ES, Iyer R, Liveris D, Wang G, Goldstein D, Schwartz I. 2020. The Lyme Disease Biobank: characterization of 550 patient and control samples from the East Coast and Upper Midwest of the United States. J Clin Microbiol 58:e00032-20. https://doi.org/10.1128/JCM.00032-20.

Editor Brad Fenwick, University of Tennessee at Knoxville

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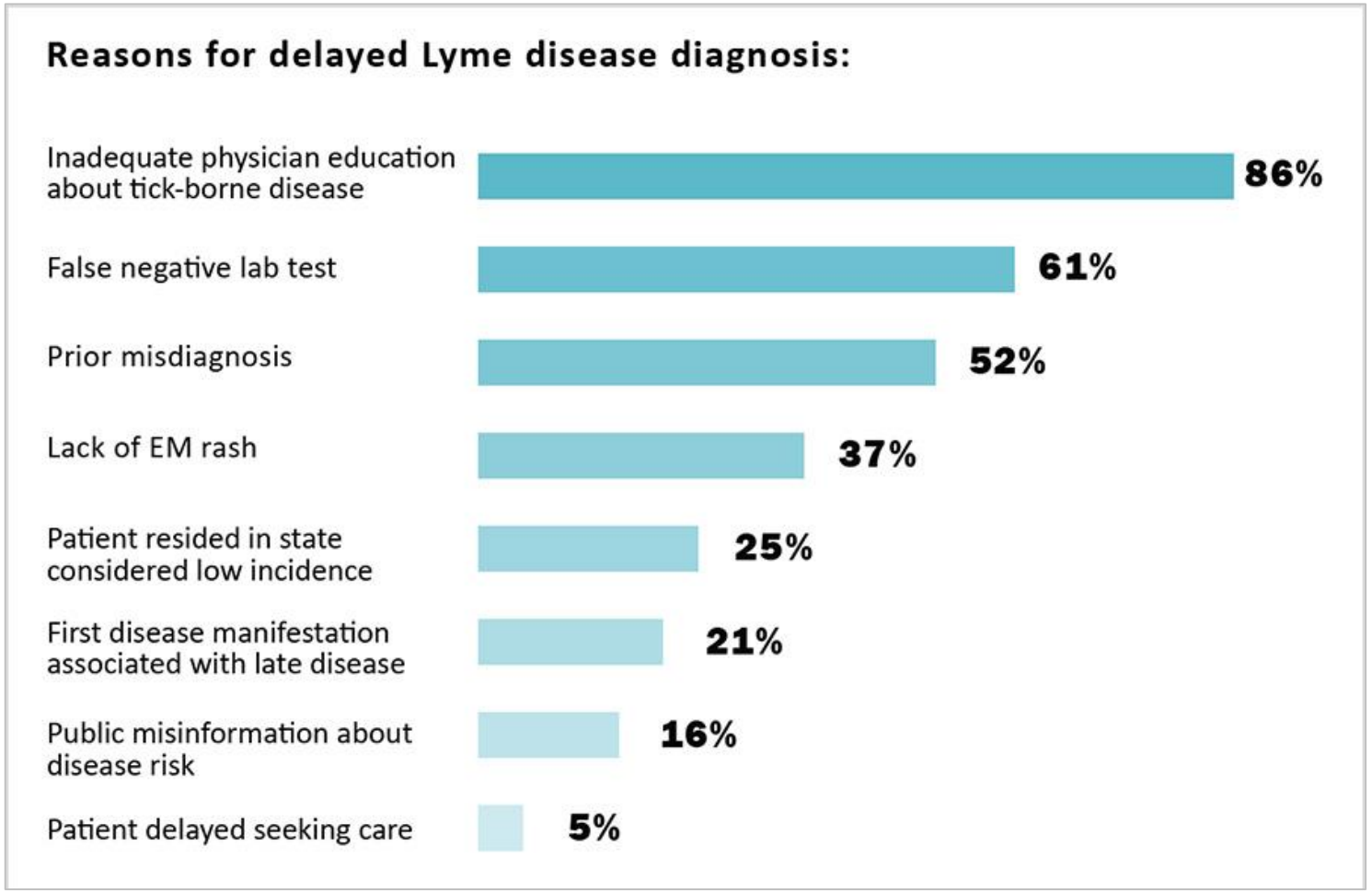
Current "two-tier" tests for Lyme disease have a high rate of FALSE NEGATIVE results

- "The results reinforce the known limitations of serologic testing in early Lyme disease, ***with only 29% of individuals presenting with EM lesion sizes of >5 cm yielding a positive result using the standard two-tier serology."***
- "A ***lack of provider awareness*** of the ***absence of EM or nonclassical EM presentations*** can lead to underdiagnosis and delayed treatment, highlighting the need for better diagnostics for early Lyme disease."

