Tickborne Diseases

CMED/EPI-526

Spring 2009

Ben Weigler, DVM, MPH, Ph.D

"Reports of tick-borne disease in Washington state are relatively few in comparison to some areas of the United States. Though tick-borne disease may not be common, the severity of these diseases generates public concern and questions."

Washington State Dept. of Health

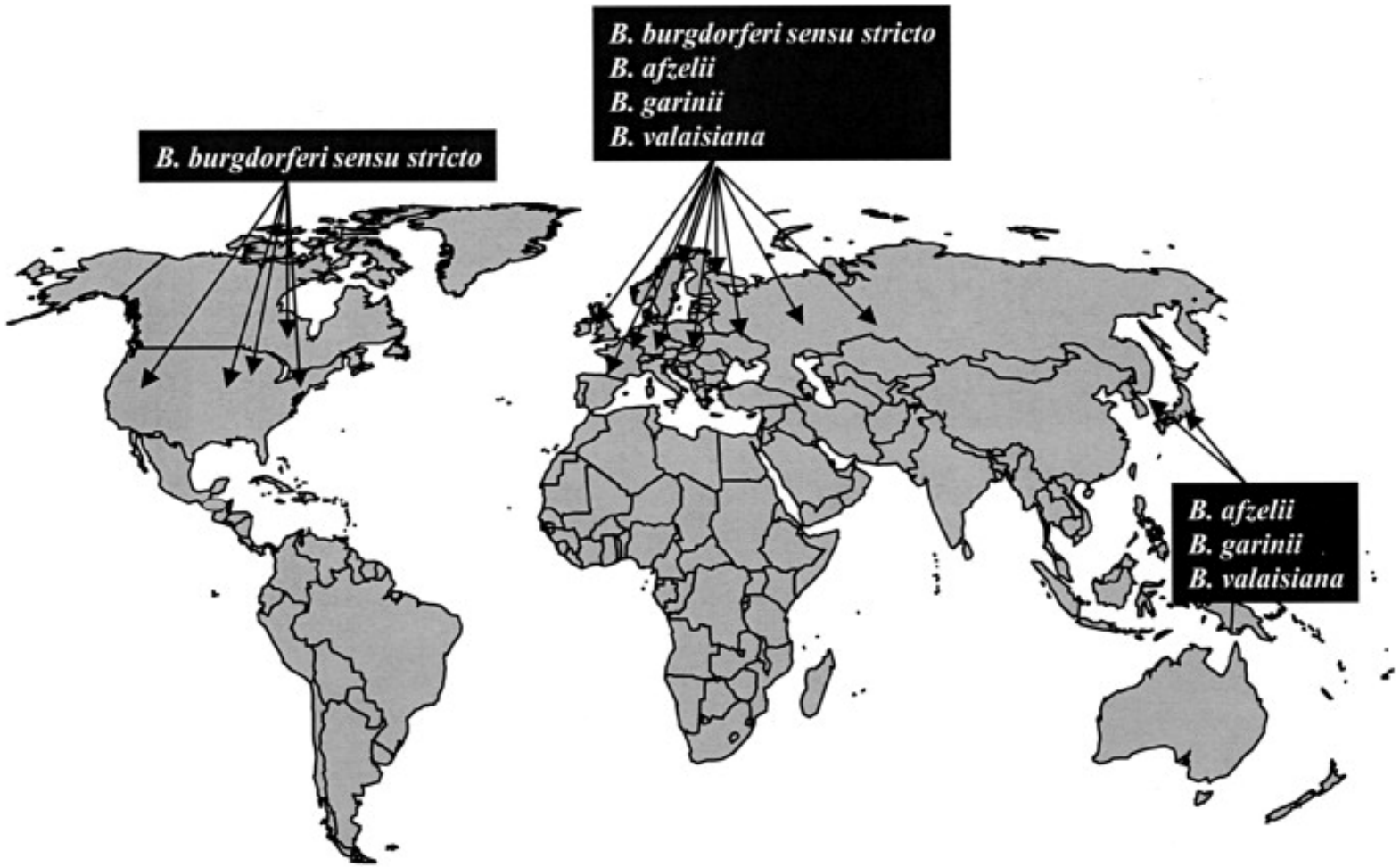
Vol 11, No 12, December 2005

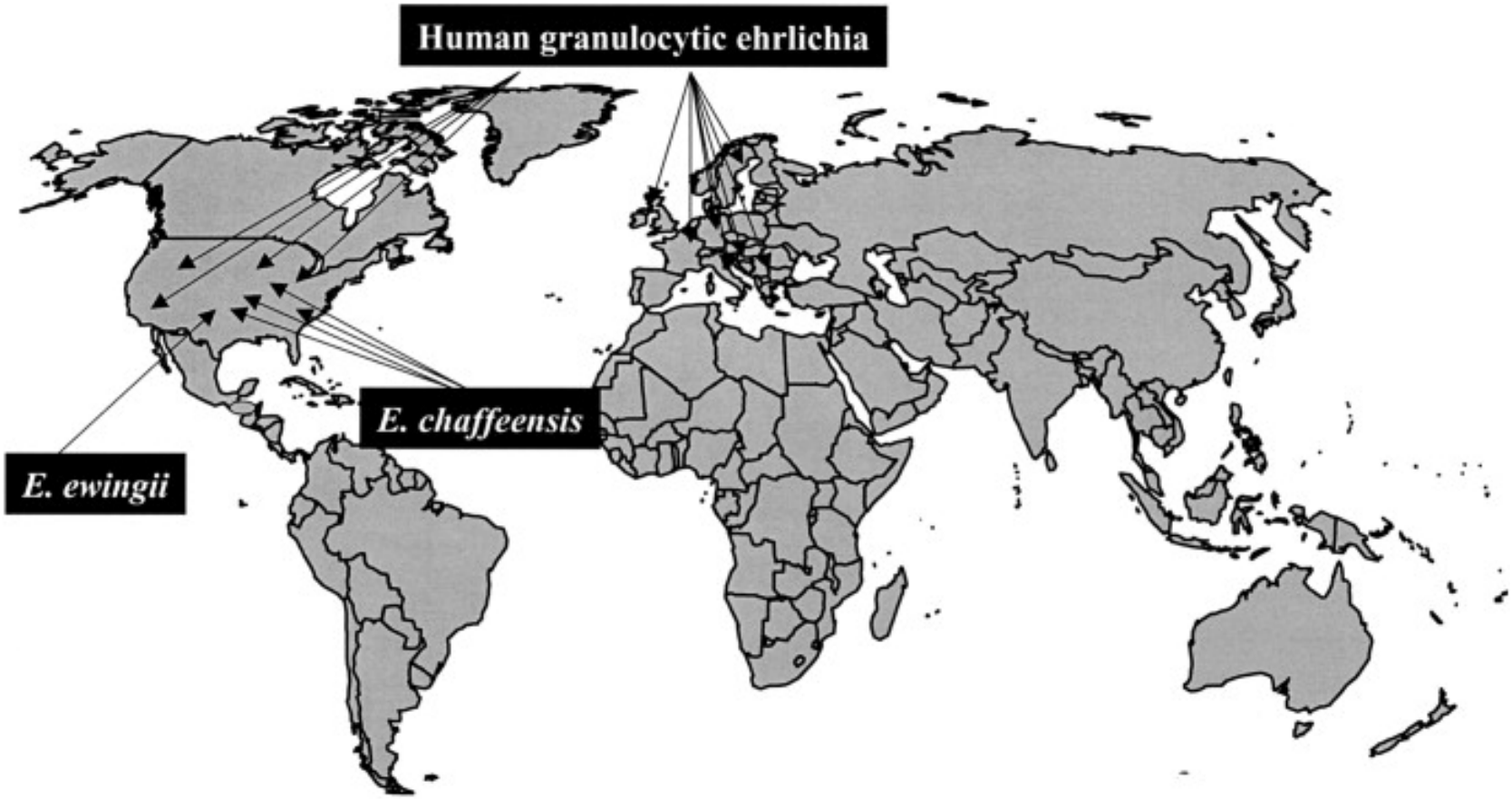
EMERGING INFECTIOUS DISEASES

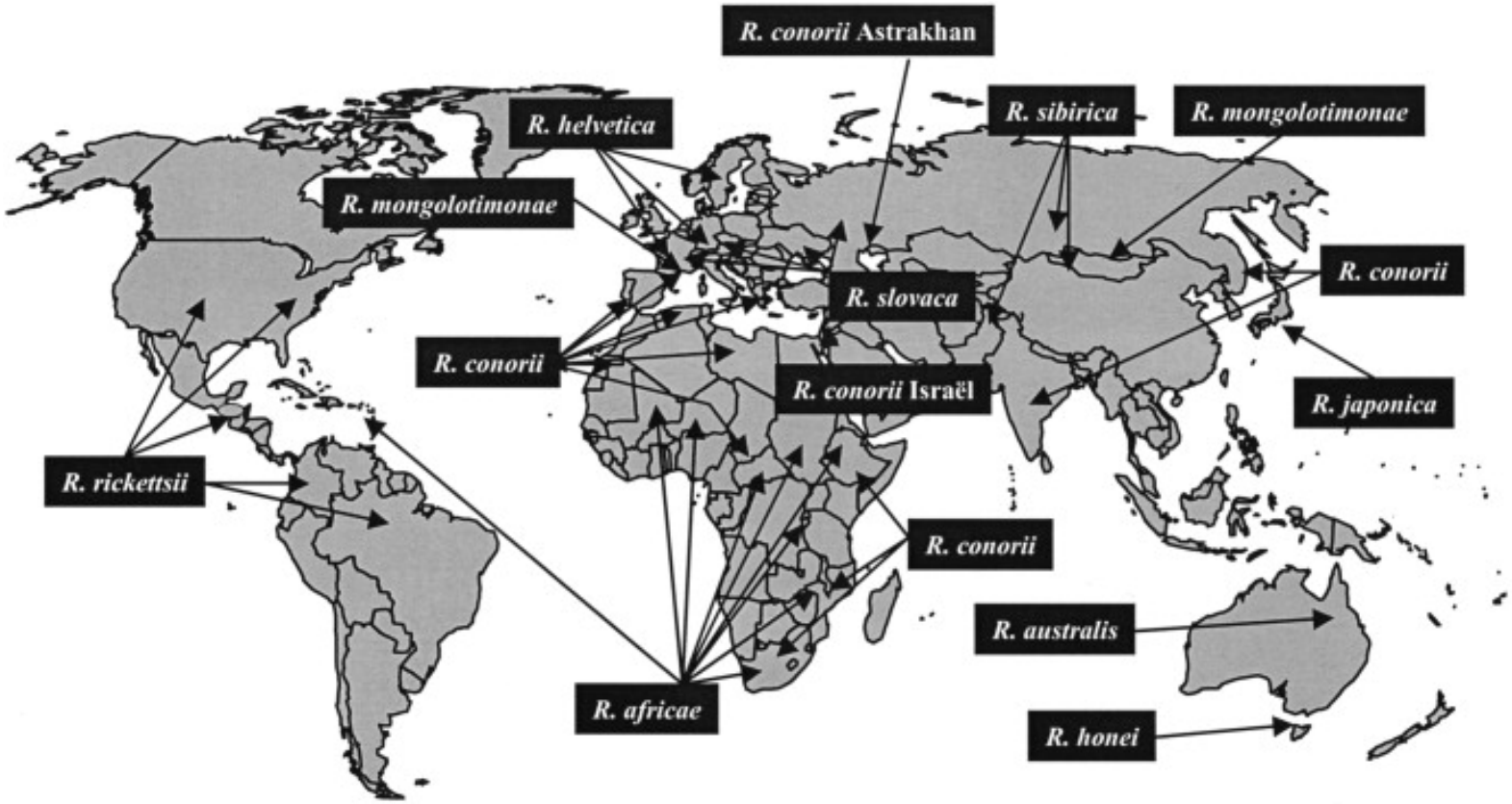
EID Online

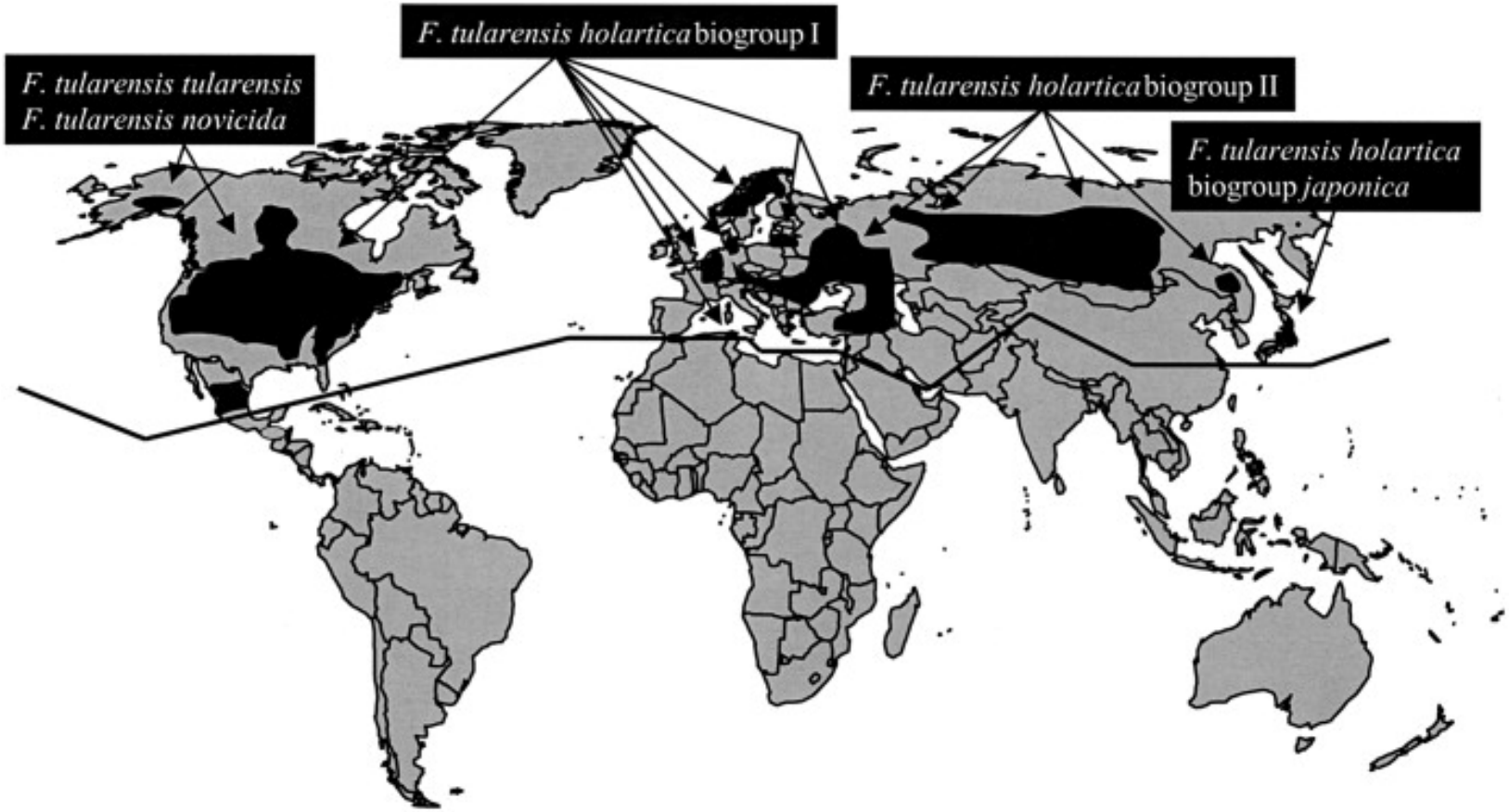
A Peer-Reviewed Journal Tracking and Analyzing Disease Trends Vol 11, No 12, December 2005

EMERGING INFECTIOUS DISEASES


B. burgdorferi sensu stricto
B. burgdorferi sensu stricto
B. afzelii
B. garinii
B. valaisiana
B. afzelii
B. garinii
B. valaisiana


Human granulocytic ehrlichia
E. chaffeensis
E. ewingii


R. conorii Astrakhan
R. sibirica
R. mongolotimonae
R. helvetica
R. mongolotimonae
R. conorii
R. slovaca
R. conorii
R. conorii Israël
R. japonica
R. rickettsii
R. conorii
R. australis
R. africae
R. honei


F. tularensis holartica biogroup I
F. tularensis tularensis
F. tularensis novicida
F. tularensis holartica biogroup II
F. tularensis holartica
biogroup japonica

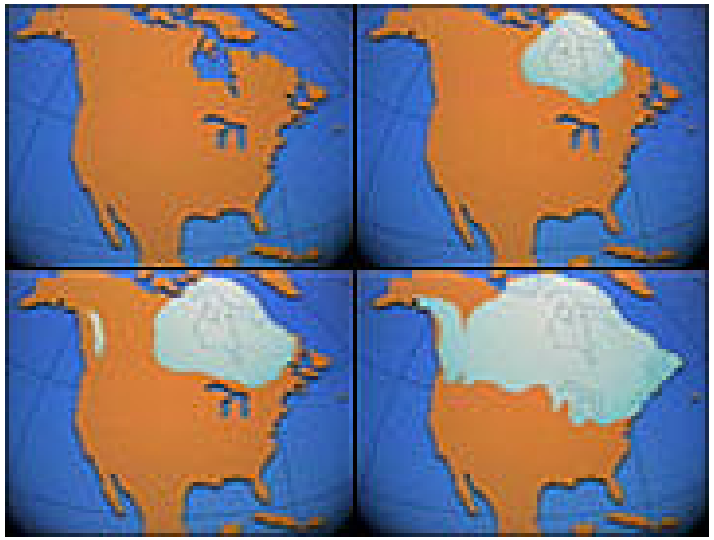
<u>Tick Vector Ecology</u>:

I. Deer ticks ("*Ixodes ricinus*-like") occur in all temperate biomes circumglobally.

II. Glacial terminal moraines = The maximun advance of a glacier during previous ice ages…. Ecologic refugia for deer tick survival and evolution.

