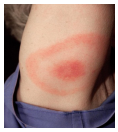
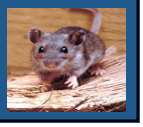


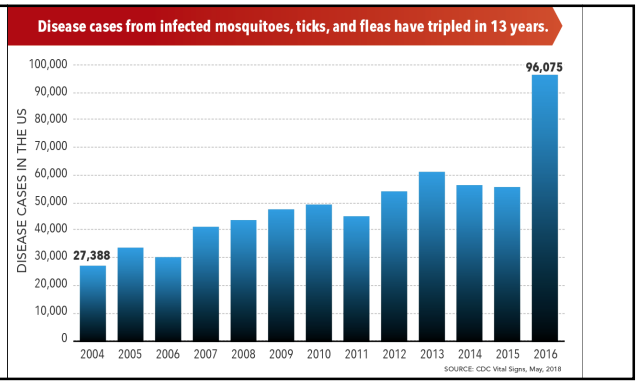
Tick-Borne Illness

Paul Carson, MD, FACP

NDSU MASTER OF PUBLIC HEALTH Management of Infectious Diseases



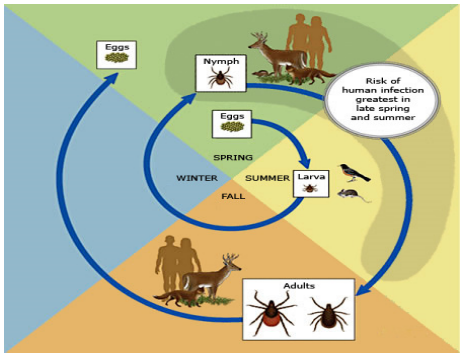
"Yeah, it's the New World, but we found a ton of ticks . . ."



Tick-Borne Illnesses in North America

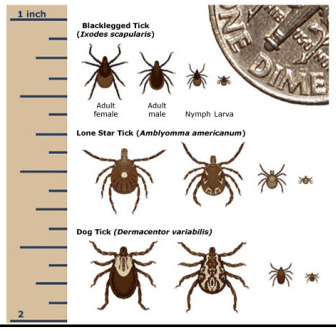
- Lyme Disease
- Anaplasmosis
- Ehrlichiosis
- Babesiosis
- Rocky Mountain Spotted Fever
- Tularemia
- Powassan Virus
- Relapsing Fever
- STARI (Southern Tick Associated Rash Illness)
- Tick Paralysis
- Colorado Tick Fever
- Rickettsia parkeri
- Rickettsia massiliae

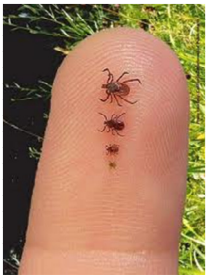
Ticks 101



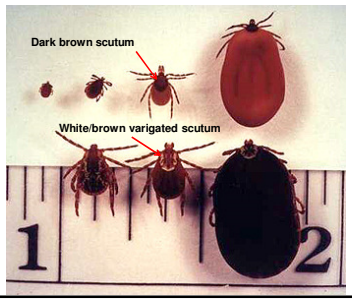
Female tick after a blood meal can lay up to 2000 - 8000 eggs

Tick Basics: Sizes and Appearance





Tick Basics



Deer Tick
I. scapularis

DogTick
D. variabilis

Blacklegged Tick Questing

- Searches for a host from the tips of low-lying vegetation
- Climbs onto a person or animal near ground level

Tick Removal

- Ticks have barbed mouth parts – ticks that are attached to the skin should be pulled out slowly and steadily

Tick Distributions and Associations

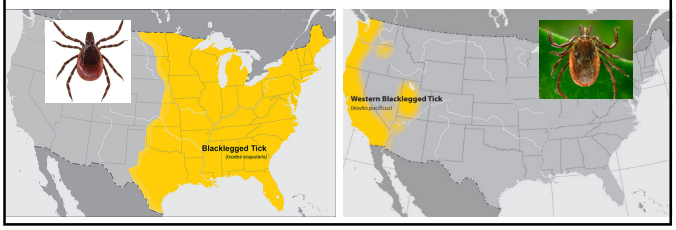
Dermecentor variabilis (American dog tick) — RMSF, Tularemia

Rhipicephalus sanguineus (Brown dog tick) — RMSF

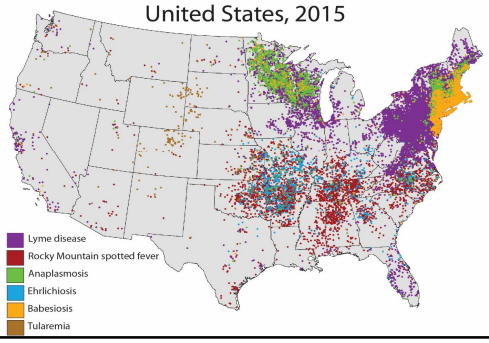
Tick Distributions and Associations

Ixodes Scapularis (Deer Tick or Black-legged tick) — Lyme Disease, Anaplasmosis, Babesiosis