Delayed diagnosis increases risk of Lyme-infection associated chronic illness (Lyme-IACI)

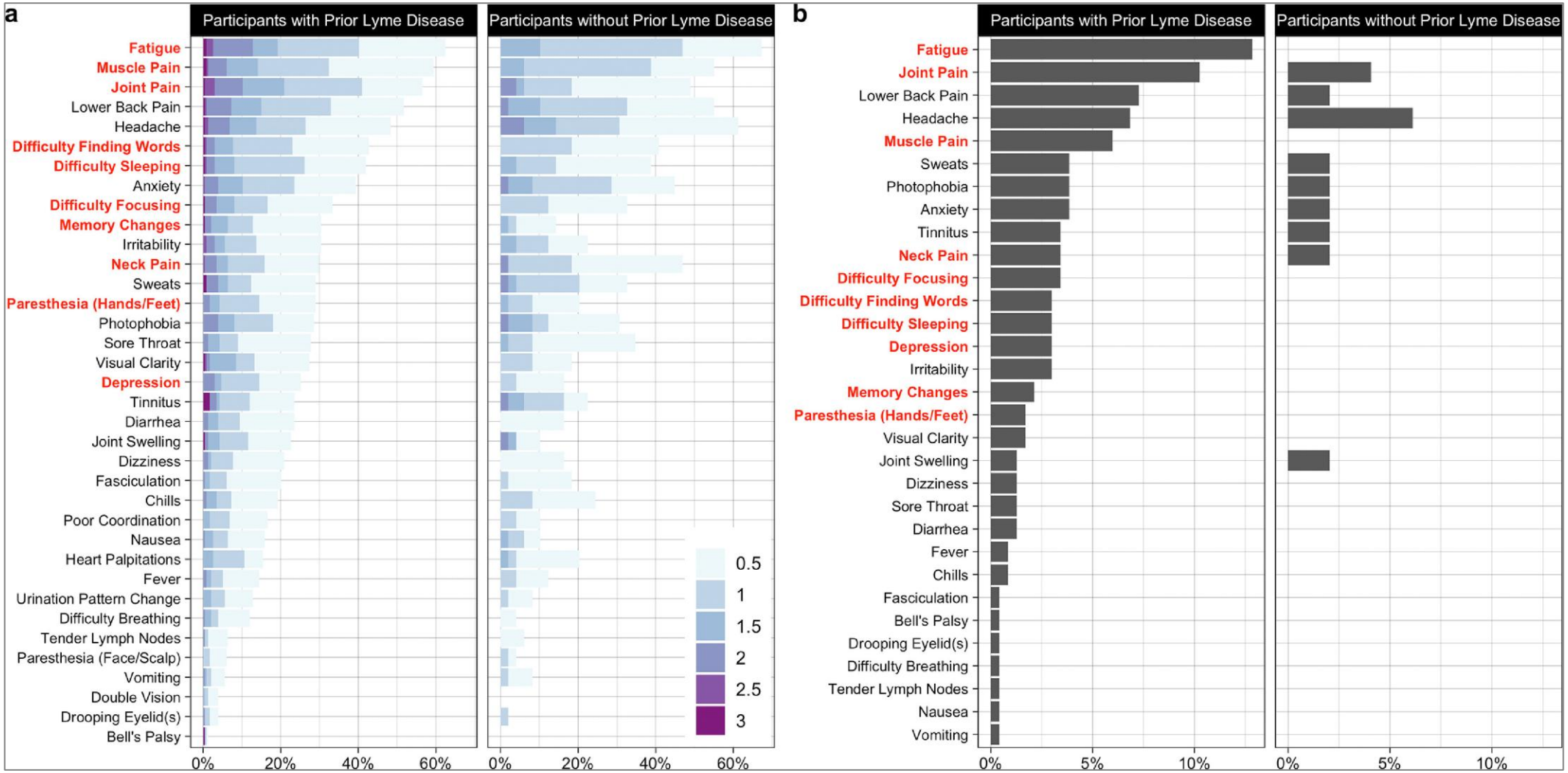
30 – 50% of patients with delayed diagnosis/treatment develop a chronic illness