III. Changing composition of lands across North America in past 2 centuries.

IV. Increasing associations of humans with wildlife.



White-tailed Deer

Odocoileus virginianus

The <u>most abundant</u> large game species in North America

Prior to European settlers: 23 to 34 Million deer in USA

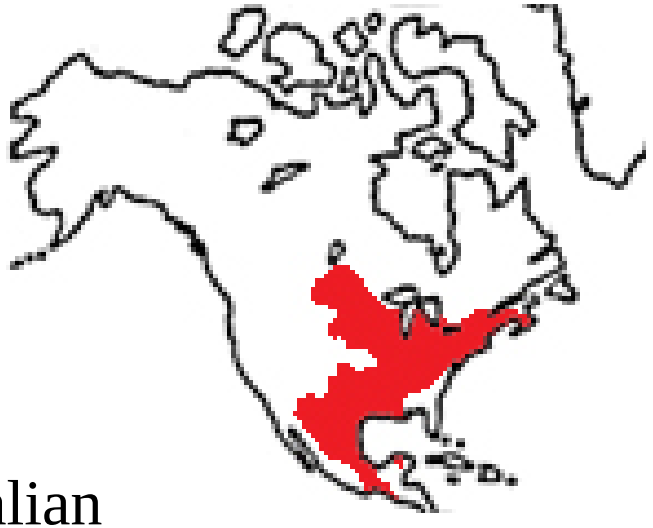
Early 1900's: 300,000 to 500,000 deer

Today: ~27 Million deer

- 1.5 Million deer/vehicle collisions annuallly
- → 130-200 human deaths

White-Footed Mouse

Peromyscus leucopus



- Principal lyme disease mammalian reservoir in North America
- First *B. burgdorferi* isolation in 1894 (museum specimens)
- Also reservoir host for Babesiosis and Ehrlichiosis

Tick-borne Disease Ecology Terms:

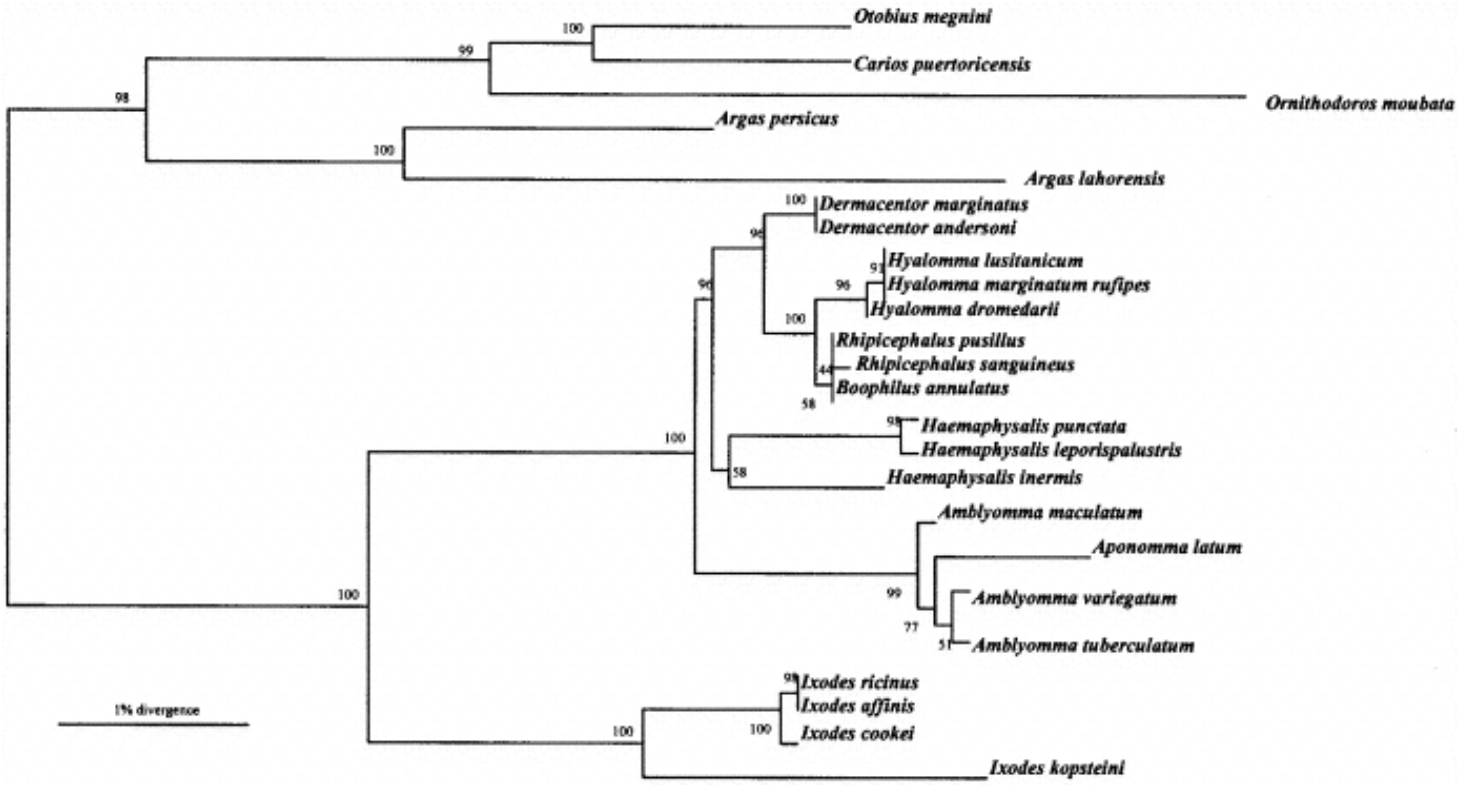
Repletion = full of blood (e.g., engorged female)

Transovarial transmission = e.g., *B. burgdorferi* in *I. Scapularis*, transmission to succeeding generations within the tick.

Transstadial transmission = among stages in life cycle, e.g., from nymph to adult

Reservoir competence = the capacity of a vertebrate animal species to maintain a pathogen as a continued source of infection for invertebrates.

Vector competence = capacity of an arthropod species to act as a biologically important source for infection of vertebrate animals, e.g, through replication of the agent within the vector.



Tick Phylogeny, based upon 18S RNA Sequence

~ 900 recognized species of ticks in the world

Some Tick Species Found in WA

- *Dermacentor spp*.– Throughout the State

  Prefer woodland areas, medium height grasses and shrubs between wetlands and woods, and sunny or open areas around woods. Immature ticks feed primarily on small mammals, particularly rodents, while the adults feed on deer, livestock, dogs, and humans.

- *Ixodes spp*. –West of the Cascades

  Live in heavily-forested or dense brushy areas, but not open areas. Preferred hosts for immature ticks are birds and small mammals, primarily rodents but humans and dogs serve as good substitutes. For adults, common hosts include livestock, dogs, and humans.

- *Ornithodoros spp*. – Mostly East of the Cascades

  Prefer burrows and nests. Usually feeds on rodents such as squirrels and chipmunks. Humans can be incidental hosts when sleeping in cabins or dwellings inhabited with tick-infested squirrels, chipmunks or other rodents.

WA-DOH: Tickborne Diseases in Washington State - 2006

1. Lyme Disease → 8 cases, perhaps 1/3 of which are imported.
2. Relapsing Fever (*Borrelia recurrentis*) → 2 cases. *Ornithidoros* spp.
3. Babesiosis "WA1"(3 cases in 1990's, 1 case in 2002) → vector not identified
4. Erlichiosis → Non-notifiable. 7 confirmed & 12 probable cases 1989-1998.
5. Rocky Mountain Spotted Fever→ Non-notifiable. At least 9 since 1998.
6. Tularemia → 1 case; tick is one of the several routes of possible exposure.
7. Tick paralysis (34 cases reported from 1946-2000) → esp. *Dermacentor andersoni* toxin. All cases occur in March through June.

Tickborne Diseases of WA State

- Lyme Disease : *I. pacificus*, but Eastern WA?
- Babesiosis : *Ixodes* spp., blood transfusions?
- RMSF : *Dermacentor spp.*
- Tularemia : *Dermacentor spp.*
- Relapsing Fever : *Ornithodoros* (soft ticks)
- Tick Paralysis : *Dermacentor* spp. In USA

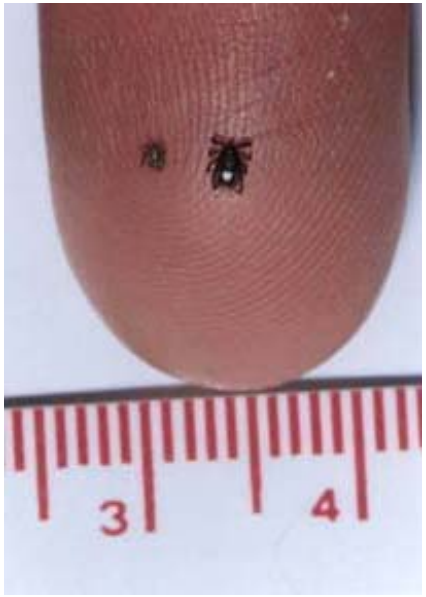
Notifiable Tick-borne Diseases in Washington

- Lyme disease (within 3 work days)
- Q fever (within 3 work days)
- Relapsing fever (immediately)
- Tularemia (within 3 days)

Washington State Department of Health

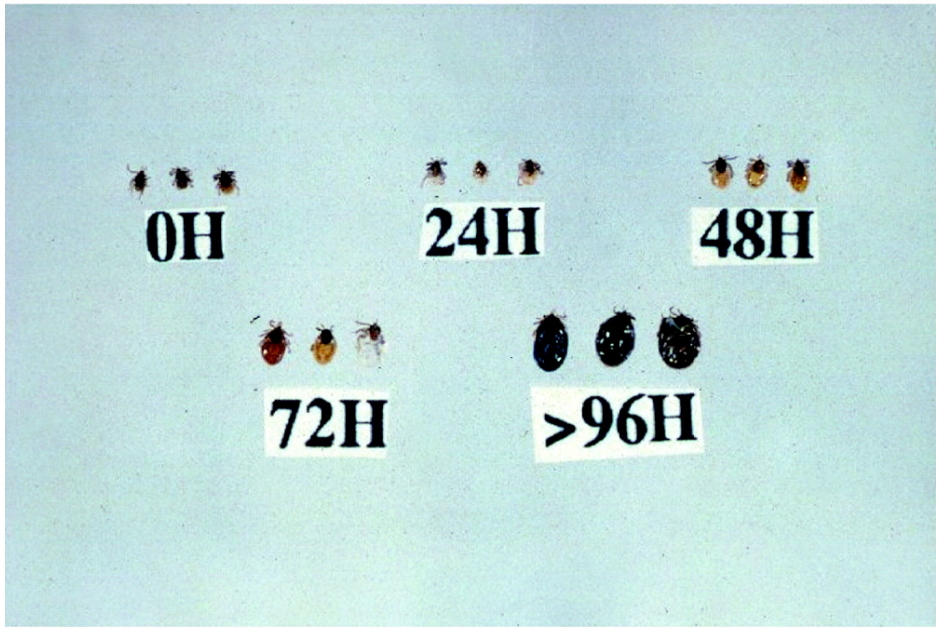
WAC 246-101

Tick Species	Distribution	Feeding Hosts	Affinity for Humans
Ixodes scapularis (Black legged tick)	East/SE USA and Canada	Small mammals, reptiles, birds. Large mammals for adults	High
Ixodes pacificus (Westrn Black Legged tick)	Canadian Pacific Coast	Small mammals, reptiles, birds. Large mammals for adults	Yes
Rhipicephalus sanguineus	USA, Africa, Middle East, India	Dogs principally (Brn dog tick)	Low
Dermacentor variabilis (Am. Dog Tick)	USA, Canada, Mexico	Small mammals, Mice, Voles, Dogs	High

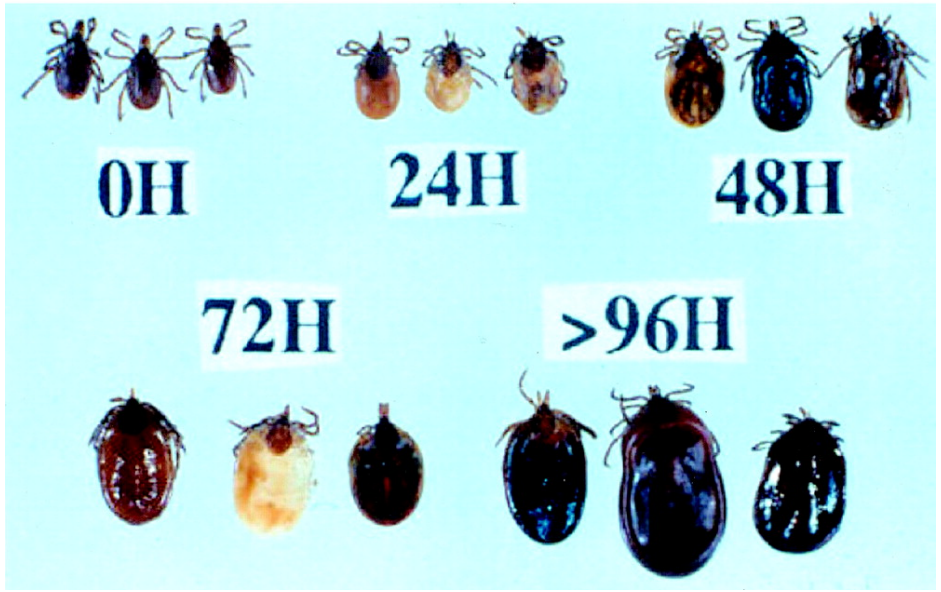


Ixodes scapularis ticks, life stages

A.



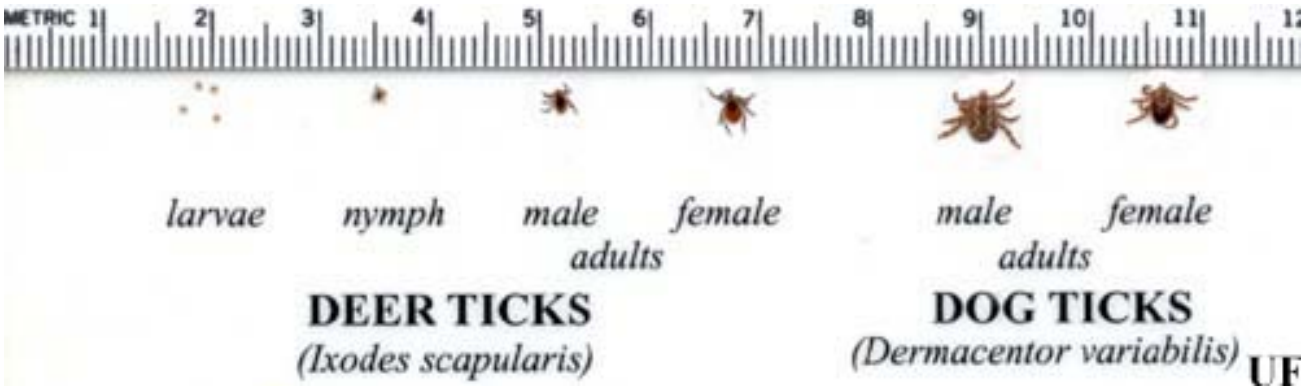
B.



***Ixodes scapularis* ticks demonstrating changes in blood engorgement after various durations of attachment.**

← **Nymphal Stage**

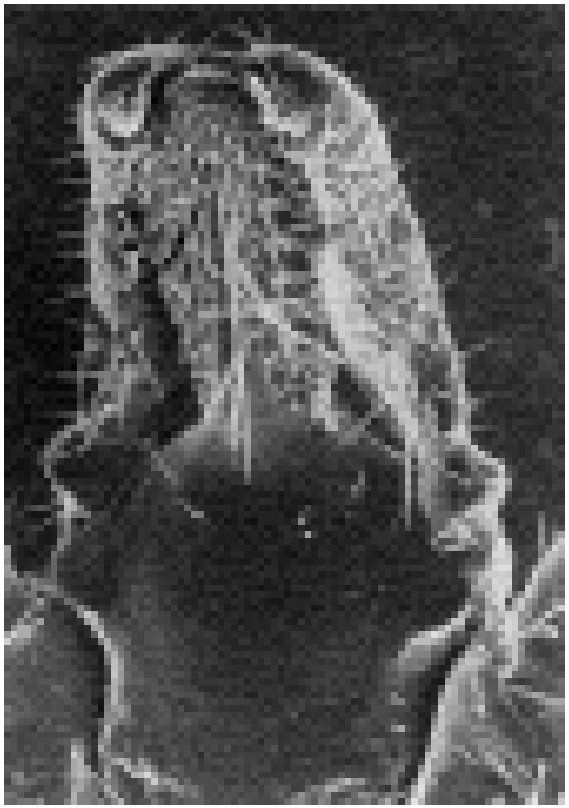
← **Adult Stage**



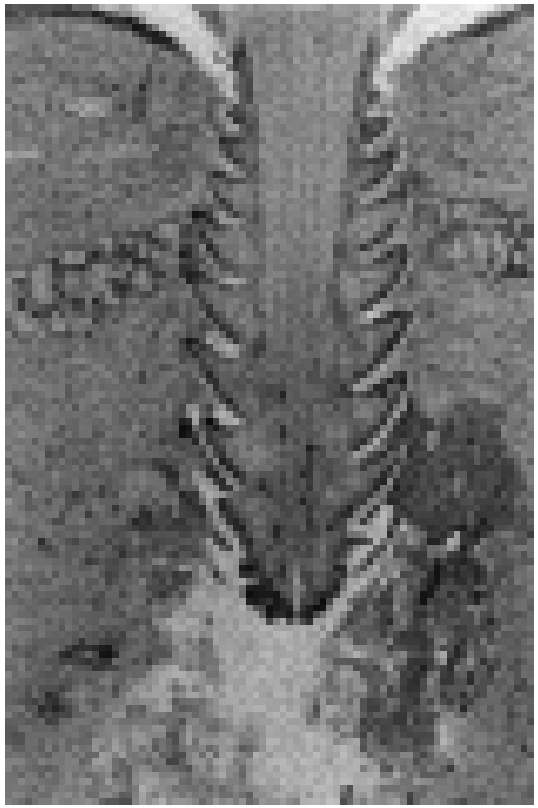
~180,000 human tick bites per year in Westchester County, NY