Ixodes pacificus (Western Black-legged tick) — Lyme Disease, Anaplasmosis



Distribution of Key Tickborne Diseases, United States, 2015



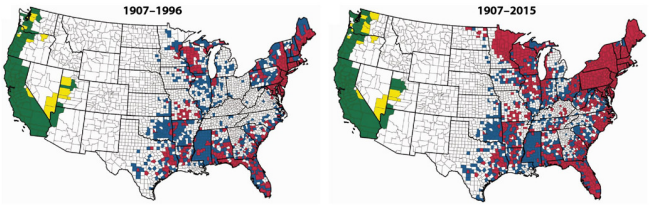
Ticks Spreading Like Wildfire Across New England, Midwest

Distribution of deer tick species *Ixodes scapularis* and *Ixodes pacificus* in the continental U.S.

At least 6 ticks or two life stages recorded in a calendar year
- *I. scapularis*
- *I. pacificus*

Fewer ticks of a single life stage reported
- *I. scapularis*
- *I. pacificus*

Deer tick
I. scapularis



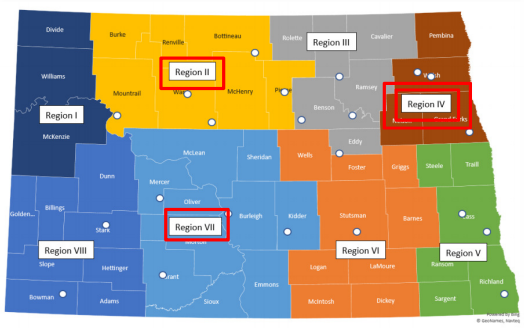
SOURCE: Oxford University Press Journal of Medical Entomology/Entomology Society of America

InsideClimate News

2017 NDDH Tick Survey

POOL LOCATION	Tick Species	Quantity	PCR Results
Region 2 Pool 1	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 2	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 3	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 4	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 5	*Dermacentor*	10	Negative
Region 2 Pool 6	*Ixodes*	1	Negative
Region 2 Pool 7	*Dermacentor*	20	Positive Tularemia
Region 2 Pool 8	*Dermacentor*	20	Postive Rickettsia spp, Positive Tularemia
Region 2 Pool 9	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 10	*Dermacentor*	20	Negative
Region 2 Pool 11	*Dermacentor*	20	Negative
Region 2 Pool 12	*Dermacentor*	20	Positive Rickettsia spp, Positive Tularemia
Region 2 Pool 13	*Dermacentor*	20	Positive Tularemia
Region 2 Pool 14	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 15	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 16	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 17	*Dermacentor*	20	Negative
Region 2 Pool 18	*Dermacentor*	20	Positive Rickettsia spp
Region 2 Pool 19	*Dermacentor*	16	Positive Rickettsia spp, Positive Tularemia
Region 2 Pool 20	*Ixodes*	3	Positive Rickettsia spp, Positive Tularemia
Region 3 Pool 1	*Dermacentor*	20	Postive Rickettsia spp
Region 3 Pool 2	*Dermacentor*	50	Postive Rickettsia spp
Region 3 Pool 3	*Dermacentor*	18	Negative
Region 3 Pool 4	*Dermacentor*	4	Negative
Region 4 Pool 1	*Dermacentor*	20	Positive Rickettsia spp
Region 4 Pool 2	*Dermacentor*	20	Negative
Region 4 Pool 3	*Dermacentor*	20	Negative
Region 4 Pool 4	*Ixodes*	4	Positive Rickettsia spp, Positive Borrelia
Region 4 Pool 5	*Dermacentor*	20	Positive Rickettsia spp
Region 4 Pool 6	*Dermacentor*	3	Negative
Region 5 Pool 1	*Dermacentor*	20	Negative
Region 5 Pool 2	*Dermacentor*	7	Negative
Region 5 Pool 3	*Dermacentor*	2	Negative
Region 6 Pool 1	*Dermacentor*	20	Positive Rickettsia spp
Region 6 Pool 2	*Dermacentor*	20	Positive Rickettsia spp
Region 6 Pool 3	*Dermacentor*	16	Positive Rickettsia spp
Region 6 Pool 4	*Dermacentor*	13	Postive Rickettsia spp
Region 7 Pool 1	*Dermacentor*	20	Positive Rickettsia spp
Region 7 Pool 2	*Dermacentor*	20	Positive Rickettsia spp
Region 7 Pool 3	*Dermacentor*	20	Negative
Region 7 Pool 4	*Dermacentor*	14	Positive Rickettsia spp
Region 7 Pool 5	*Ixodes*	1	Positive Rickettsia spp
Region 7 Pool 6	*Dermacentor*	20	Positive Rickettsia spp
Region 7 Pool 7	*Dermacentor*	20	Negative
Region 7 Pool 8	*Dermacentor*	9	Positive Rickettsia spp
Region 8 Pool 1	*Dermacentor*	5	Postive Tularemia
Miscellaneous	*Dermacentor*	1	Negative