- 70 – 75% of patients diagnosed with Lyme disease do not recall a tick/bite
- 37% saw no EM rash – no study ever published has conclusively shown how many people with Lyme disease actually develop an EM rash!
- 61% had false negative lab test results



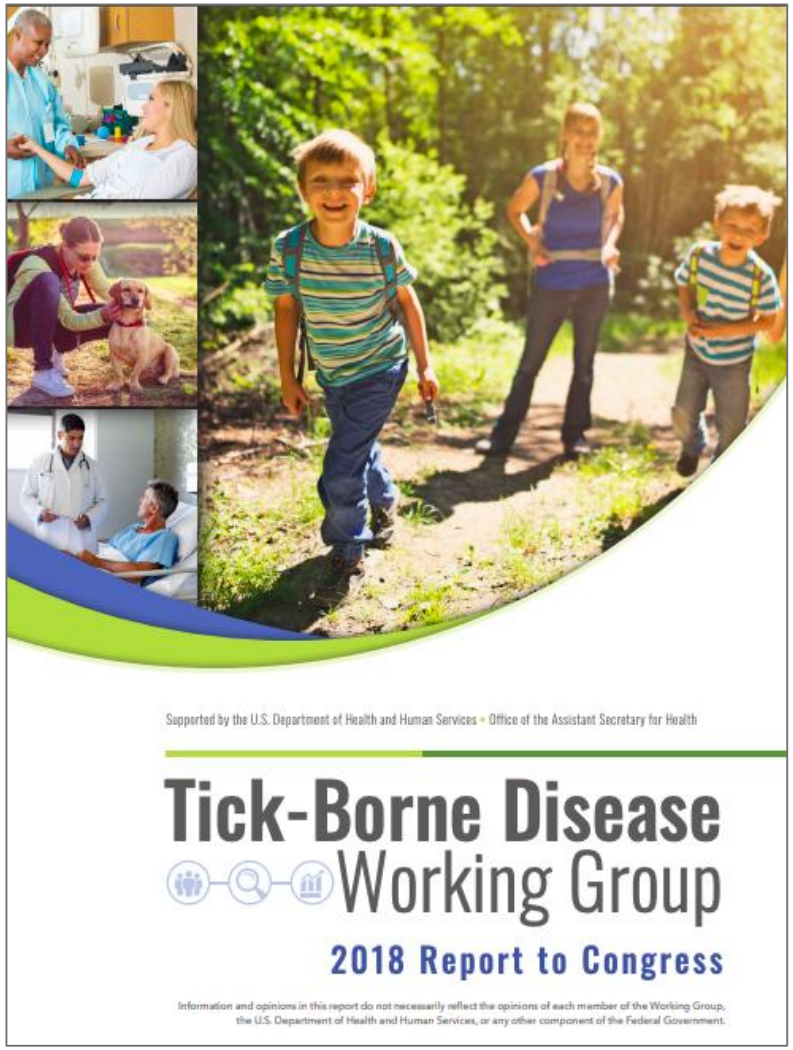
Source: LymeDisease.org MyLymeData

Figure 1. Distributions by participant group of **average scores (Panel a)** and the **percentage reporting "moderate" or "severe" (Panel b)** for individual symptoms included on the Post-Lyme Questionnaire of Symptoms (PLQS).