~ 15% of those persons experience a second bite within 6 weeks

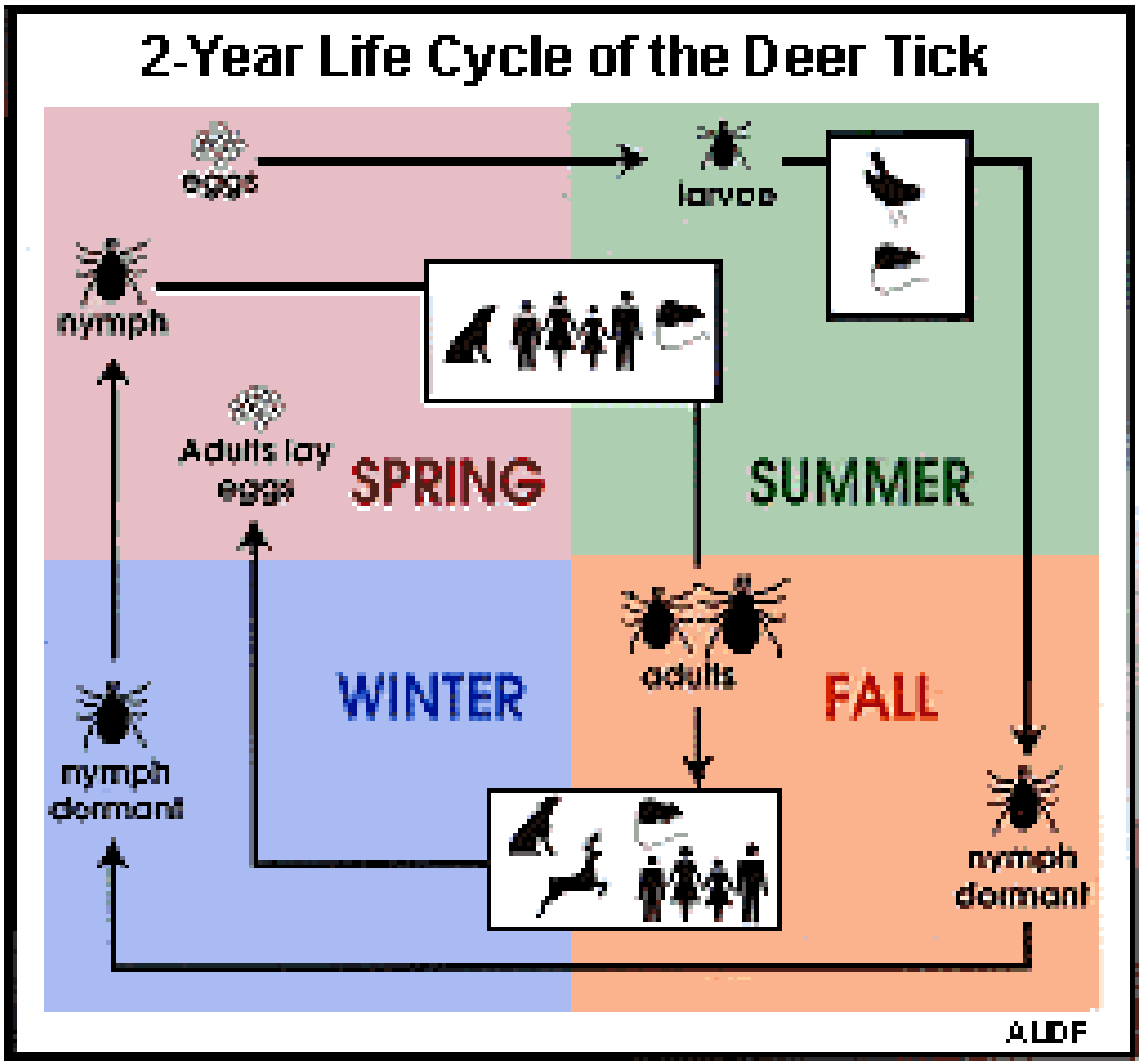
Westchester County Census = 850,000 residents

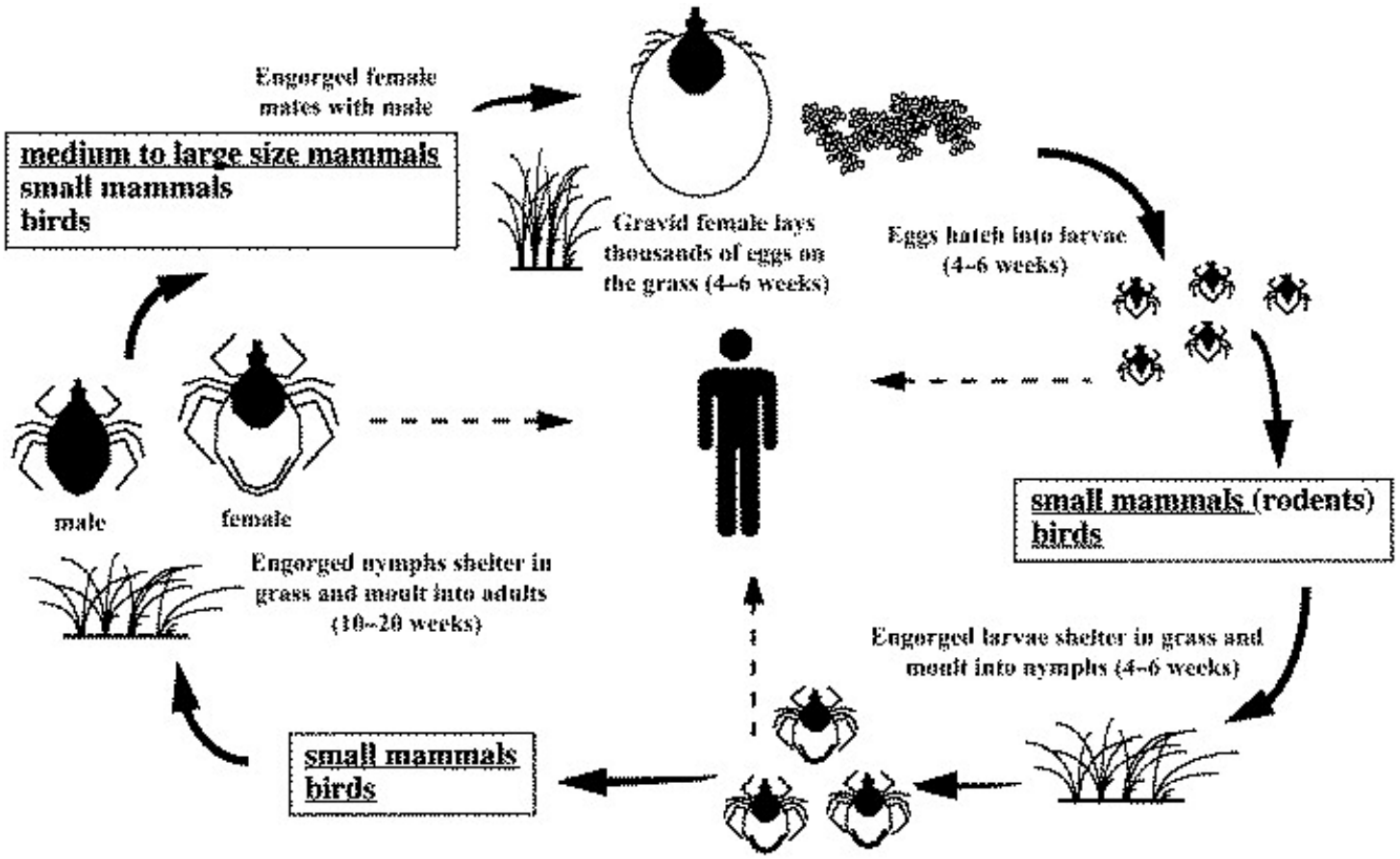


Scanning EM of
Ixodid mouthparts

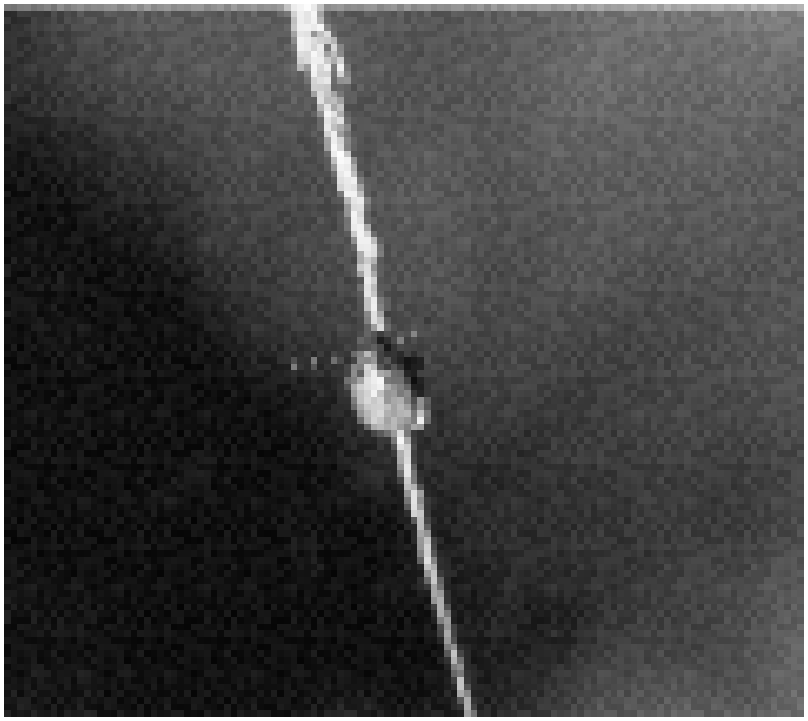


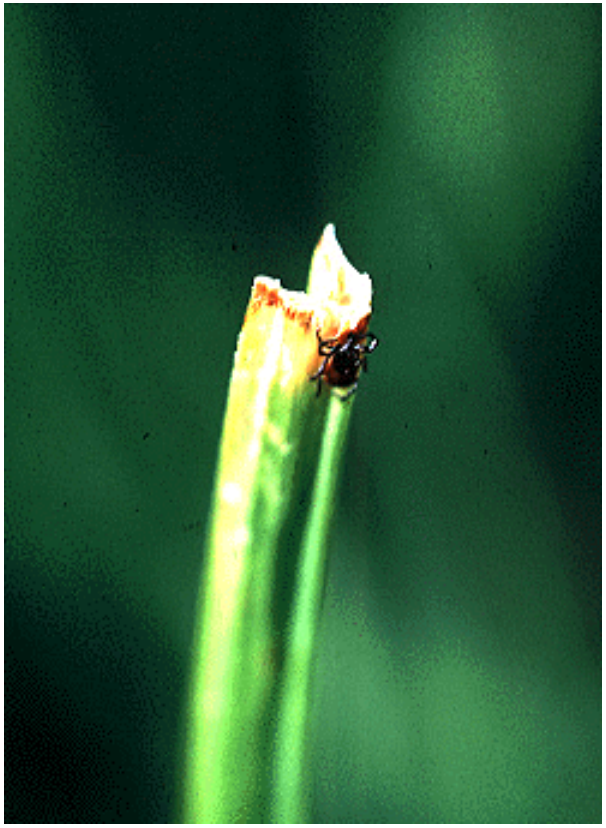
Ixodid tick hypostome
inserted into skin


2-Year Life Cycle of the Deer Tick
eggs
larvae
nymph
Adults lay eggs
SPRING
SUMMER
WINTER
FALL
adults
nymph dormant
nymph dormant
ALDF

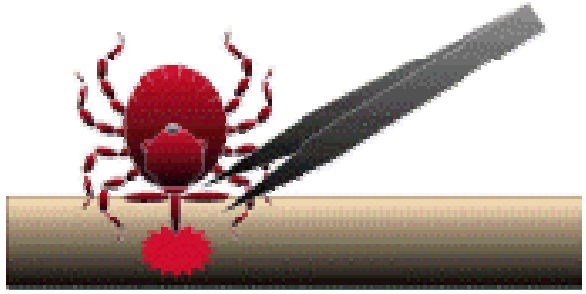


Ixodes tick life cycle



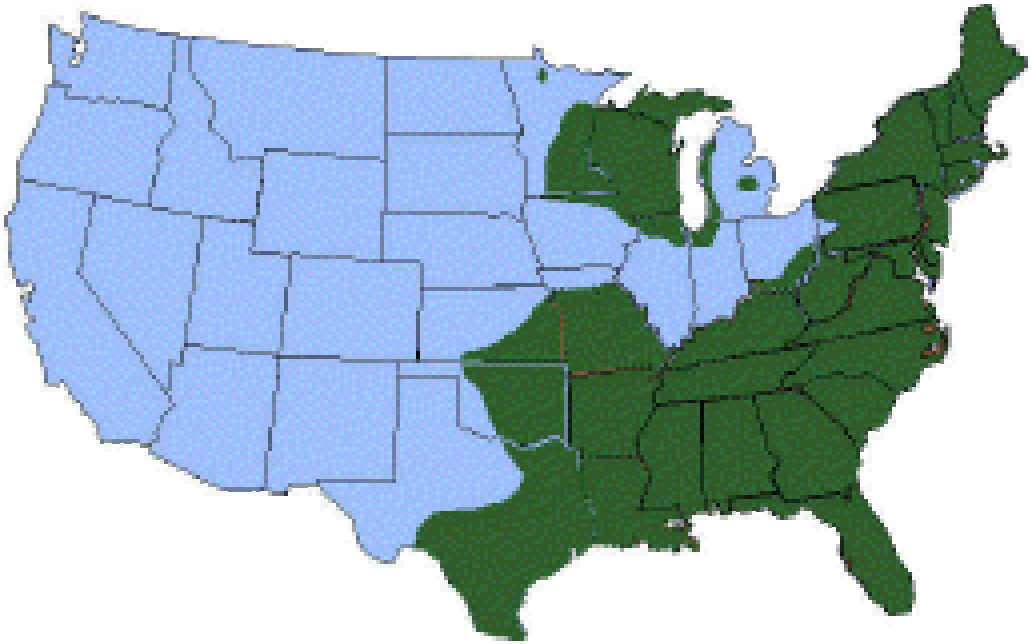


Deer tick on vegetation – “questing behavior”



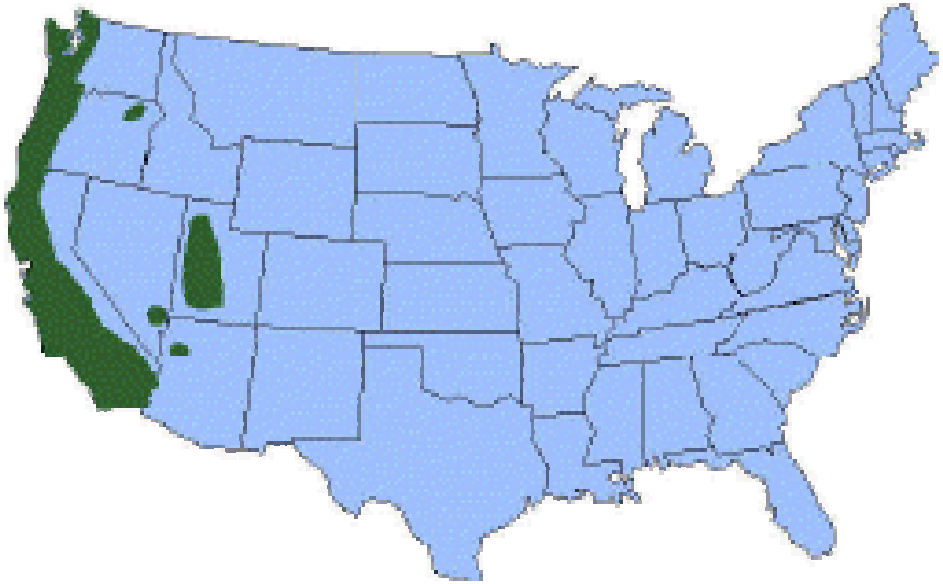
Tick removal methods

Engorged on human skin



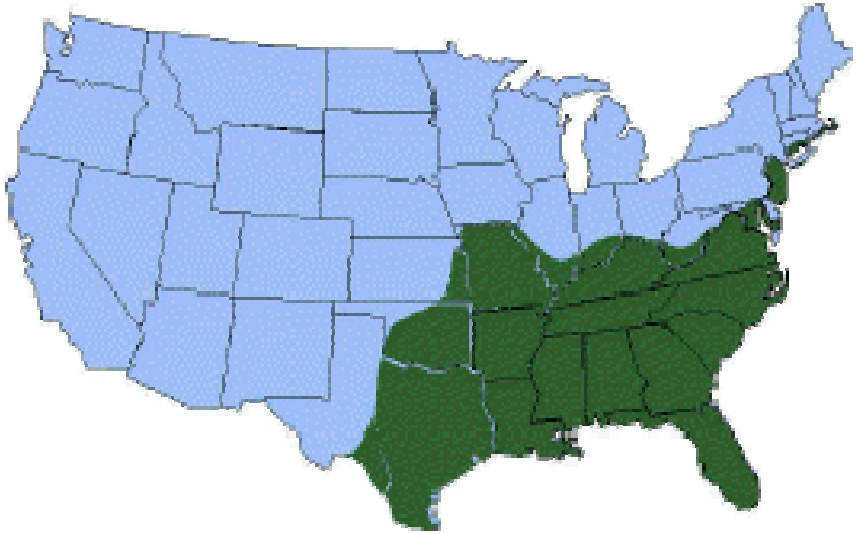
Ixodes scapularis and its distribution

(Black legged tick)



Ixodes pacificus and its distribution

(Western black legged tick)



Lone Star Tick and its distribution

(Amblyomma americanum)

Rhipicephalus sanguineus (Brown dog tick)

American Dog Tick

(Dermacentor variabilis)

Dragging for Ticks, woodland habitat

CDC Notifiable Disease Report: USA Year 2002

- Ehrlichiosis – 511
- Anaplasmosis – 216
- Lyme Disease – 23,763 (tripled since 1991)
  (11,873 Mid Atlantic, 7,807 New England)
- Q Fever – 61
- RMSF – 1,104
- Tularemia - 90