2017 Tick Surveillance Sites



The Following Counties Are Included in Each Region:

Region	Counties
I	Divide, Williams, McKenzie
II	Burke, Renville, Bottineau, Mountrail, Ward, McHenry, Pierce
III	Rolette, Towner, Cavalier, Ramsey, Benson, Eddy
IV	Pembina, Walsh, Nelson, Grand Forks
V	Steele, Traill, Cass, Ransom, Sargent, Richland
VI	Wells, Foster, Griggs, Stutsman, Barnes, Logan, LaMoure, McIntosh, Dickey
VII	McLean, Sheridan, Mercer, Oliver, Burleigh, Kidder, Morton, Grant, Sioux, Emmons
VIII	Dunn, Golden Valley, Billings, Stark, Slope, Hettinger, Bowman, Adams

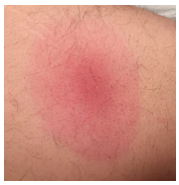
Prevention of Tick-Bites

- Permethrin
  - Synthetic neurototoxin to most arthropods
  - Spray for clothing (Sawyer Permethrin™ Spray for Clothing)
    - Spray on clothing 30-45 secs, let dry. Good for 1 week and several washings
  - Impregnated clothing and gear
    - Insect Shield™
    - Maintains potency through 70 laundry cycles
  - Decreases nymphal tick attachment ~ 4 fold, those that attach usu dead in 2.5 hrs
- DEET
  - CDC recommends 20-30% DEET
  - Effectiveness plateaus at 30%, higher concentrations extend duration (24% lasts about 5 hrs)

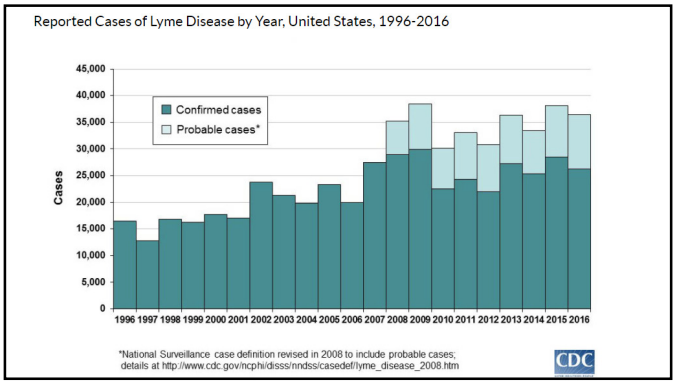
Tick Protective Clothing

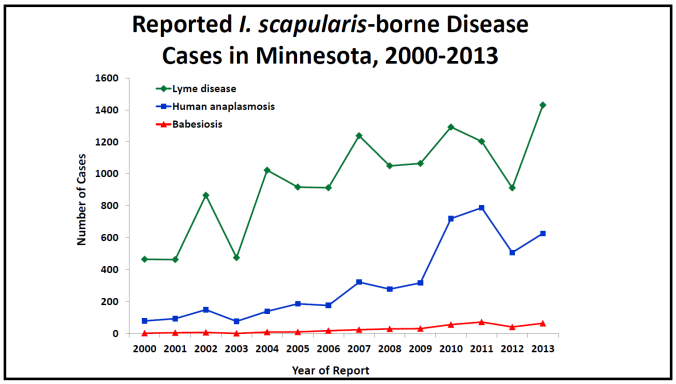
Question

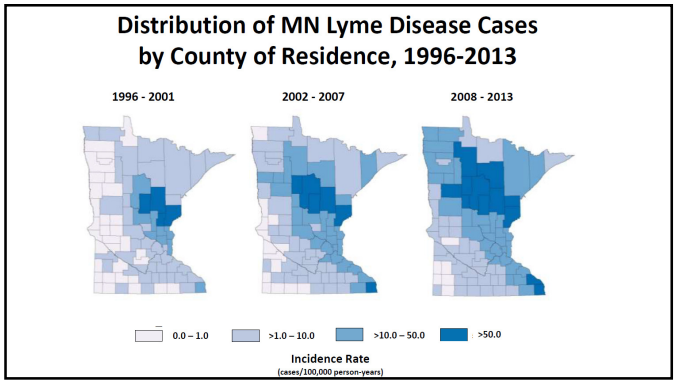
- A 55 year old white male is clearing brush at his lake cottage in western MN in late June. He is unaware of any tick bites but did not do a tick check after this activity. 2 ½ weeks later he develops diffuse muscle and joint aches, headache, low grade fever, and fatigue. There is no rash. This resolves after a few days, but while vacationing in CO he notices marked fatigue while trying to hike and mountain bike. He returns home to ND and again experiences diffuse pain and headache. He now notices a new rash on his thigh. What do you recommend?