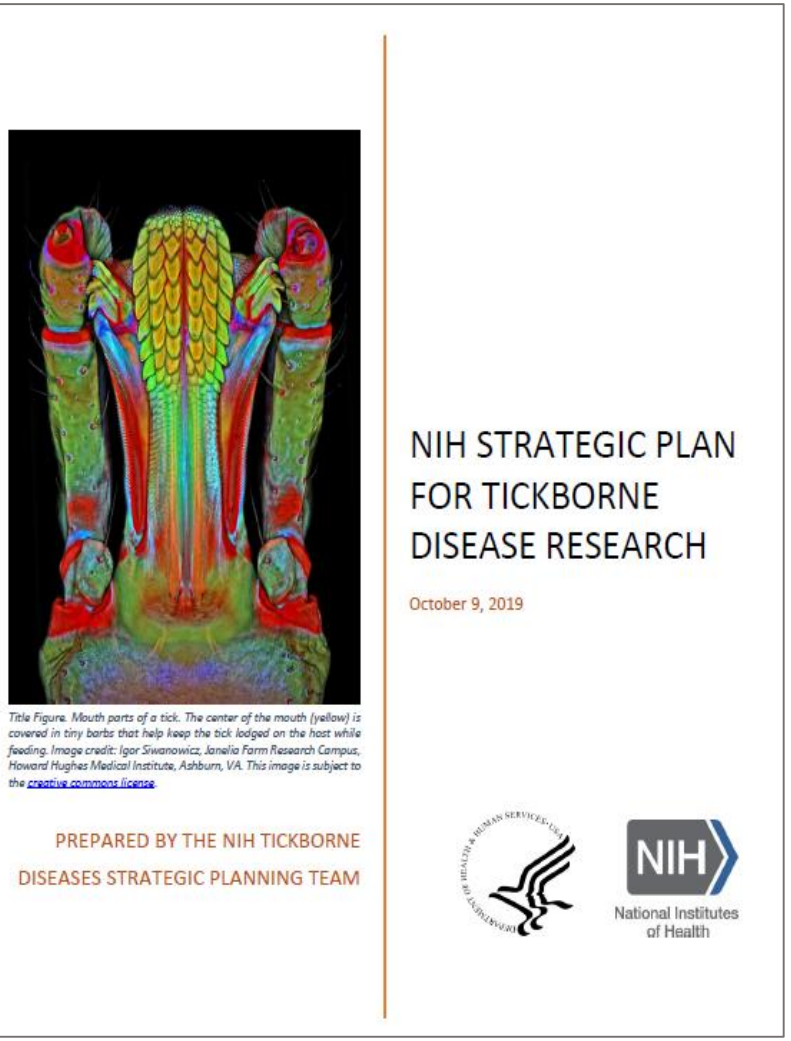


John N. Aucott, Ting Yang, Isaac Yoon, Debra Powell, Steven A. Geller, Alison W. Rebman. Risk of post-treatment Lyme disease in patients with ideally-treated early Lyme disease: A prospective cohort study. International Journal of Infectious Diseases, Volume 116,2022 https://doi.org/10.1016/j.ijid.2022.01.033

Ticks may not be the only route of transmission



- Transplacental transmission of the human fetus is recognized for both ***Lyme disease*** and ***relapsing fever borreliosis***
- Gestational tick-borne disease can be transmitted to unborn children in-utero and ***has the potential to cause premature labor, fetal/offspring abnormalities, fetal death and stillbirth.***
- Hormonal changes during pregnancy can ***lead to changes in immune function that may affect detection of clinical or laboratory findings***.