Case-Clusters in Olde Lyme, CT

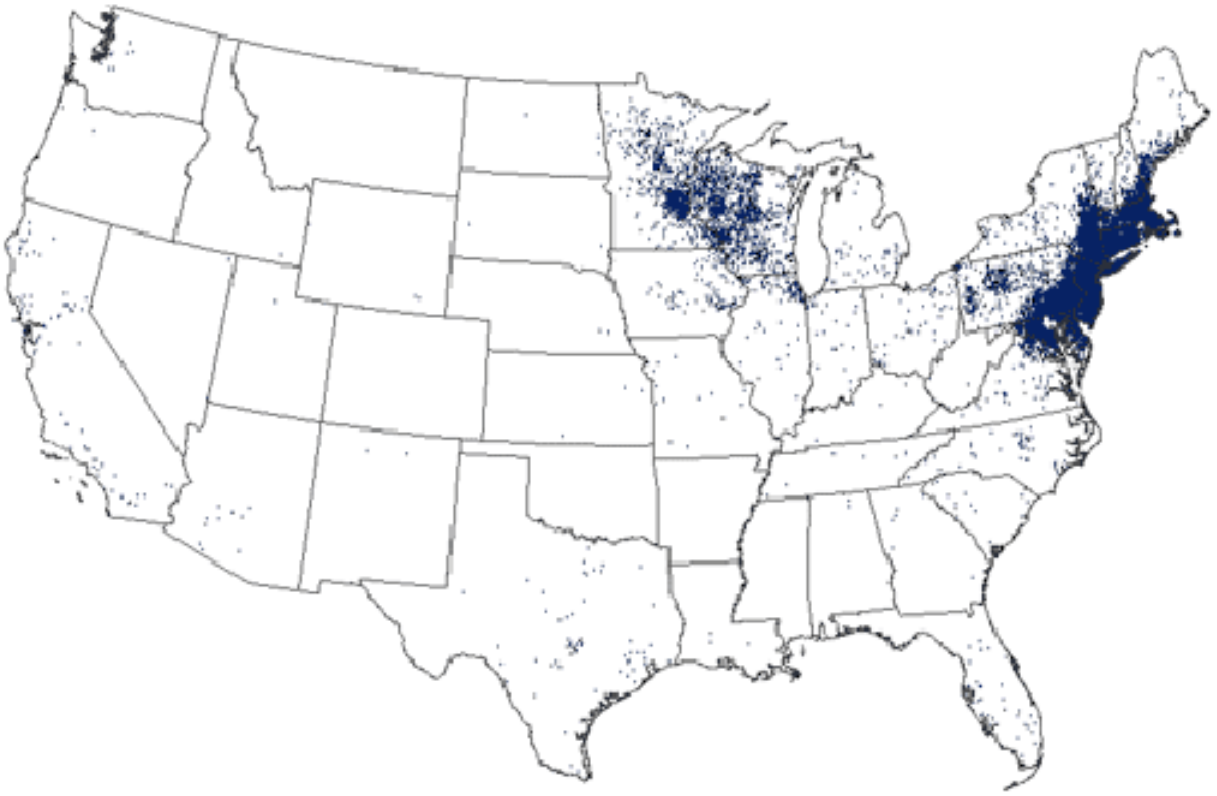
Arthritis Rheum. 1977 Jan-Feb;20(1):7-17.

Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three connecticut communities.

Steere AC, Malawista SE, Snydman DR, Shope RE, Andiman WA, Ross MR, Steele FM

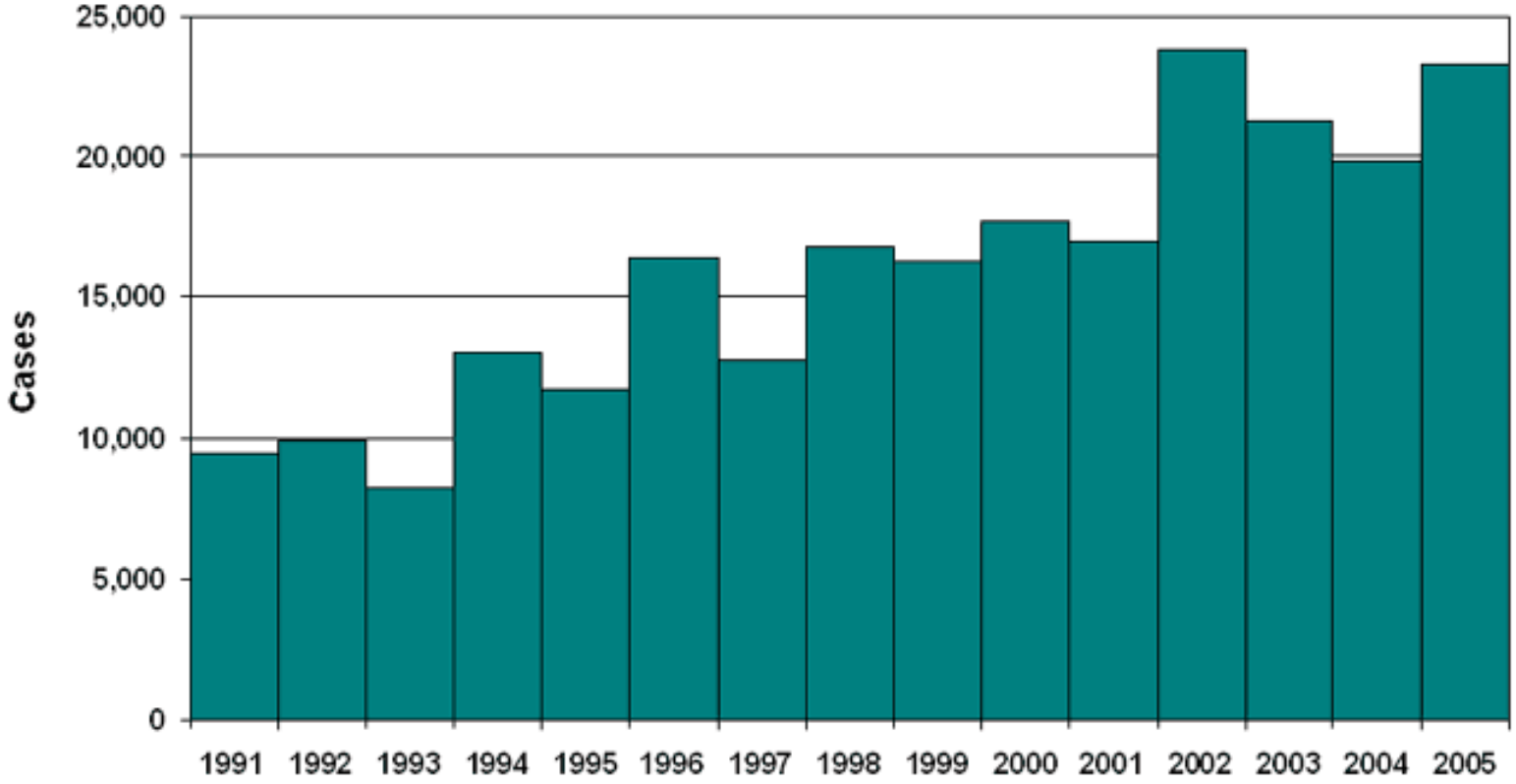
"An epidemic form of arthritis has been occurring in eastern Connecticut at least since 1972, with the peak incidence of new cases in the summer and early fall. Its identification has been possible because of tight geographic clustering in some areas, and because of a characteristic preceding skin lesion in some patients….."

Reported cases of Lyme disease—United States, 2005



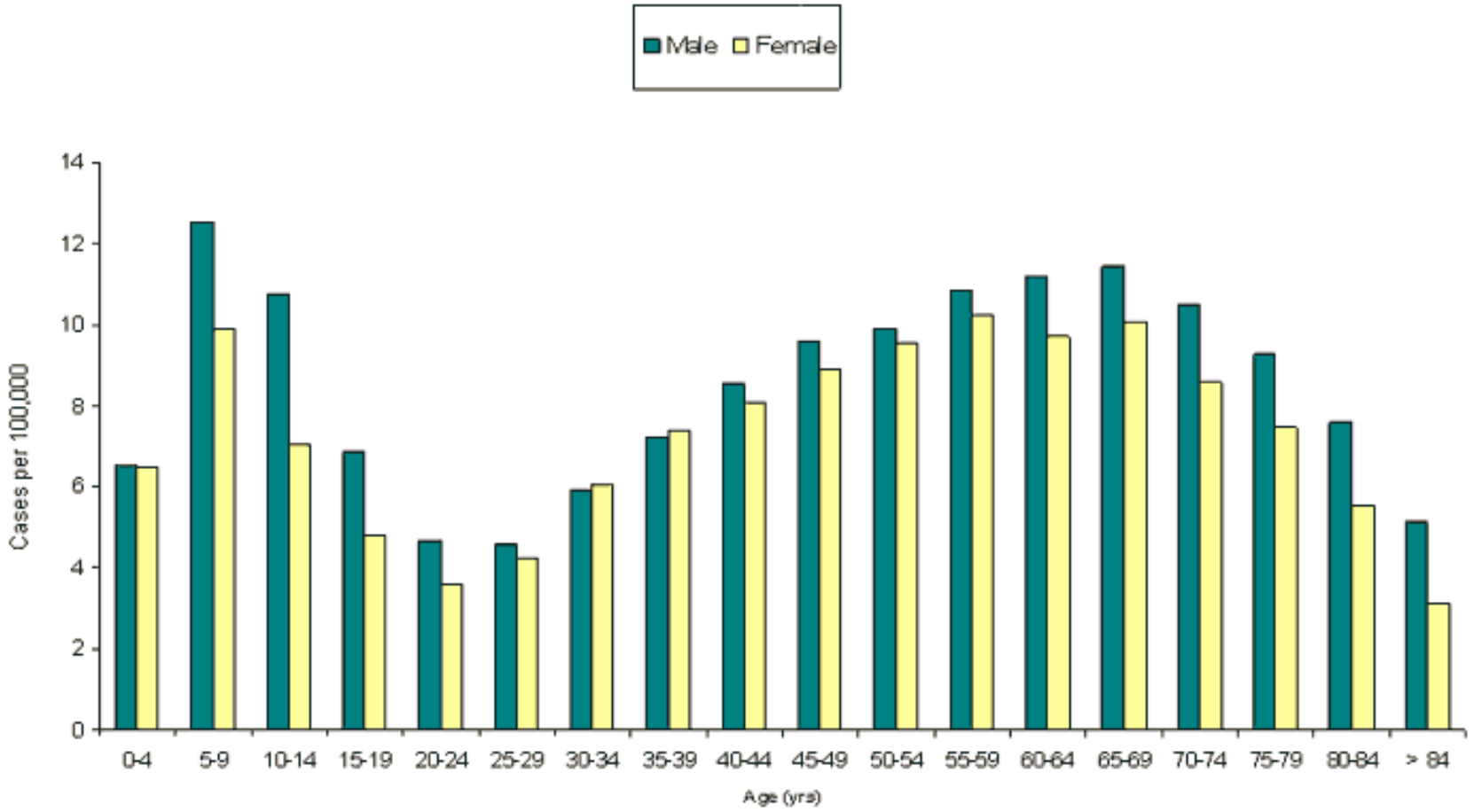
1 dot placed randomly within county of residence for each reported case

Reported Cases of Lyme Disease by Year, United States, 1991-2005

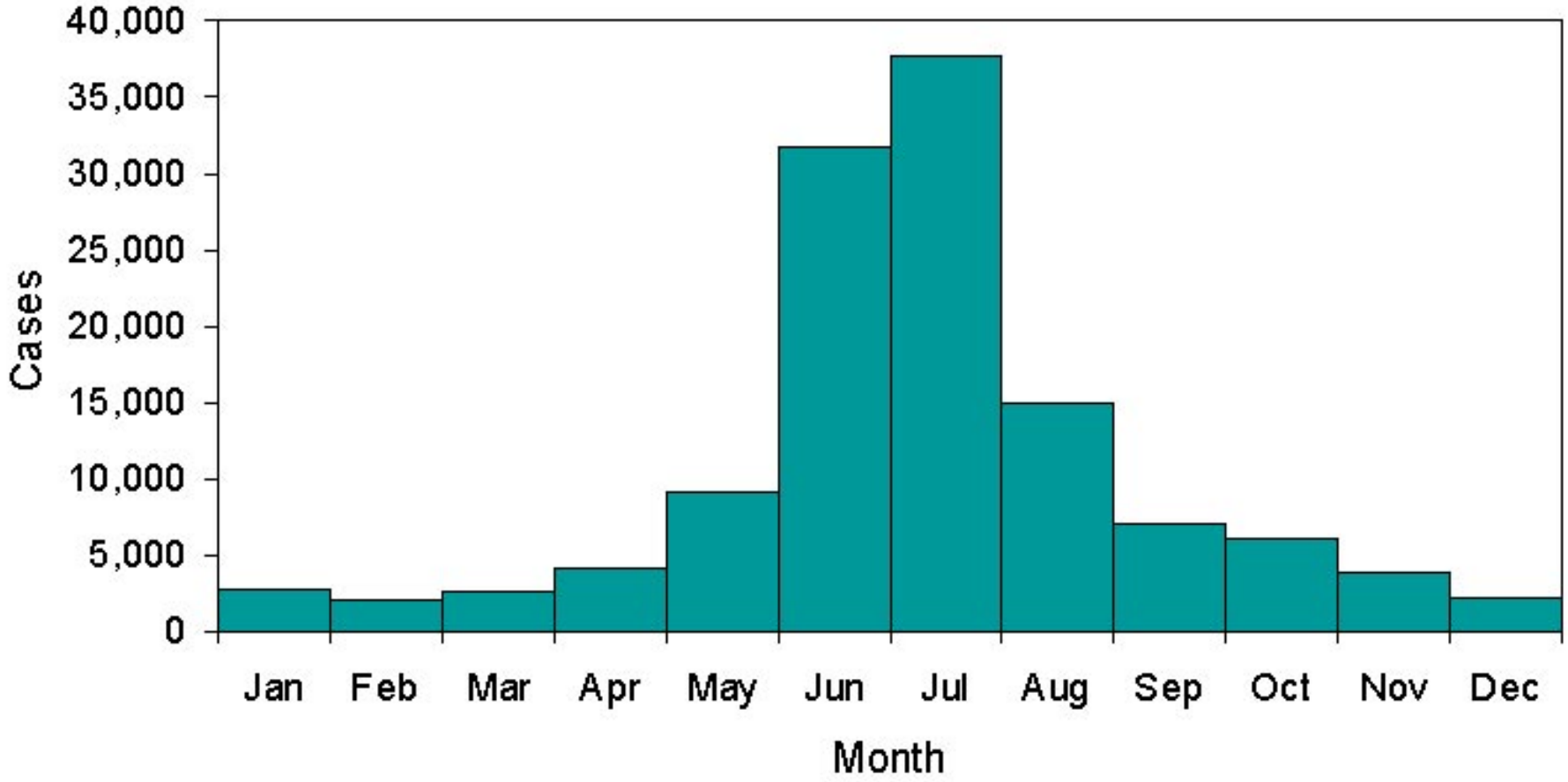


- Bimodal distribution by age; highest in 5-9 year olds & 50-59 year olds.
- More likely in males (53.6% male) over all age groups.

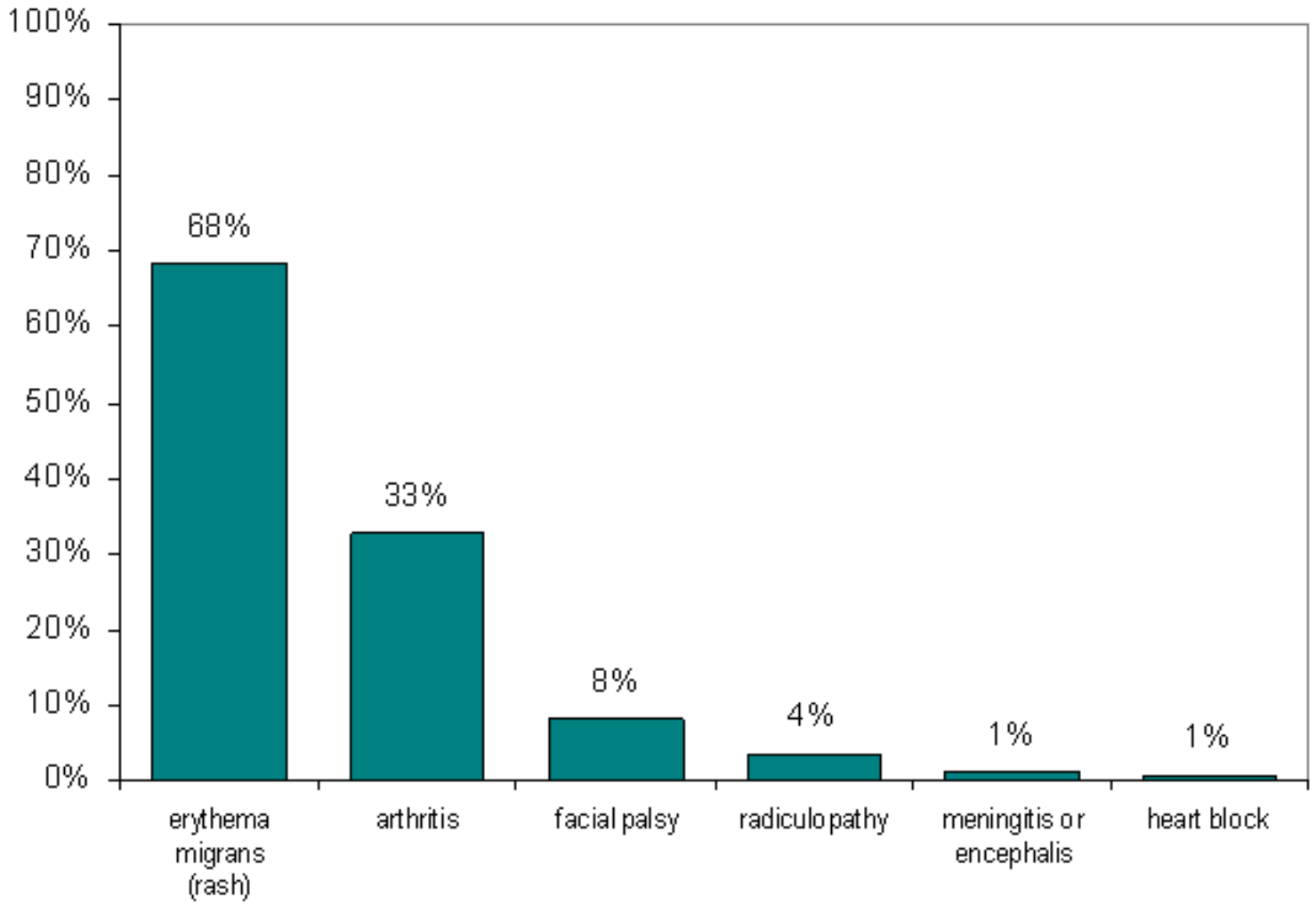
Average Annual Incidence of Reported Cases of Lyme Disease by Age Group and Sex , United States, 1992-2004.