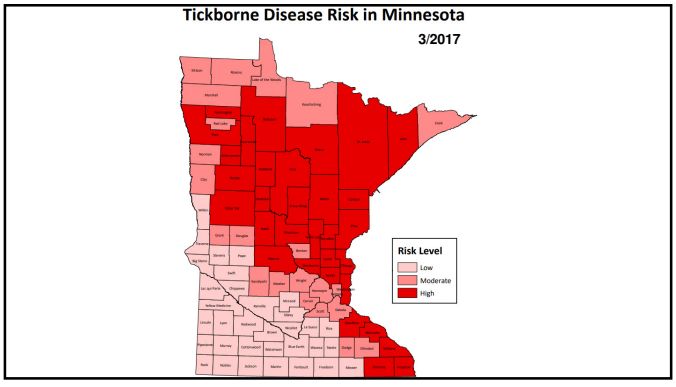


- Prophylax potential prior tick bite with one dose of doxycycline
- 2 stage testing for Lyme disease
- Treat with doxycycline for 2-3 weeks
- Return to clinic in 2-3 weeks when serologic testing is more likely to be positive

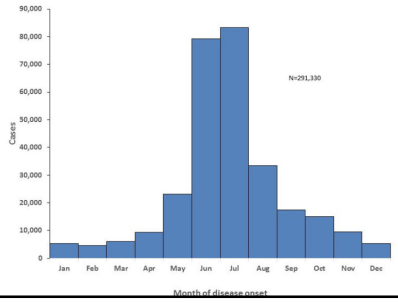






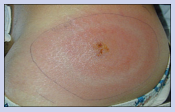


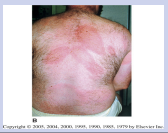
Confirmed Lyme Cases by Month of Onset – U.S. 2001-2016



Clinical Manifestations

Stage 1 Early - Localized	Stage 2 Early - Disseminated	Stage 3 Late Disease - Persistent
Erythema migrans – 80%	Fever – 30-40% AV-nodal block Mononeuritis Hepatitis Ophthalmitis	Arthritis – up to 60% Encephalopathy Polyneuropathy

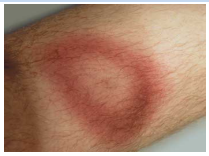


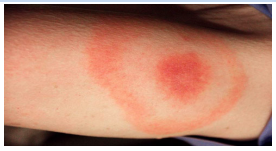


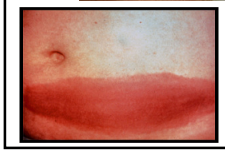
Early Localized Lyme

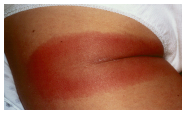
- Only 25% recall a tickbite, symptoms develop in 2-4 weeks
- 80% will develop Erythema chronicum migrans, usu at ~ 4 wks
- Constitutional symptoms in up to ~50%
  - Fatigue, myalgias, arthralgias, headache, anorexia, fever, regional adenopathy, neck stiffness
- Serology only positive in 20-40%

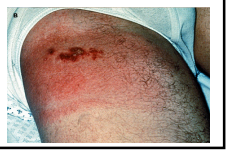
Erythema Chronicum Migrans











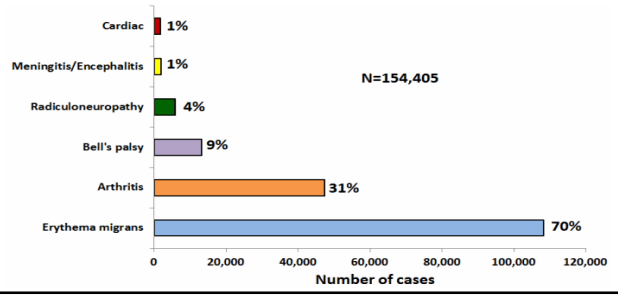
Early Disseminated Disease

- Occurs weeks to months after infection
- Neurologic: cranial neuropathies, peripheral neuropathy, radiculopathy, aseptic meningitis, encephalomyelitis
- Cardiac: myopericarditis, fluctuating degrees of heart block
- Other: rare ocular findings – iritis, conjunctivitis, retinitis, optic neuritis
- Nearly all seropositive

Late Disease

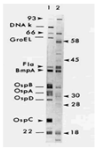
- Months to years after onset of infection
- Arthritis
  - 60% of untreated patients
  - Tends to be intermittent/recurrent
  - Small percentage (~10%) will be persistent/destructive
- Neurologic
  - Lyme encephalopathy – subtle cognitive impairments
  - Chronic axonal polyneuropathy – spinal radicular pain and distal parasthesias

Clinical Manifestations of Confirmed Lyme Cases, U.S. 2001-2010



CDC Recommended 2-Tier Serologic Testing for Lyme

- Screening ELISA – First tier
  - Uses whole cell sonicate of B. burgdorferi grown in vitro to detect IgG or IgM antibodies
  - If negative, reported as negative. If positive or indeterminate, go on to Western Immunoblot
- Wester Blot – Second Tier
  - IgM – positive is 2/3 bands present (24, 39, 41)
  - IgG – positive if any 5/10 bands positive (18, 23, 28, 30, 39, 41, 45, 58,66, 93)



2-Tier Laboratory Testing for Lyme Disease

Stage of Disease	Sensitivity	Specificity
Early stage (ECM, flu-like symptoms)	20-40%	95-100%
Early Disseminated (neuritis, carditis)	87-96%	
Late-stage (arthritis, encephalitis)	97-100%	

Bottom Line: Testing is good if later stage disease. If high suspicion of early disease (e.g. ECM present), treat empirically or repeat test in ~ 2 weeks.