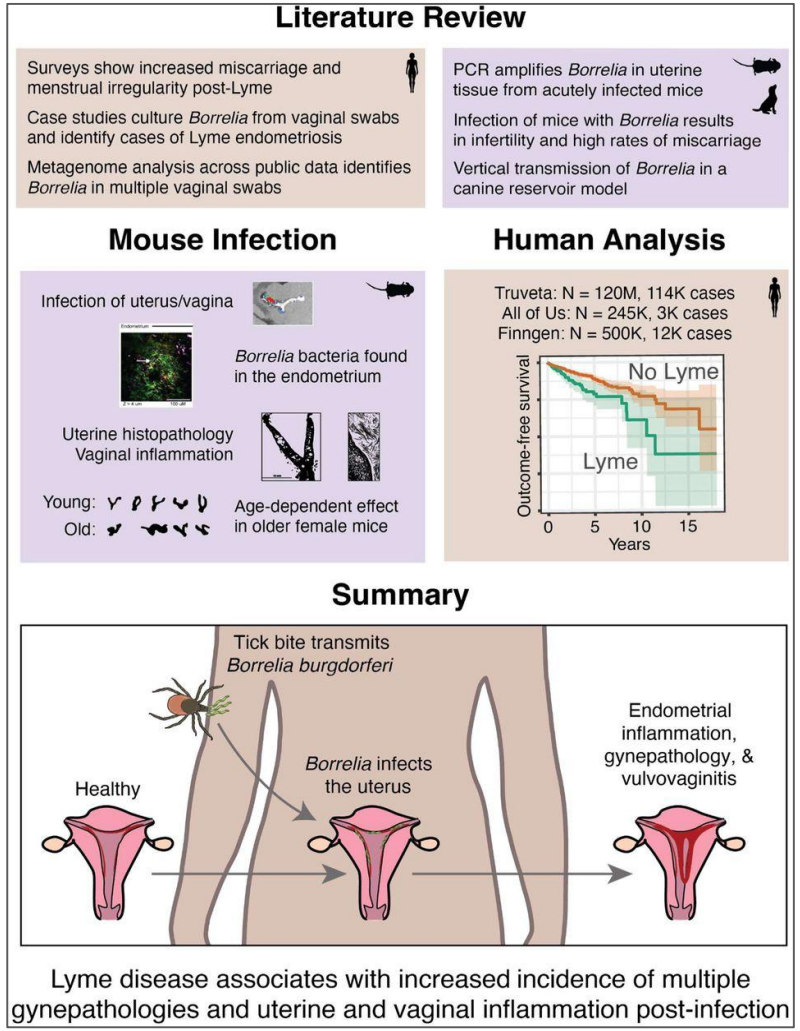
https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf

https://www.niaid.nih.gov/sites/default/files/NIH-Strategic-Plan-Tickborne-Disease-Research-2019.pdf

“Lyme disease increases risk for multiple gynecological conditions”

Mice infected with *B. burgdorferi*:

- Enlarged uterus
- Ovarian cysts
- Thickening of the vaginal lining
- Inflammation of internal and external tissues.
- *Notably, older mice experienced more severe outcomes*.



Women diagnosed with Lyme disease:

Increased risk of:

- Endometriosis
- Dysmenorrhea (cramps)
- Menorrhagia (heavy bleeding
- Miscarriage
- Uterine polyps
- *Adverse fetal outcomes in pregnant women*

Hansen–Colburn PS, Blacker G, Galloway S, Feng Q, Padmanabham PS, Pisani G, Lee BT, Loeser G, Perez MW, Liu K, Kuan J, Von Saltza E, Strausz S, Mattei L, Nahass GR, Kitjasateanphun A, Potula HS, Shoham MA, Mascetti VL, Gars E, Ollila HM, Bruner-Tran KL, Weissman IL, You S, Pollack B, Griffith L, Sinnott-Armstrong N, Tal MC. (2025). **Lyme disease increases risk for multiple gynecological conditions**. medRxiv. https://doi.org/10.1101/2025.03.03.25323258.

Adverse fetal outcomes in pregnant moms with Lyme disease

"…appraised by fetal loss and stillbirth, pre-term birth, offspring malformations…"

2010

"Adverse outcomes" in **12%** of **IV treated moms**; **31.6%** of **oral treated moms**; and **60%** of **untreated moms**

International Journal of Infectious Diseases

Maternal Lyme borreliosis and pregnancy outcome

András Lakos [a,*], Norbert Solymosi [b]

2018

"Adverse outcomes" in **11%** of **treated** moms and **50%** of **untreated moms**

PLOS ONE

RESEARCH ARTICLE

A systematic review on the impact of gestational Lyme disease in humans on the fetus and newborn

Lisa A. Waddell[1]*, Judy Greig[1], L. Robbin Lindsay[2], Alison F. Hinckley[3], Nicholas H. Ogden[4]