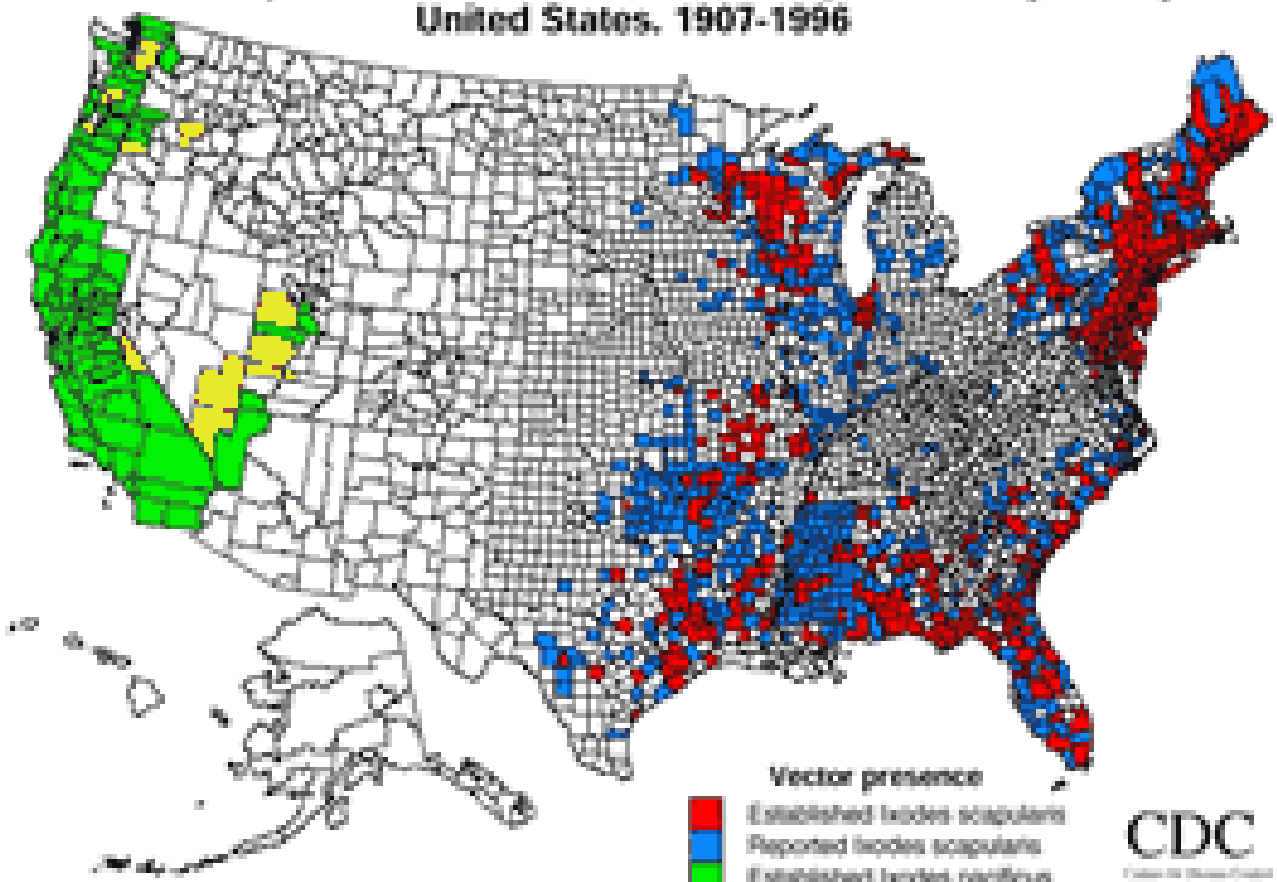
Reported Cases of Lyme Disease by Month of Illness Onset United States, 1992-2004



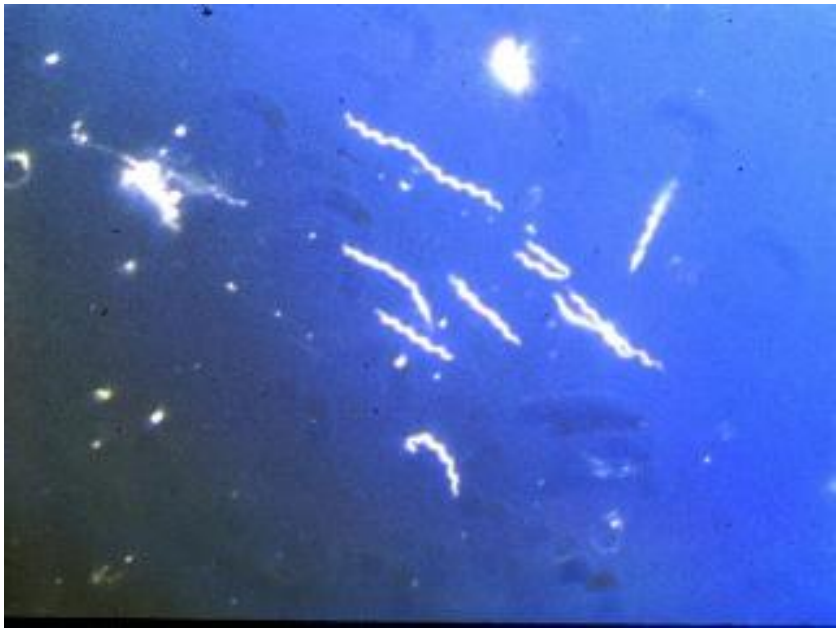
Reported Clinical Findings Among Lyme Disease Patients, 1992-2004



Established* and reported distribution of the Lyme disease vectors Ixodes scapularis (I. dammini) and Ixodes pacificus, by county, United States, 1907-1996**



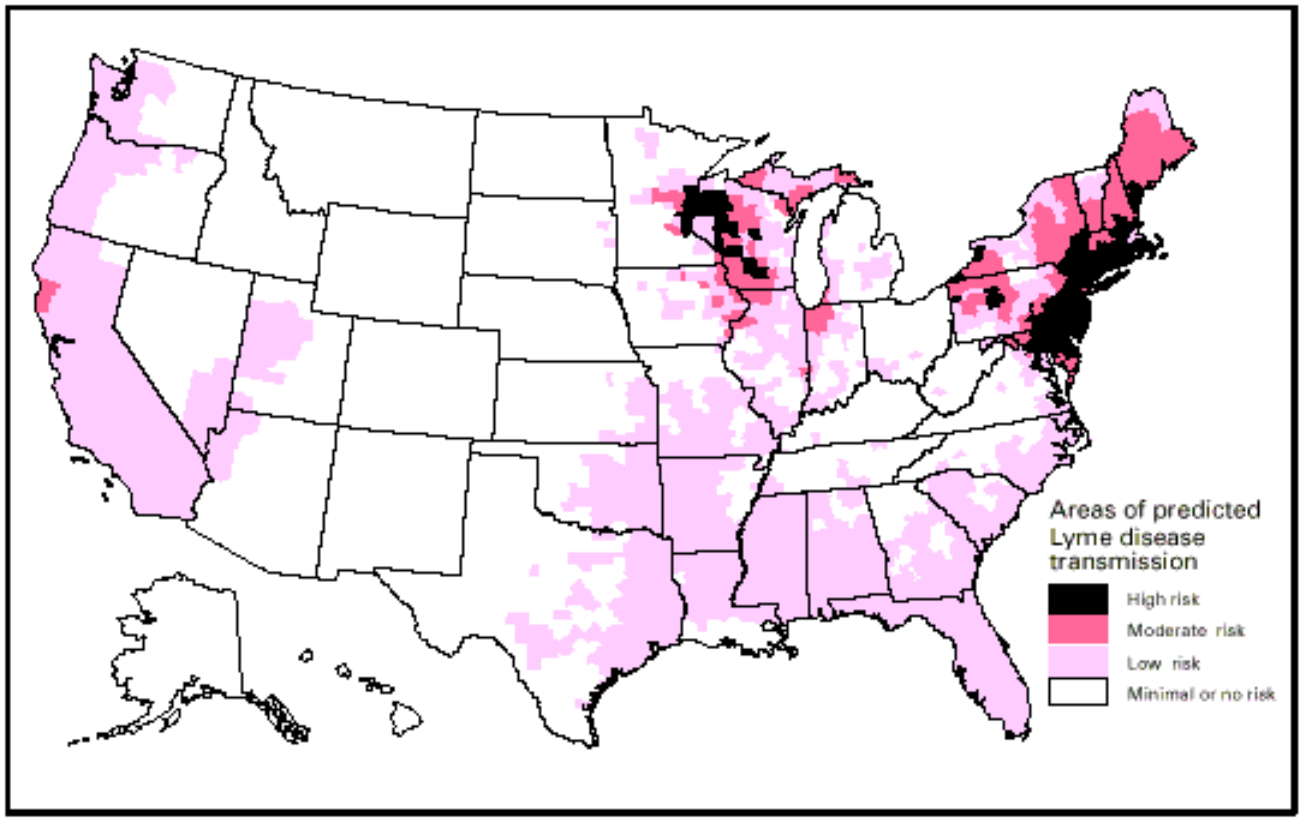
*at least 6 ticks or 2 life stages (larvae, nymphs, adults) identified.
**at least 1 tick identified.



***Borrelia burgdorferi* spirochetes**

ECM Lesions

National Lyme disease risk map with four categories of risk



Note: This map demonstrates an approximate distribution of predicted Lyme disease risk in the United States. The true relative risk in any given county compared with other counties might differ from that shown here and might change from year to year. Risk categories are defined in the accompanying text. Information on risk distribution within states and counties is best obtained from state and local public health authorities.

In endemic areas, p(Lyme|Tick Bite) = 0.012 to 0.05.

Lyme$_{rix}$ vaccine

Vaccine Maker Pulls Drug Off Market

Tue Feb 26, 2002 5:32 PM ET

By LAURAN NEERGAARD, AP Medical Writer

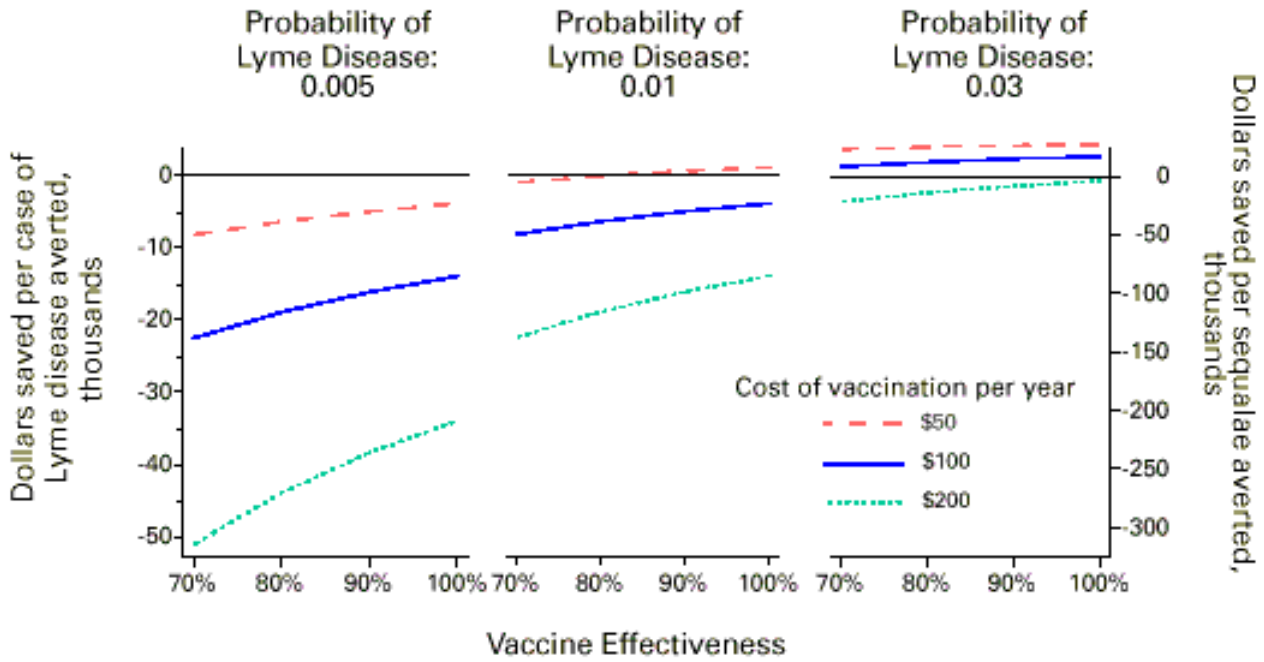
WASHINGTON - With tick season approaching, the maker of the nation's only vaccine against Lyme disease pulled it off the market, citing poor sales.

Lymerix had caused controversy in recent years, as patients said they were sickened by the vaccine and asked the government to restrict sales. Some filed lawsuits against maker GlaxoSmithKline.

Federal health officials said Tuesday they had found no evidence that the vaccine was dangerous. They urged people in Lyme-plagued states to take precautions against the pin-sized ticks that spread the disease.

Lymerix had $40 million in sales its first year on the market, and hundreds of thousands were vaccinated. But GlaxoSmithKline projected that fewer than 10,000 people would seek vaccination this year, and ended sales because "there's just no demand for it," said company spokeswoman Ramona Dubose.

FIGURE 1. Cost-effectiveness of Lyme disease vaccination



Note: This graph documents the effect of variations in cost of vaccination, vaccine effectiveness, and the probability of contracting Lyme disease on the cost-effectiveness of vaccination. The left-hand y-axis measures cost per case of Lyme disease averted. The right-hand y-axis measures the cost per long-term sequelae (e.g., cardiac, neurologic, and musculoskeletal sequelae) averted. Underlying assumptions are as follows: probability of identifying and treating early Lyme disease, 85%; cost of treating cardiac sequelae, $6,845; cost of treating neurologic sequelae, $61,193; cost of arthritis $34,304; cost of treating early Lyme disease without sequelae $161).

washingtonpost.com

Lyme Disease Vaccine Is Taken Off Market

Associated Press
Wednesday, February 27, 2002

The maker of the nation's only Lyme disease vaccine pulled it off the market yesterday, citing poor sales.

Lymerix had caused controversy in recent years, as patients who argued they were sickened by the vaccine asked the government to restrict sales and filed numerous lawsuits against maker GlaxoSmithKline.

But after a year of investigation, the Food and Drug Administration had found no proof that the vaccine was dangerous and thus did not tell the manufacturer to end sales, an agency spokeswoman said yesterday.

Lymerix had $40 million in sales its first year on the market, and hundreds of thousands were vaccinated. But GlaxoSmithKline projected that fewer than 10,000 people would seek vaccination this year, and decided it didn't make financial sense to keep selling the vaccine.

Office of
Technology Assessment

- **Vaccine Development Timeline: 7-12 years**
- **Stages: Discovery, Early Development, Advanced Development, Preparation of FDA Application**
- **Then: On to Phase 1, Phase 2, and Phase 3 Trial (FDA)**
- **Total Cost to Licensure: $110 Million to $802 Million**

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Gary P. Wormser,[1] Raymond J. Dattwyler,[2] Eugene D. Shapiro,[5,6] John J. Halperin,[3,4] Allen C. Steere,[9] Mark S. Klempner,[10] Peter J. Krause,[8] Johan S. Bakken,[11] Franc Strle,[13] Gerold Stanek,[14] Linda Bockenstedt,[7] Durland Fish,[6] J. Stephen Dumler,[12] and Robert B. Nadelman[1]

Clinical Infectious Diseases 2006;43:1089-1134

1058-4838/2006/4309-0001$15.00

Table 2. Recommended antimicrobial regimens for treatment of patients with Lyme disease.

Drug	Dosage for adults	Dosage for children
Preferred oral regimens		
Amoxicillin	500 mg 3 times per day[a]	50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose)[a]
Doxycycline	100 mg twice per day[b]	Not recommended for children aged <8 years For children aged ≥8 years, 4 mg/kg per day in 2 divided doses (maximum, 100 mg per dose)
Cefuroxime axetil	500 mg twice per day	30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)
Alternative oral regimens		
Selected macrolides[c]	For recommended dosing regimens, see footnote *d* in table 3	For recommended dosing regimens, see footnote in table 3
Preferred parenteral regimen		
Ceftriaxone	2 g intravenously once per day	50–75 mg/kg intravenously per day in a single dose (maximum, 2 g)
Alternative parenteral regimens		
Cefotaxime	2 g intravenously every 8 h[d]	150–200 mg/kg per day intravenously in 3–4 divided doses (maximum, 6 g per day)[d]
Penicillin G	18–24 million U per day intravenously, divided every 4 h[d]	200,000–400,000 U/kg per day divided every 4 h[d] (not to exceed 18–24 million U per day)

[a] Although a higher dosage given twice per day might be equally as effective, in view of the absence of data on efficacy, twice-daily administration is not recommended.

[b] Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age.

[c] Because of their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins.

[d] Dosage should be reduced for patients with impaired renal function.

Human Ehrlichiosis

- Family *Anaplasmataceae*
- Acute febrile multisystemic illnesses
- *Ehrlichia chaffeensis* (HME agent), isolated in 1987.