Novel EIAs - C6 peptide and V1sE1

- Additional FDA-cleared EIAs that use 1 to several antigens
- Conserved surface proteins
  - **C6 surface protein** and variable major protein-like sequence 1 (**V1sE1**)
- Similar sensitivity to whole sonicate EIA with improved specificity. Earlier IgG positivity
- EIAs offer advantage of automation and objectivity (Wester Blot open to interpretation)
- Now being proposed with 2-tier EIA only testing with similar sensitivity and specificity as EIA/WB 2 tier testing. Not yet FDA approved.

Other Considerations with Lyme Testing

- Background seropositivity
  - 5% of participants in a seroepidemiologic survey in New York were (+) - 59% of those denied previous hx of Lyme dz
- Antibodies may remain present for years
  - Not good for "test of cure"
- PCR on serum and CSF has very low sensitivity
- PCR on synovial fluid has > 75% sensitivity for Lyme arthritis

Treatment for Lyme Disease

Drug Regimen (10-28 days)	Conditions
Doxycycline 100 mg bid	Early Disease (ECM) First degree heart block Bell's Palsy Arthritis w/o neurologic sx's
Amoxicillin 500 mg tid Cefuroxime 500mg bid	Early Disease (ECM) First degree heart block Arthritis w/o neurologic sx's
Ceftriaxone 2 gm IV qd	Meningitis or neuritis 2nd or 3rd degree heart block Arthritis with neurologic sx's

Lyme Advocacy Groups and Small Group of Alternative Providers Contend:

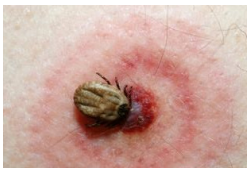
- Much more common (up to 10x) and geographically diverse than reported by CDC
- Is easy to catch
- Can cause a host of nonspecific symptoms
- Difficult to diagnose due to poor performance of serologic tests
- May develop into "Chronic Lyme Disease" – not defined, but usu meant as persistent Borrelia infection often despite conventional treatment, with or without confirmatory serologic evidence
- Propose alternate serologic testing criteria, not FDA approved
- Current treatment recommendations are frequently inadequate, and appropriate therapy must be individualized to patient response. This can take months to sometimes years of antibiotics
- Care should be given by a "Lyme-Literate" physician
- Significant opposition to IDSA guidelines

Post-Treatment Lyme Disease Syndrome

- Hx of objective manifestation of Lyme disease that was treated
- Ongoing subjective symptoms that interfere with functioning (musculoskeletal pain, cognitive impairment, radicular pain, dysethesias, parasthesias, fatigue)
- Symptom onset within 6 mos of original dx and persisting > 6 mos
- No evidence that longer or repeated courses of antibiotics of any benefit

Case

A hunter out in western ND finds this tick attached to himself along with the noted rash the next morning after returning home. The patient sends you a picture and calls your office for advice. What do you recommend?



A) Offer doxycycline prophylaxis 200 mg 1 dose
B) Treat for Lyme disease with 2 weeks of doxycycline
C) Test for Lyme disease with EIA
D) Reassure the patient and do nothing

Criteria for Tick-Bite Prophylaxis

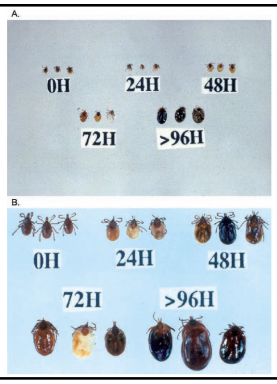
- *Ixodes scapularis* tick (deer tick).
- Attached for ≥36 hours (by degree of engorgement or time of exposure).
- Prophylaxis is begun within 72 hours of tick removal.
- Local rate of infection of ticks with B. burgdorferi is ≥20 percent (these rates of infection have been shown to occur in parts of New England, parts of the mid-Atlantic States, and parts of Minnesota and Wisconsin).
- Doxycycline is not contraindicated (i.e., the patient is not <8 years of age, pregnant, or lactating).