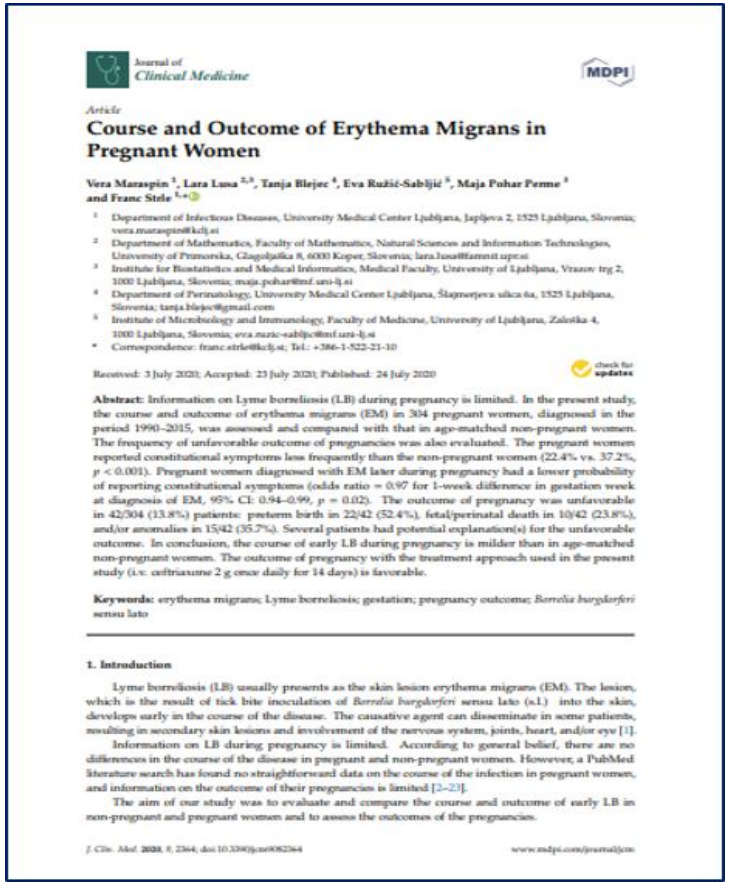
1 National Microbiology Laboratory, Public Health Agency of Canada, Guelph, Ontario, Canada, 2 National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, Canada, 3 Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Division of Vector-Borne Diseases, Fort Collins, Colorado, United States of America, 4 National Microbiology Laboratory, Public Health Agency of Canada, Saint-Hyacinthe, Quebec, Canada

* lisa.waddell@canada.ca

Abstract

2020

"Adverse outcomes" in **14%** of IV treated moms. All pregnant moms were treated



Journal of Clinical Medicine

MDPI

Article

Course and Outcome of Erythema Migrans in Pregnant Women

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Abstract: Information on Lyme borreliosis (LB) during pregnancy is limited. In the present study, the course and outcome of erythema migrans (EM) in 304 pregnant women, diagnosed in the period 1990–2015, was assessed and compared with that in age-matched non-pregnant women. The frequency of unfavorable outcome of pregnancies was also evaluated. The pregnant women reported constitutional symptoms less frequently than the non-pregnant women (22.4% vs. 37.2%, $p < 0.001$). Pregnant women diagnosed with EM later during pregnancy had a lower probability of reporting constitutional symptoms (odds ratio = 0.97 for 1-week difference in gestation week at diagnosis of EM, 95% CI: 0.94–0.99, $p = 0.02$). The outcome of pregnancy was unfavorable in 42/304 (13.8%) patients: preterm birth in 22/42 (52.4%), fetal/perinatal death in 10/42 (23.8%), and/or anomalies in 15/42 (35.7%). Several patients had potential explanation(s) for the unfavorable outcome. In conclusion, the course of early LB during pregnancy is milder than in age-matched non-pregnant women. The outcome of pregnancy with the treatment approach used in the present study (i.v. ceftriaxone 2 g once daily for 14 days) is favorable.

Keywords: erythema migrans; Lyme borreliosis; gestation; pregnancy outcome; *Borrelia burgdorferi* sensu lato

1. Introduction

Resources:

Research Funding

- Stephen and Alexandra Cohen Foundation
- Project Lyme
- Bay Area Lyme Foundation
- LymeDisease.org
- Global Lyme Alliance
- Focus on Lyme

Advocacy and Information

- Center for Lyme Action
- Lyme Action Network
- Central New York Lyme and TBD Alliance
- Southern Tier Lyme Support
- Lyme WNY

Treatment Grants

- LivLyme Foundation
- LymeLight Foundation