  Main vector = *Amblyomma americanum*
- *Anaplasma phagocytophilum* (human granulocytic ehrlichia agent) related to but distinct from *Ehrlichia equi*, isolated in 1994.

  Main vector = *Ixodes scapularis, I. pacificus*
- *Ehrlichia ewingii* (human and canine granulocytic ehrlichia agent), isolated in 1999.

  Main vector = *Amblyomma americanum*

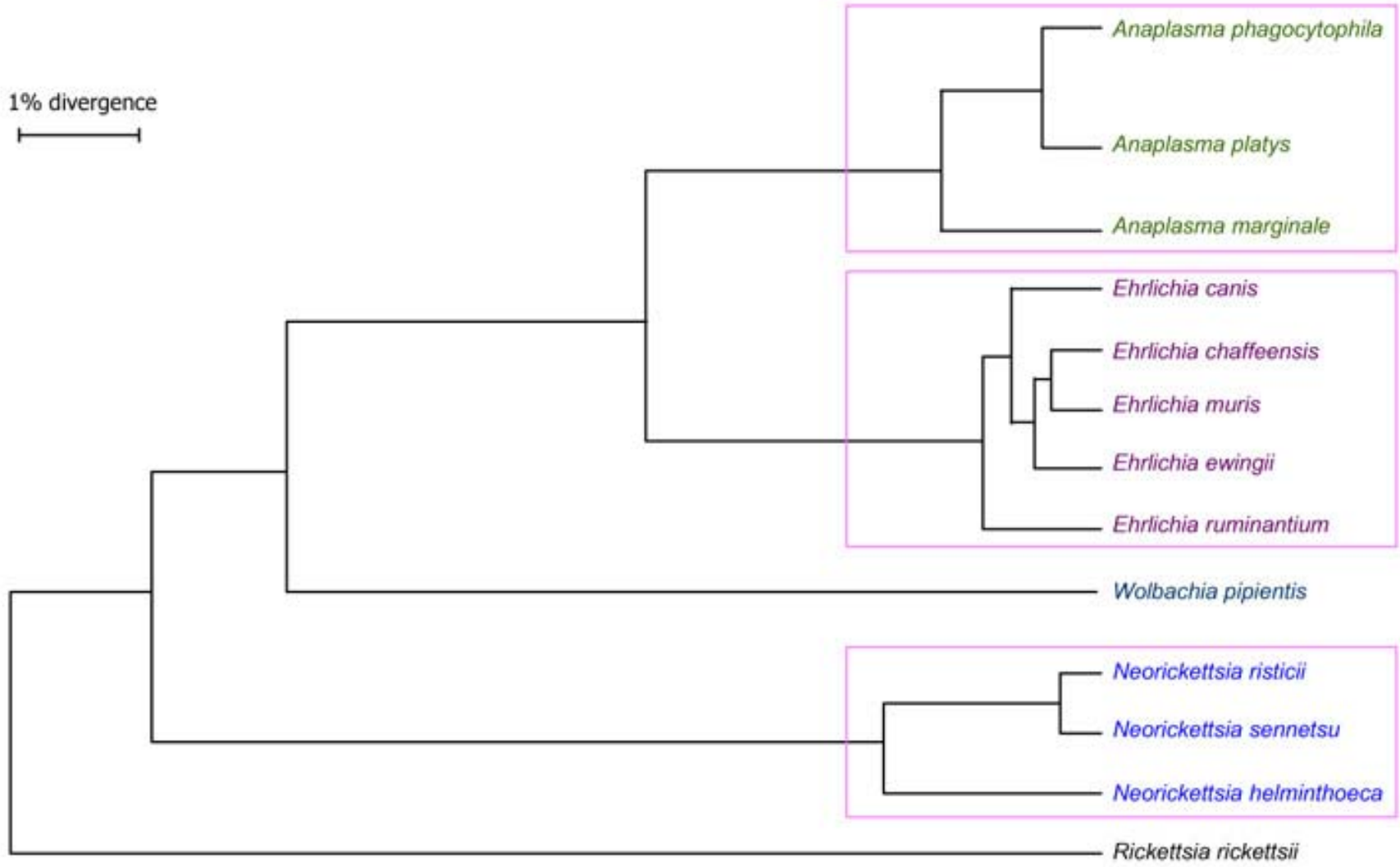
The NEW ENGLAND JOURNAL of MEDICINE

1987 Apr 2;316(14):853-6.

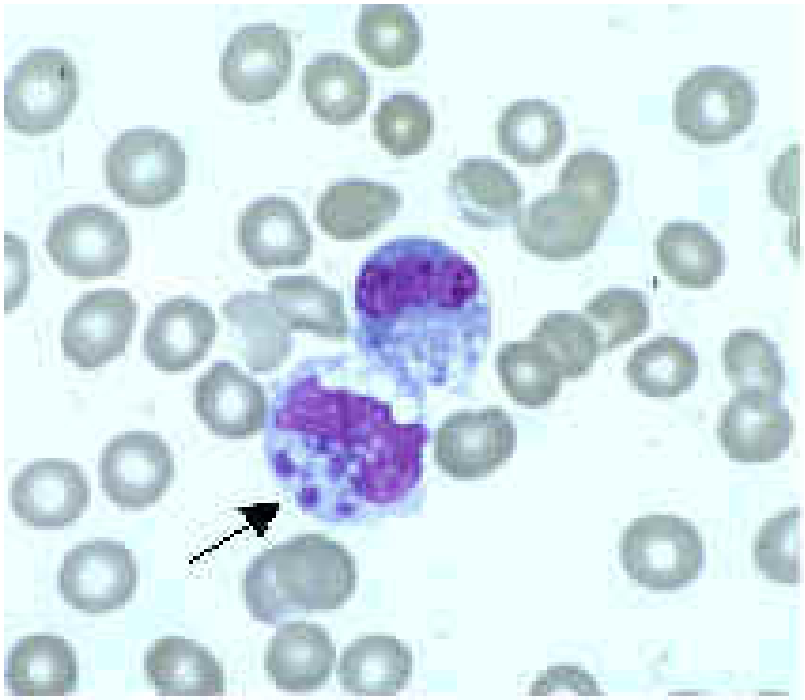
Human infection with *Ehrlichia canis*, a leukocytic rickettsia.

Maeda K, Markowitz N, Hawley RC, Ristic M, Cox D, McDade JE.
Henry Ford Hospital, Detroit, MI.

- First identification of *E. chaffeensis*
- Resembled RMSF, but no rash.

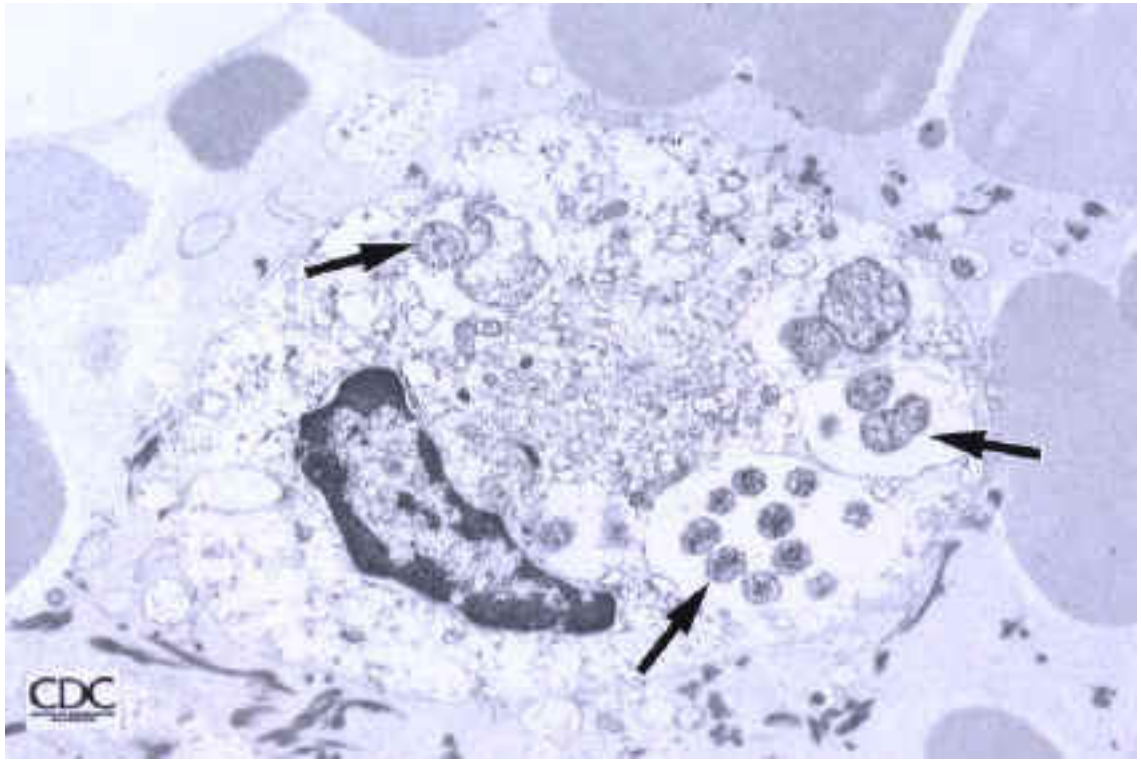


Phylogram tree of the Family *Anaplasmataceae* based on 16S rRNA sequence similarity

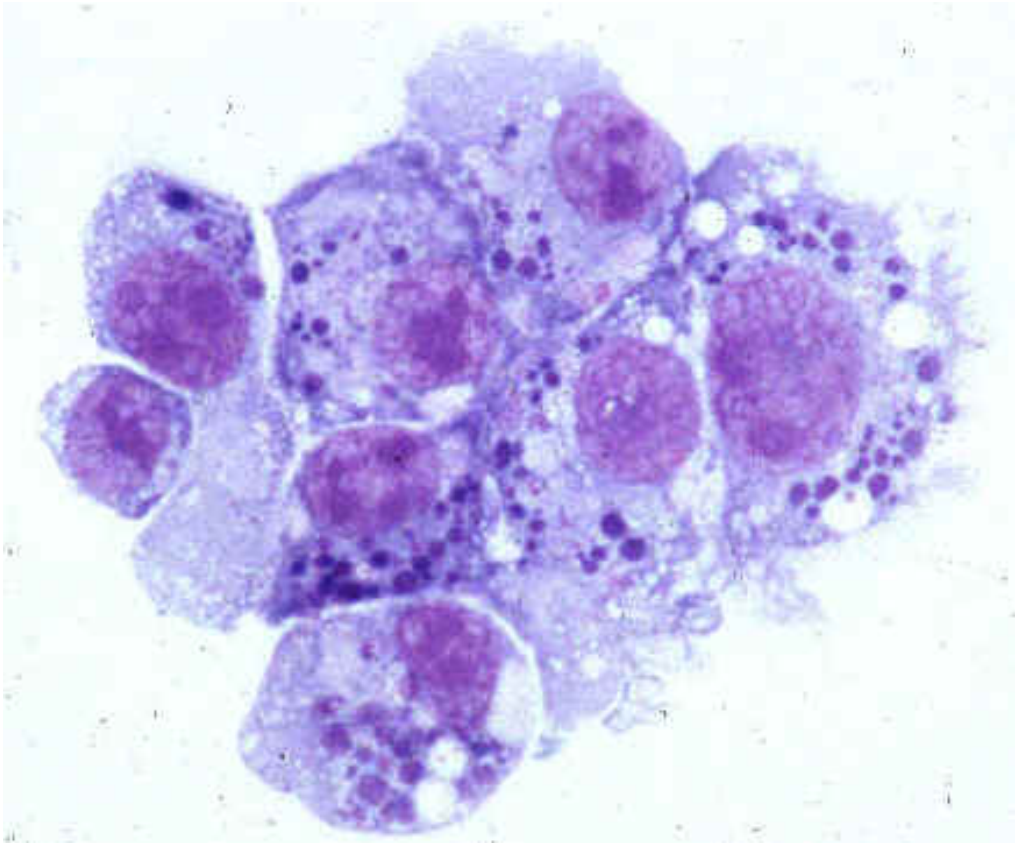


Ehrlichia chaffeensis

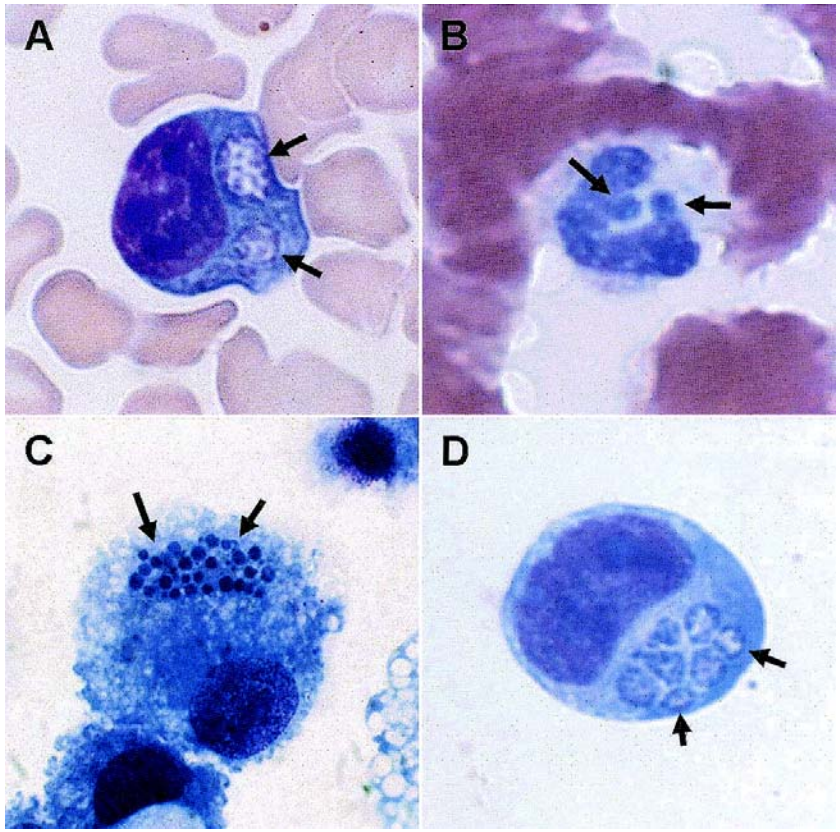
Within monocyte



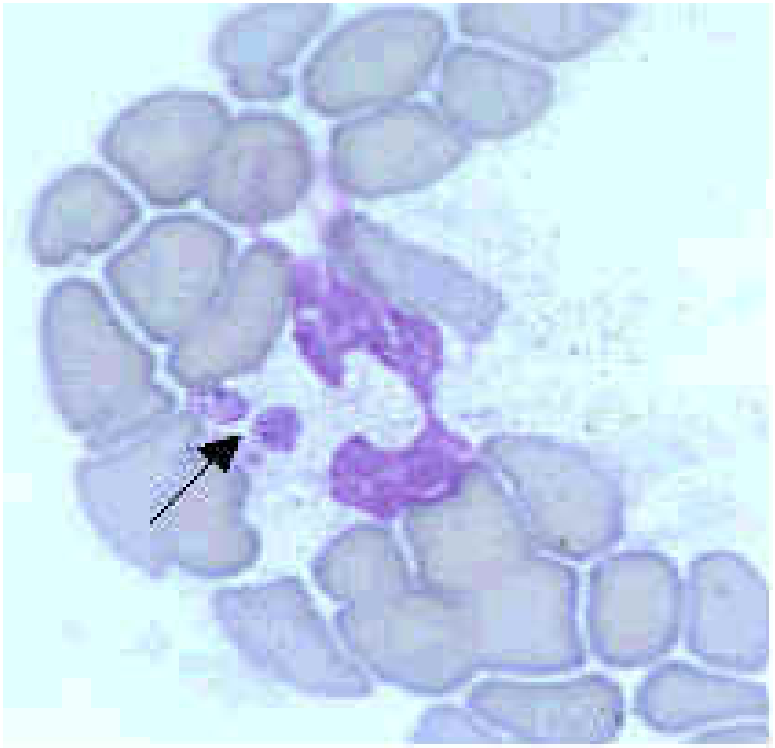
Ehrlichia within bone marrow cells



Diff-Quick Stain for Ehrlichia



Ehrlichia chaffeensis (A and C; Wright stain) and *Anaplasma phagocytophilum* (B and D; Hema 3 stain) morulae (arrows) in peripheral blood monocytes (A), peripheral blood neutrophils (B), DH82 canine histiocytic cell culture (C), and human HL-60 promyelocytic cell culture (D). Original magnification, ×260. (Panel A courtesy of A. Marty.)