IDSA Guidelines 2009

Transmission of Tick-Borne Dz in MN

Disease	Resides in Tick	Attachment	Likelihood
Powassan	?	? minutes	?
Babesia	Salivary gland	36-48 h	0-11% ticks
Anaplasma	Salivary gland	12-24 hrs	5-22% ticks
Lyme	Midgut	> 48-72 hrs	20-58% ticks

Hours After Engorgement



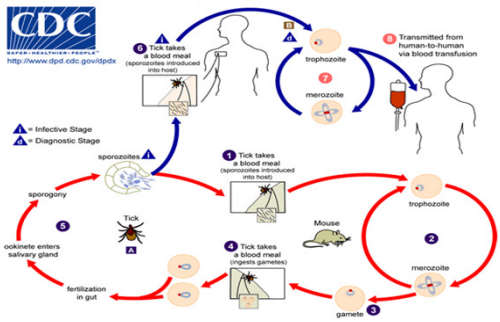
Ixodes Nymphs

Ixodes Adults

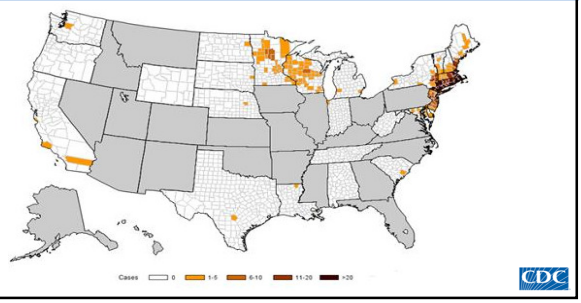
Babesiosis

- Intracellular RBC parasite similar to malaria, causes hemolysis
- Main species infecting humans is *B. microti*
- Reservoir is White Footed Mouse (up to 60% infected in MN)
- Vector: *Ixodes scapularis.* Also from Blood Tx
- Humans and deer are accidental dead-end hosts
- Incubation 1-6 weeks after tick-bite
- 20% will be co-infected with Lyme disease

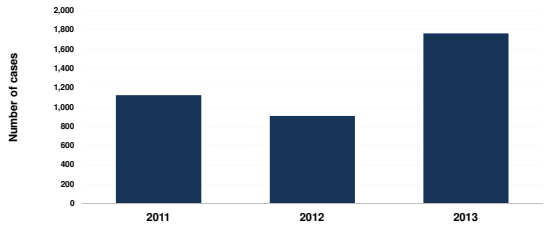
Babesia Life Cycle



Number of Reported Cases of Babesiosis by County of Residence - 2013

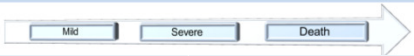


Number of Reported Cases of Babesiosis by Year*



*Note: Became a nationally notifiable dz in 2011

Clinical

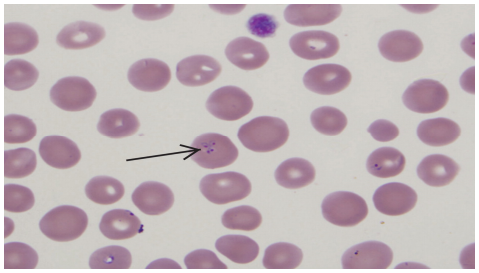


Mild	Severe
Immunocompetent	Immunosuppressed • Age >50 years • Splenectomy • Coinfection with HIV or Borrelia burgdorferi • Cancer chemotherapy or transplantation • TNF-α blockers
Fevers, myalgias, chills	Severe hemolytic anemia
Hemolytic anemia	Renal failure
Thrombocytopenia	CHF / DIC / ARDS
LFTs	Recurrent infection

Diagnosis

Microscopy	• Thin smears only • Difficult at onset of symptoms
PCR	• Most useful at onset / convalescence • Detects to 0.0001% parasitemia
Serology	• Useful for PCR –ve / Microscopy –ve • Symptoms precede serology by 7d • Useless in rituximab treated patients

B. microti on Blood Smear



Babesiosis – Indications for Treatment

- Positive DNA test or blood smear and:
  - Symptomatic disease
  - Asx but persistent parasitemia > 3 mos
  - Treated patients, aymptomatic, with persistent parasitemia > 3 mos

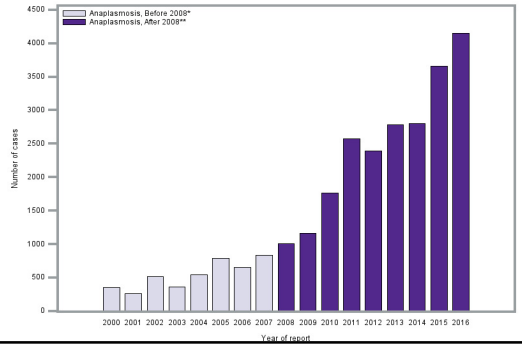
Babesiosis - Treatment

Severity	Treatment	Length	Comments
Mild	azithromycin 500mg/d on day 1; 250mg/d day from day 2 PLUS atovaquone 750 mg q12h	7- 10 days	Myalgias may be present for 3 months If recurs treat > 6 weeks
Severe	clindamycin 300 – 600 mg IV every 6 hours PLUS quinine 650 mg po every 6 hours consider exchange transfusion	> 6 weeks	Prior to DC abx patient needs to be without parasitemia for 2 weeks

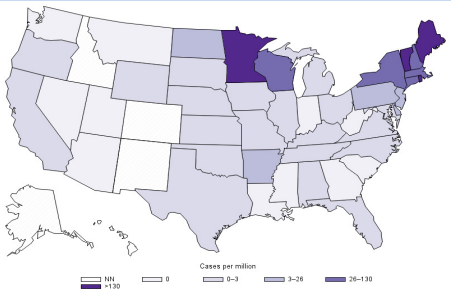
Anaplasma Phagocytophila

- Obligate intracellular gram negative bacteria, infects PMNs
- Endemic in MN, WI, CT, NY, MD
- I. scapularis is vector, deer and white-footed mouse are principal animal reservoirs
- Coinfection with Lyme dz in 3-15%

Figure 1 – Number of U.S. anaplasmosis cases reported to CDC, 2000–2016



Annual Reported Incidence of Anaplasmosis U.S. 2016



Clinical Manifestations

Clinical	Dermatologic
Tick bites or exposure >90% Fevers (>90%) Headaches (>85%) Malaise (>70%) Myalgias (>70%) Rigors (60%) Leukopenia / Thrombocytopenia	Rash (10%): Maculopapular, not petechial (as in RMSF). Evidence for vasculitis not observed.

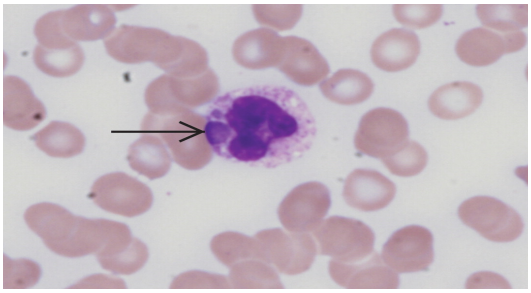
Anaplasmosis: Clinical Manifestations

- Symptoms usually appear 4-12 days after tickbite
- 50-90% will have a combination of leukopenia, thrombocytopenia, and elevated transaminases
- Onset of illness is typically rapid
- May develop severe illness with resp failure, CHF, sepsis-like syndrome, renal failure

Findings and Treatment

Laboratory Findings	Leukopenia Thrombocytopenia Elevation in transaminases
Diagnosis	• 4-fold increase between acute and convalescent IFA •PCR (beware of E. muris) • Blood smears with morulae ~ 20-80% (Anaplasmosis > Ehrlichiosis)
Treatment	• doxycyline 200mg / d = 10 days •If no improvement in 48h consider alternative diagnosis •Anecdotal evidence for rifampin / levofloxacin

Morulae of Anaplasmosis



Minnesota Records 1st Death From Tick-Borne Virus

By: Lee Voss | June 29, 2011

Getty Images

ST. PAUL (AP) – Minnesota has recorded its first death in connection with a tick-borne disease called the Powassan virus.

The Department of Health says Wednesday that a woman in her 60s from northern Minnesota has died from a brain infection caused by the disease.

The state has identified one other likely case of the Powassan this year – in an Anoka County man in his 60s. He was hospitalized with a brain infection but is recovering at home.

Health officials are reminding the public to prevent tick bites by using a tick-repellant and checking for ticks when coming inside.

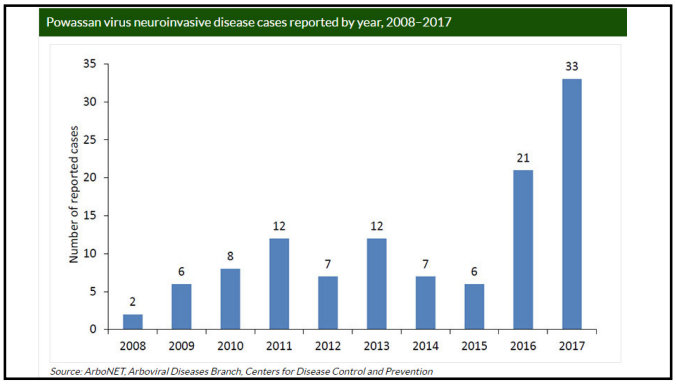
In Minnesota, the Powassan virus can be transmitted by the blacklegged tick, also called the deer tick. There have been about 60 cases of the disease identified in North America, including eight in Minnesota.

Powassan Virus

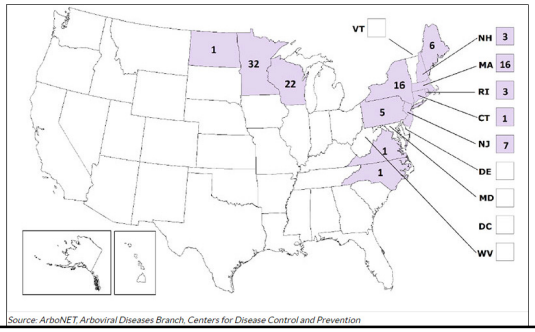
- Named for first case in Powassan Ontario, 1958
- Vector: *Ixodes cookei* (feed on woodchucks), also can infect *I. scapularis* (deer tick) – newly recognized variant
- Virus: Flavivirus, closely related to West Nile virus
- Causes Meningoencephalitis
- 60 cases reported in U.S. since 1958, 15 cases in MN from 2008-2011 (Cass, Carlton, Hubbard, Itasca, and Kanabec counties)

Powassan Virus (cont.)