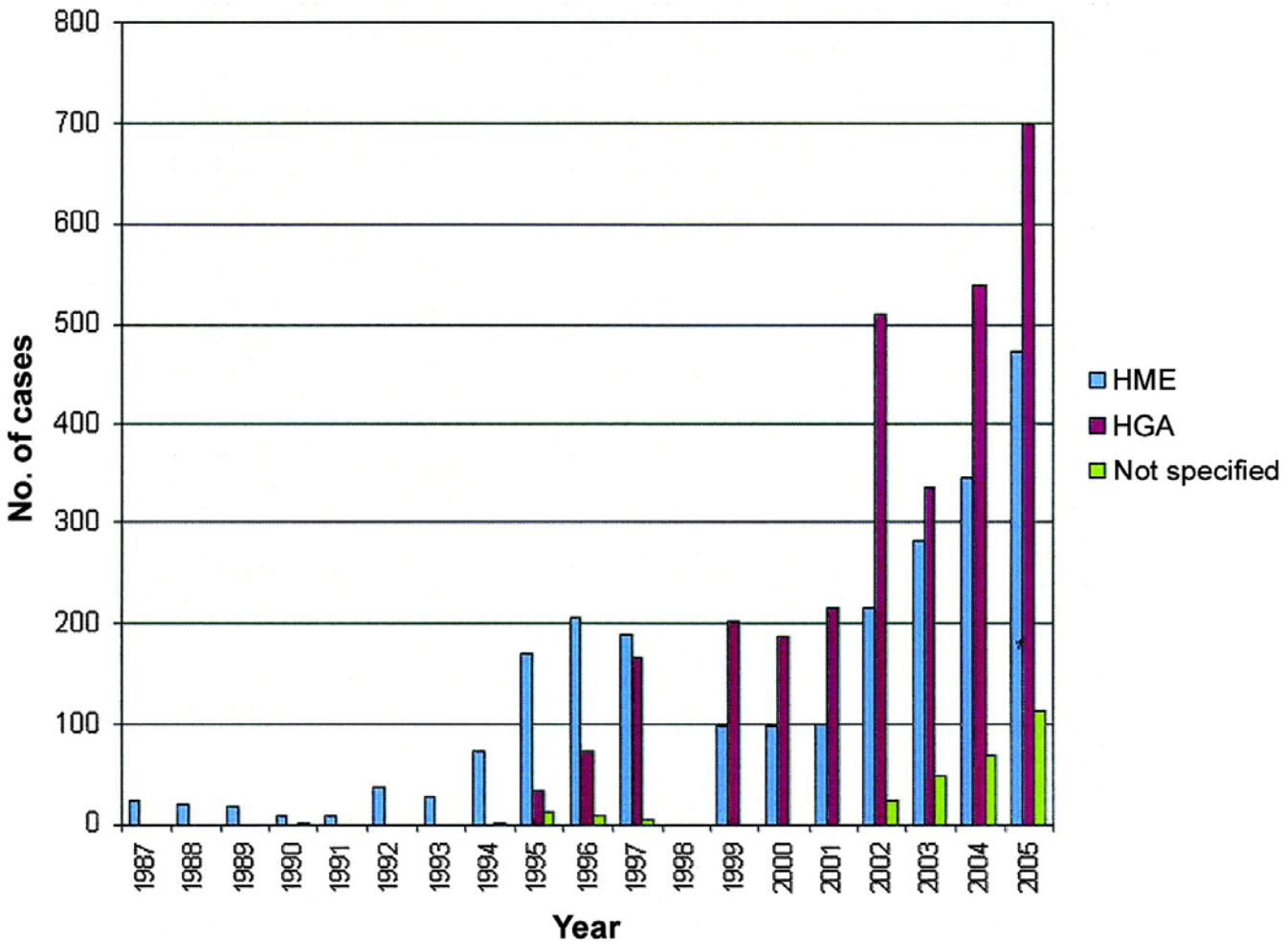


Anaplasma phagocytophilum

Viral and Rickettsial Zoonoses Branch
Human Ehrlichiosis in the United States

Laboratory Detection

Ehrlichial infections pose difficult diagnostic challenges to both clinicians and laboratorians, and the availability of confirmatory assays is limited. Therefore, treatment decisions should be based on epidemiologic and clinical clues, and should never be delayed while waiting for confirmation. Similarly, test results should be interpreted in the context of the patient's illness and the epidemiologic setting. **Problems arise from overuse of specialized tests for patients with a low probability of the disease and in areas with a low prevalence of disease.** Fundamental understanding of the signs, symptoms, and epidemiology of the disease is crucial in guiding requests for tests for ehrlichiosis and interpretation of testing results. Routine clinical laboratory tests indicative of ehrlichiosis include low white blood cell count, low platelet count, and elevated liver enzymes. The organisms can be demonstrated in blood smears by staining with Diff-Quik or Giemsa stains.



Cases of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) reported in the United States since 1986. The data reflect information available until January 2006; data for the year 1998 were unavailable.

Table 1. Meta-analysis of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) symptoms, signs, and laboratory findings.

Symptom, sign, or finding	Patients, % (no. evaluated)	
	HME	HGA
Symptom or sign		
Fever	97 (633)	93 (521)
Myalgia	57 (250)	77 (516)
Headache	80 (240)	76 (385)
Malaise	82 (234)	94 (288)
Nausea	64 (143)	38 (258)
Vomiting	33 (192)	26 (90)
Diarrhea	23 (197)	16 (95)
Cough	26 (155)	19 (260)
Arthralgias	41 (211)	46 (504)
Rash	31 (286)	6 (357)
Stiff neck	3 (240)	21 (24)
Confusion	19 (279)	17 (211)
Laboratory finding		
Leukopenia	62 (276)	49 (336)
Thrombocytopenia	71 (247)	71 (336)
Elevated serum AST or ALT level	83 (276)	71 (177)

NOTE. Data are from [1]. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

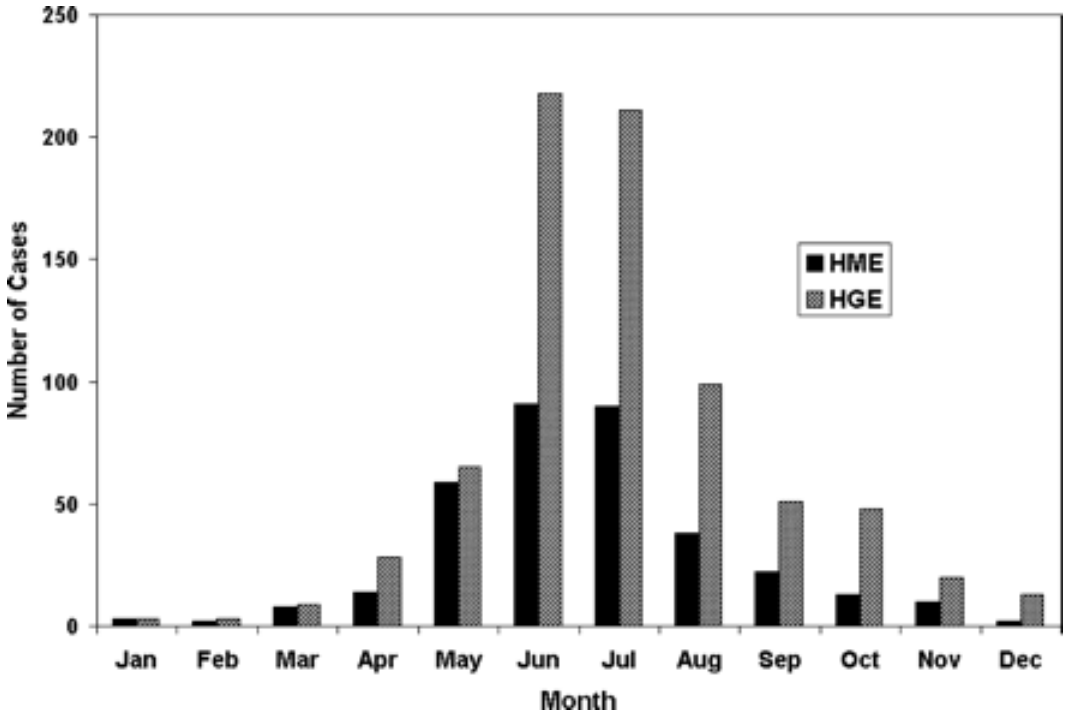

250
200
150
100
50
0
Number of Cases
HME
HGE
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month

Table 3. Diagnostic tests for human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), by time interval after onset of clinical illness.

	Sensitivity, %	
Weeks after onset, diagnostic test	HME	HGA
⩽1		
Blood smear evaluation	2–38	25–75
PCR	60–85	67–90
Culture	Highly variable[a]	⩾55[b]
Serologic testing	22–55 (IgM, ⩽44)	24–44 (IgM, 33)
1–2		
Blood smear evaluation	Unknown	63
PCR	Unknown	68
Culture	Unknown	33
Serologic testing	68	91
⩾3		
Serologic testing	⩾90	⩾95

[a] May require weeks of incubation.
[b] May require weeks of incubation; results are often positive within 2 weeks.

From CLIN INFECT DIS 45(S1):S45-S51.

Table 4. Currently recommended therapeutic regimens for human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA).

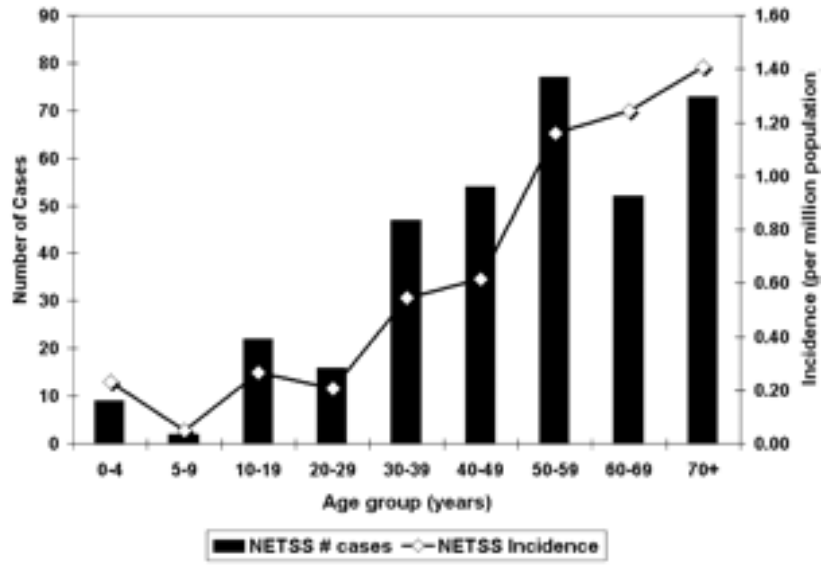
Antibiotic	Dosage		Treatment duration[a]
	Adult	Pediatric	
Doxycycline hyclate	100 mg iv or po every 12 h	2.2 mg/kg po every 12 h	5–14 days
Tetracycline hydrochloride	500 mg po every 6 h	25–50 mg/kg/day po in 4 divided doses	5–14 days
Rifampin[b]	300 mg po every 12 h	10 mg/kg po every 12 h	7–10 days

NOTE. Data are from [8]. Antibiotic treatment is not recommended for seropositive patients who are asymptomatic or who lack the typical manifestations of HME or HGA. iv, intravenously; po, by mouth.

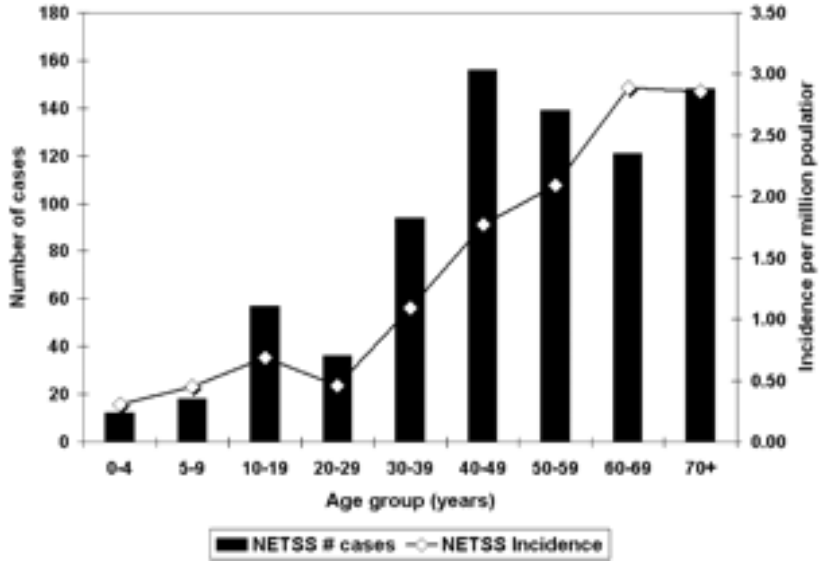
[a] Antibiotic therapy should be continued for 3–5 days after fever subsides.

[b] Rifampin is recommended only for patients with contraindications to doxycycline or tetracycline therapy (e.g., allergy and pregnancy).

A.


Number of Cases
Incidence (per million population
0-4
5-9
10-19
20-29
30-39
40-49
50-59
60-69
70+
Age group (years)
NETSS # cases
NETSS Incidence

B.

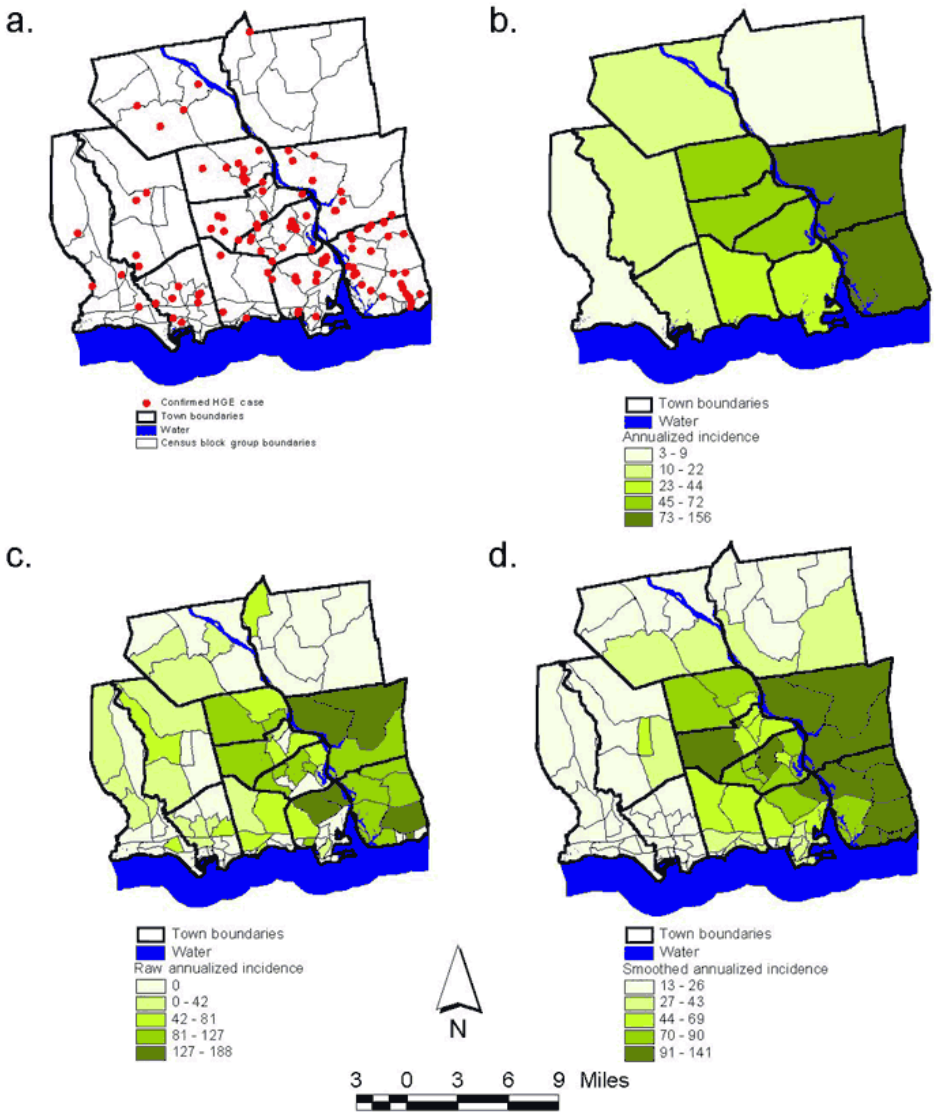

Number of cases
Incidence per million poulation
0-4
5-9
10-19
20-29
30-39
40-49
50-59
60-69
70+
Age group (years)
NETSS # cases
NETSS Incidence

Human Anaplasmosis:

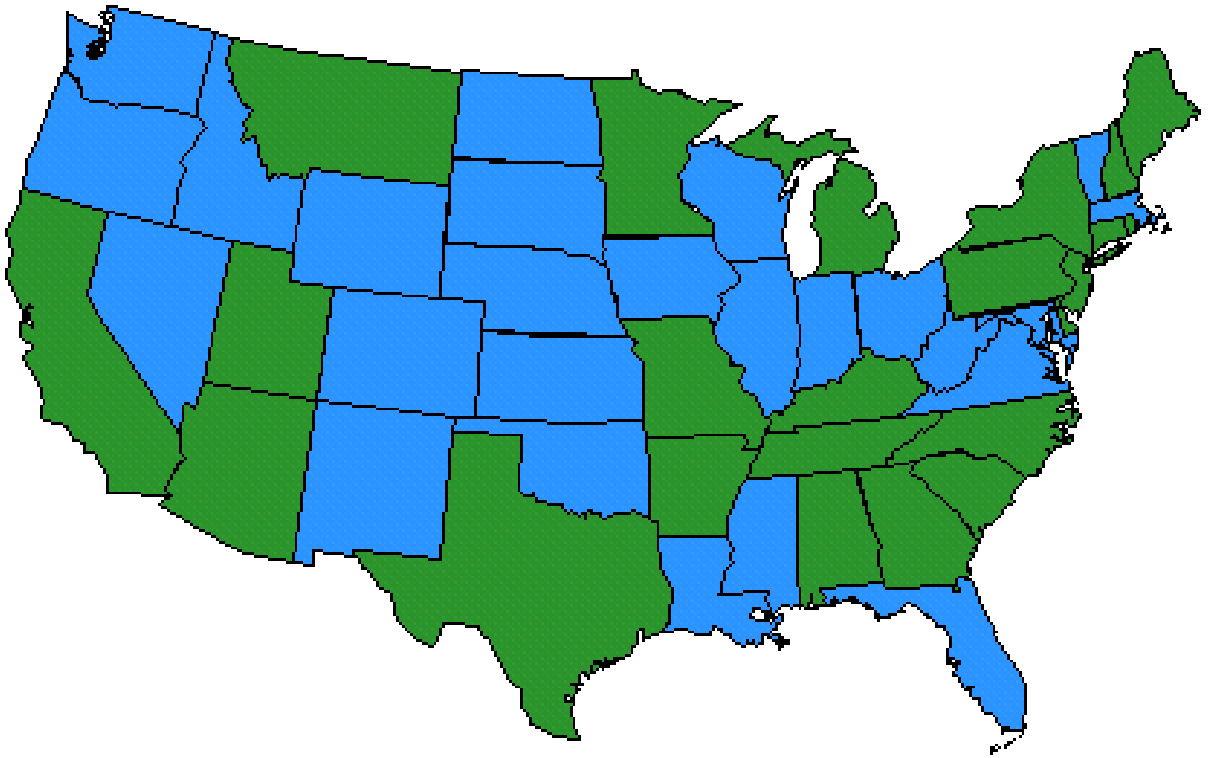
Spatial Analysis,

Lyme, Connecticut

→ Cases are not distributed randomly!