- Onset of illness 8-34 days after exposure
- Asymptomatic and mild infection probable
- Fever, headache, vomiting, weakness, confusion, loss of coordination, speech difficulty, and memory loss
- 10% - 15% mortality, chronic sequelae common
- Diagnosis: Serologic through MDOH/CDC
- Treatment: supportive

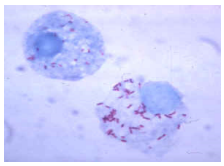


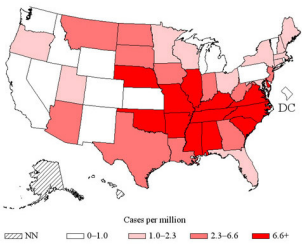
Powassan Cases U.S. Through 2017



RMSF

- *Rickettsia rickettsii*
  - intracellular pathogen
  - not visualized by routine staining





Centers for Disease Control and Prevention. Summary of notifiable diseases -- United States, 2007. MMWR Morb Mortal Wkly Rep 2009; 56:1.

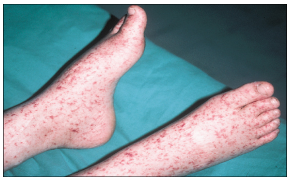
RMSF

American dog tick
Dermcentor variabilis

Rocky Mountain wood tick
Dermacentor andersonii

Brown dog tick
Rhipicephalus sanguineus

Clinical Manifestations

Clinical	Dermatologic
Initial symptoms : • fever (99%) • severe headache (91%) • myalgias (83%) • nausea/vomiting (60%) • conjunctival suffussion / periorbital edema (30%) • stupor (26%) Mortality: • 3-5% mortality (highest in elderly) • vasculitis • pneumonitis	• Rash: 2-5 days after fever (88%) •Early: small, flat, pink, non-itchy macules and petechiaeon the wrists, forearms, and ankles 

RMSF

Diagnostic Pearls	Serology
•Fever, rash, and history of tick bite. • ***Treat based on epidemiologic and clinical clues.*** •***Never be delayed while waiting for confirmation by laboratory results.***	• IgM titers > 5 days of symptoms • IgG antibody after two weeks of illness.

Treatment: doxycycline 200mg / daily

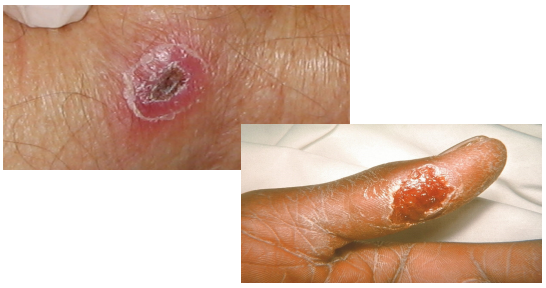
Tularemia

Tularemia

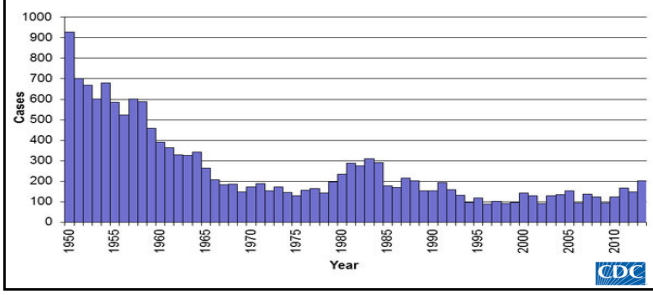
- Epidemiology:
  - Francisella tularensis: slow growing gram negative

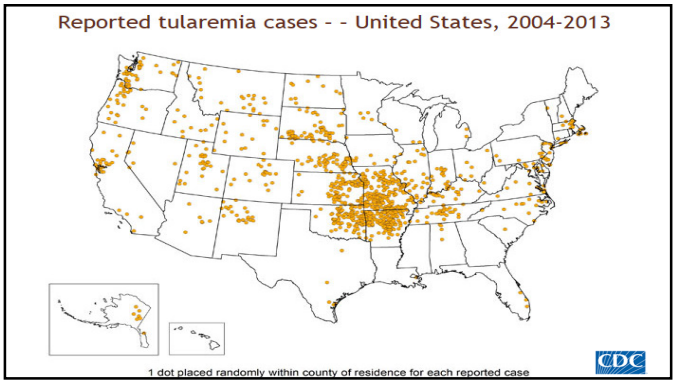
Ticks	Contact	Meat / Water	Airborne
Most common	Handling infected animals	Contaminated sources	Contaminated dust / hay
Dog / Rocky Mountain Wood / Lone star tick	Rubbing eyes / splasing	Survives in brackish / frozen water	Bioterrorism
ulceroglandular	oculoglandular	oropharyngeal	pulmonic
typhoidal / pulmonic			

Tularemia



Reported Tularemia Cases by Year in U.S. 1950-2013





Tularemia

- Diagnosis
  - high index of suspicion
  - cultures are almost always negative
  - serology (rarely positive acutely)
  - PCR
- Treatment
  - streptomycin x 10 days
  - mild disease may be treated with doxycycline / fluoroquinolones