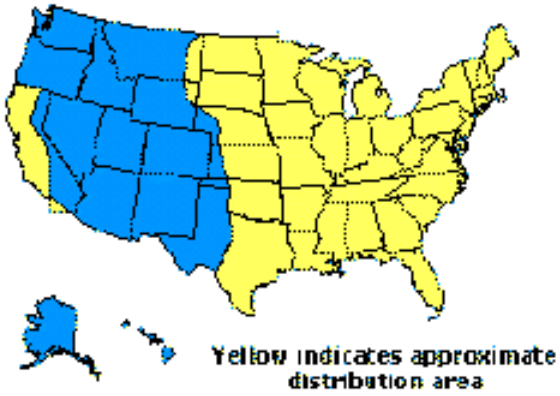
CDC:EID Volume 8, Number 9, September 2002



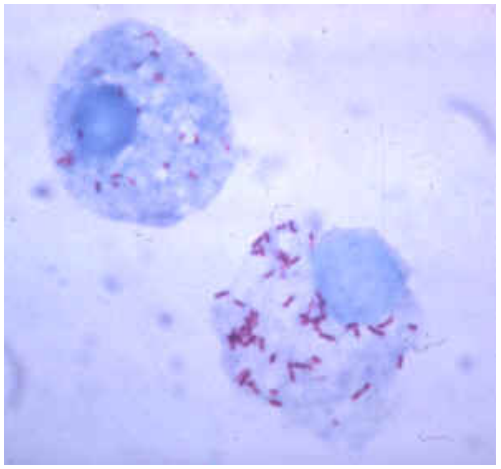
US States where Ehrlichiosis is a notifiable disease

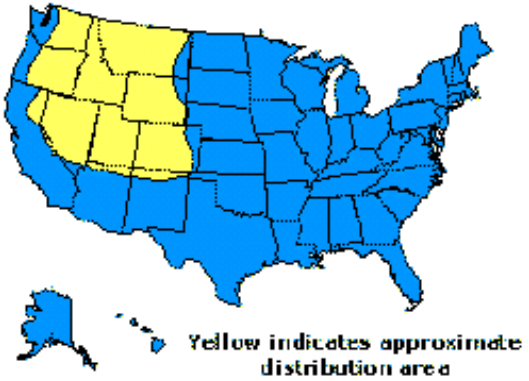
Rocky Mountain Spotted Fever

RMSF – *Rickettsia rickettsii*



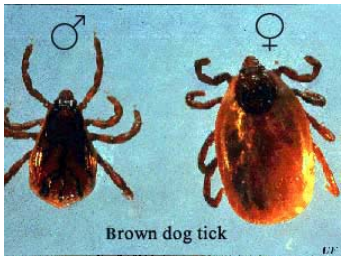
American dog tick
(*Dermacentor variabilis*)

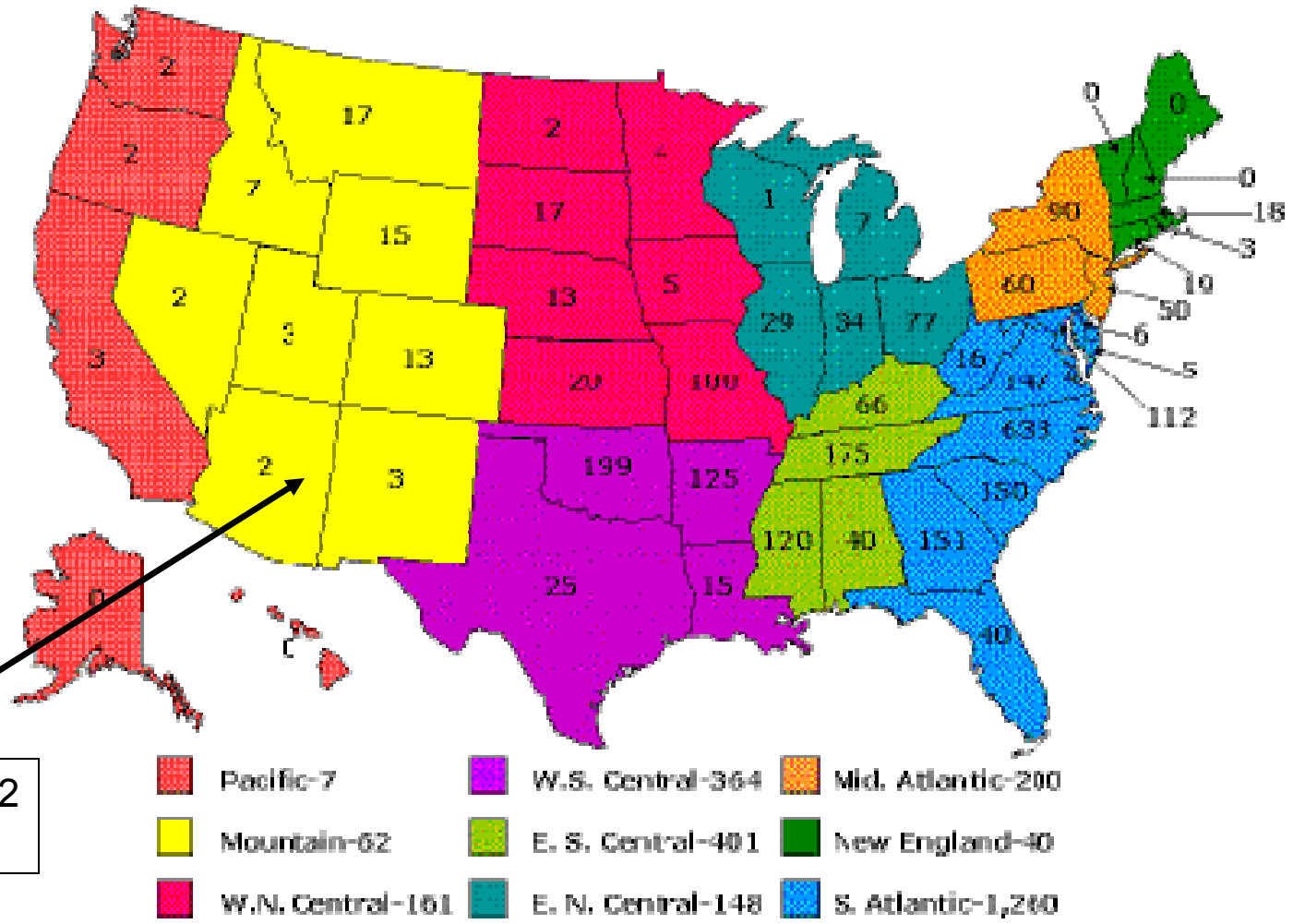




Rocky Mountain wood tick
(*Dermacentor andersoni*)

Number of reported cases of Rocky Mountain spotted fever by state and region, 1994-1998





2002: 16 patients, 2 deaths. Endemic.

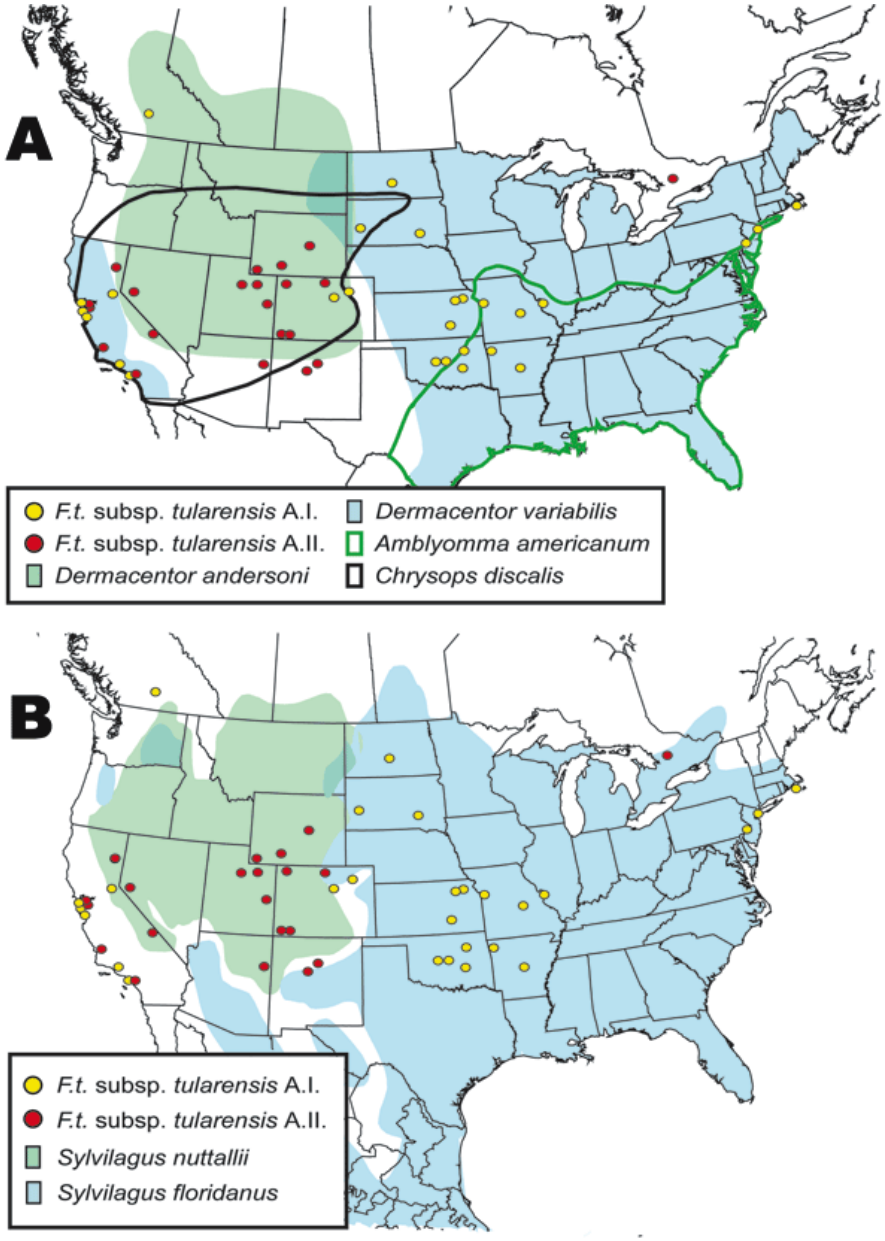


Figure 7. Spatial distributions of isolates from the A.I. and A.II. subpopulations of *Francisella tularensis* subsp. *tularensis* relative to A) distribution of tularemia vectors *Dermacentor variabilis*, *D. andersoni*, *Amblyomma americanum*, and *Chrysops discalis*; and B) distribution of tularemia hosts *Sylvilagus nuttallii* and *S. floridanus*.

EMERGING INFECTIOUS DISEASES

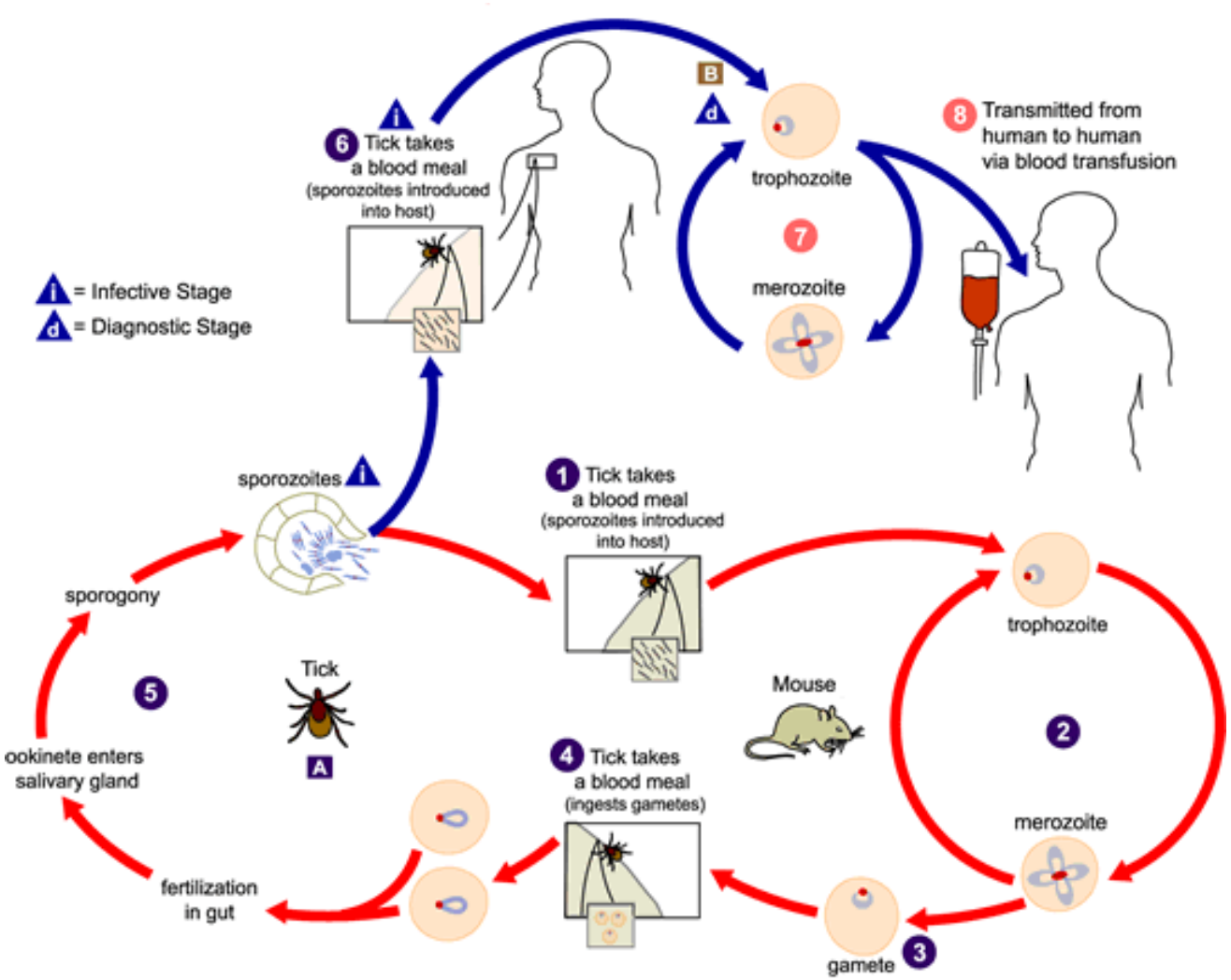
January 15, 2003

Dispatch

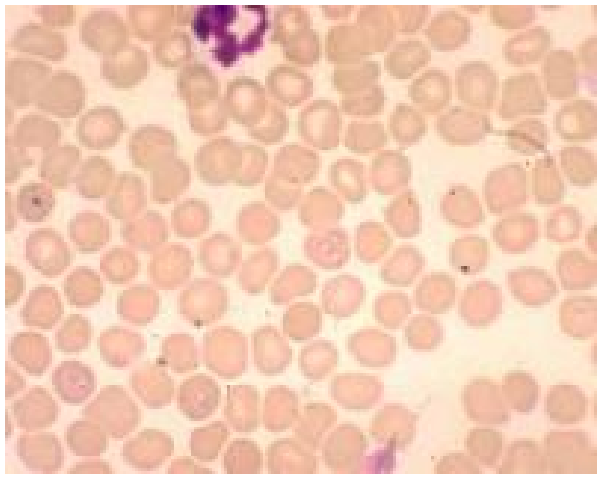
Transfusion-Associated Babesiosis after Heart Transplant

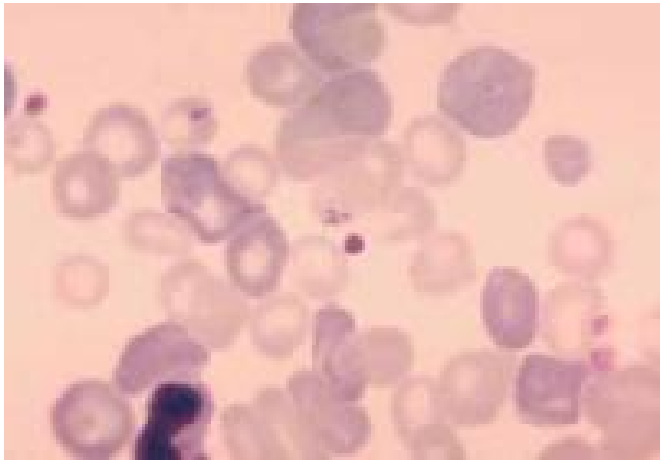
Joseph Z. Lux,* Don Weiss,† Jeanne V. Linden,‡ Debra Kessler,§ Barbara L. Herwaldt,¶ Susan J. Wong,‡ Jan Keithly,‡ Phyllis Della-Latta,# and Brian E. Scully*

We describe a 54-year-old spleen-intact man with transfusion-associated *Babesia microti* infection after a heart transplant. Adult respiratory distress syndrome developed in the patient, and he required mechanical ventilation. Our experiences with this patient suggest that babesiosis should be considered in the differential diagnosis of transplant patients who have fever and hemolytic anemia.



Babesia Life Cycle





Babesia microti in human blood smears

Tick Exposure Prevention

DEET!

Frequent Checks!

Remove Promptly!

KM Corapi et al. Strategies for primary and secondary prevention of Lyme Dz.
Nat Clin Pract Rheumatol 2007;3(1):20-5.

"Numerous prevention strategies are available, and although they vary in cost, acceptability and effectiveness, uptake has been universally poor. Research in areas where Lyme disease is endemic has demonstrated that **despite adequate knowledge about its symptoms & transmission, many people do not perform behaviors to reduce their risk of infection**."

Therapeutic Options

Lyme Disease:	Doxycycline (100 mg twice daily)
	Amoxicillin (500 mg 3-4 times daily)
	If neuro involvement, ceftriaxone IV
Ehrlichiosis:	Doxycycline (but maybe more monitoring)
	Rifampin for young kids?
RMSF:	Doxycycline
Babesiosis:	Clindamycin (600 mg qid) & Quinine (650 mg tid)
	Better - Azithromycin and Atovaquone