OHAP Policy Challenge Lecture – Lyme disease vaccines

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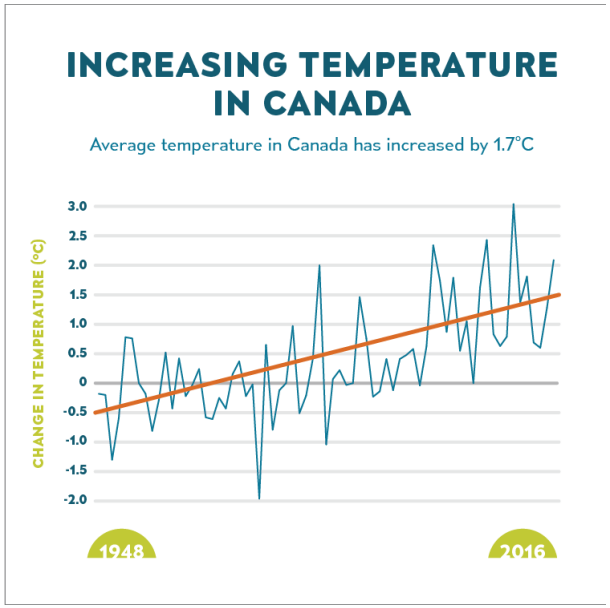
My Background

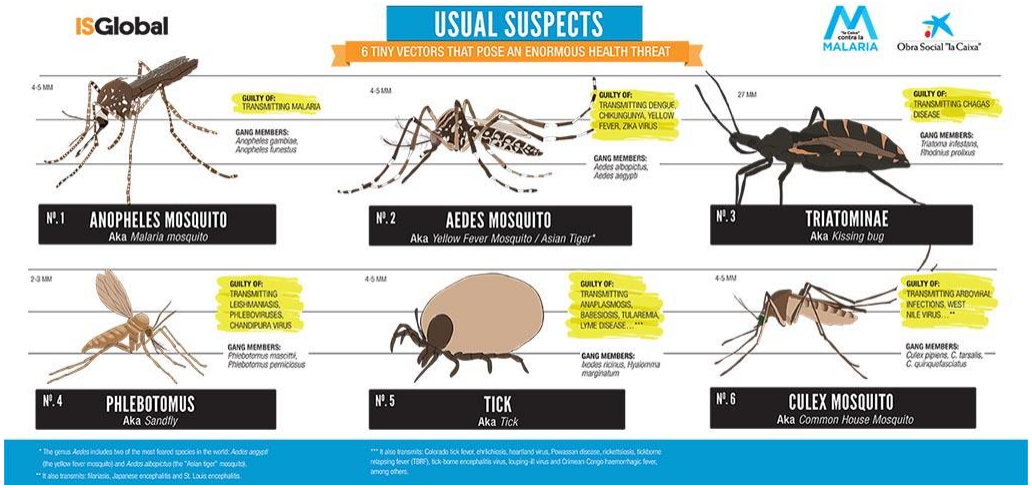
- Ecologist and evolutionary biologist
- BSc and PhD in Biology at the University of Victoria
- Postdoc in England and USA on vector-borne diseases
- Assistant professor in Institute of Biology at the University of Neuchatel, Switzerland (2011-2018)
- Associate professor in Vet Micro at WCVM (2018 to present)
- Research on Lyme borreliosis, a tick-borne zoonotic disease

Climate change and vector-borne diseases



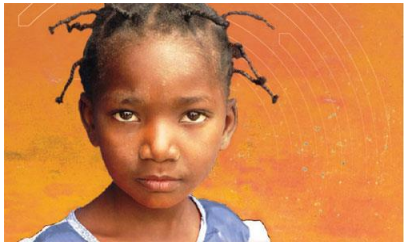
- Greenhouse gasses has led to climate change and global warming
- From 1948 to 2016, mean temperature in Canada increased by 1.7 degrees Celsius
- Vector-borne pathogens are transmitted by arthropod vectors
- Arthropods are sensitive to climate variables like temperature and humidity
- Medically important arthropods will shift their range in a warmer world

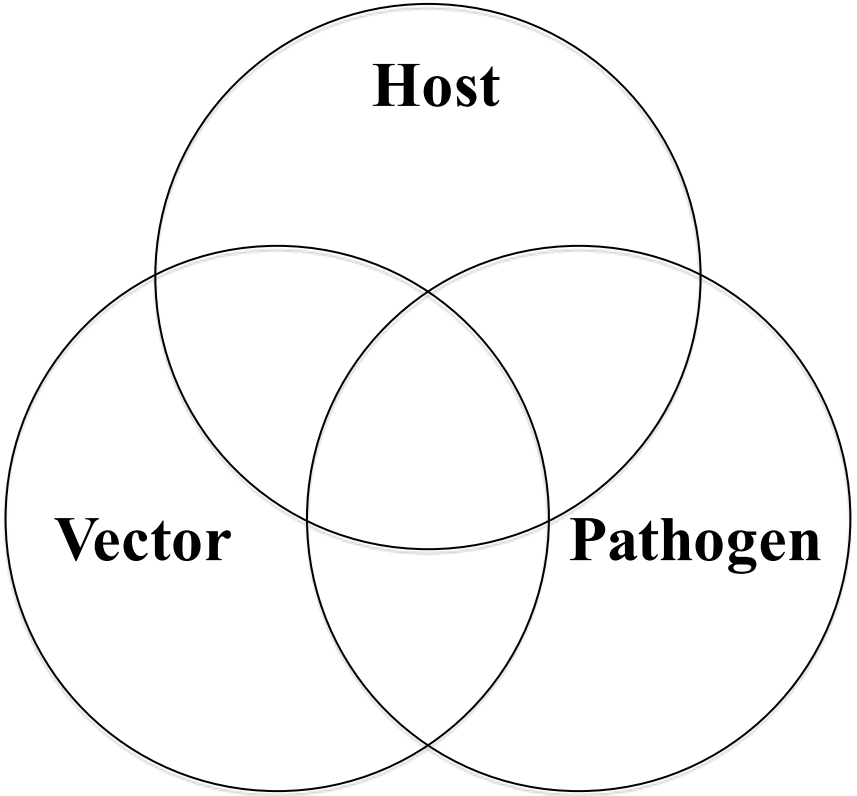
Vector-borne diseases and arthropod vectors

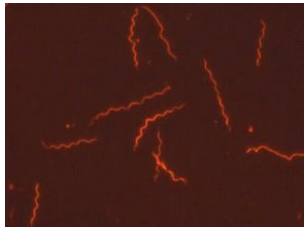


- Vector-borne diseases caused by **vector-borne pathogens** that are transmitted among vertebrate hosts by **hematophagous** (blood-feeding) arthropod vectors
- Important arthropod vectors include mosquitoes, ticks, sandflies, and assassin bugs
- Arthropod vectors transmit the vector-borne pathogens during the blood meal
- Vector-borne pathogens include viruses, bacteria, protozoan parasites, and nematode worms

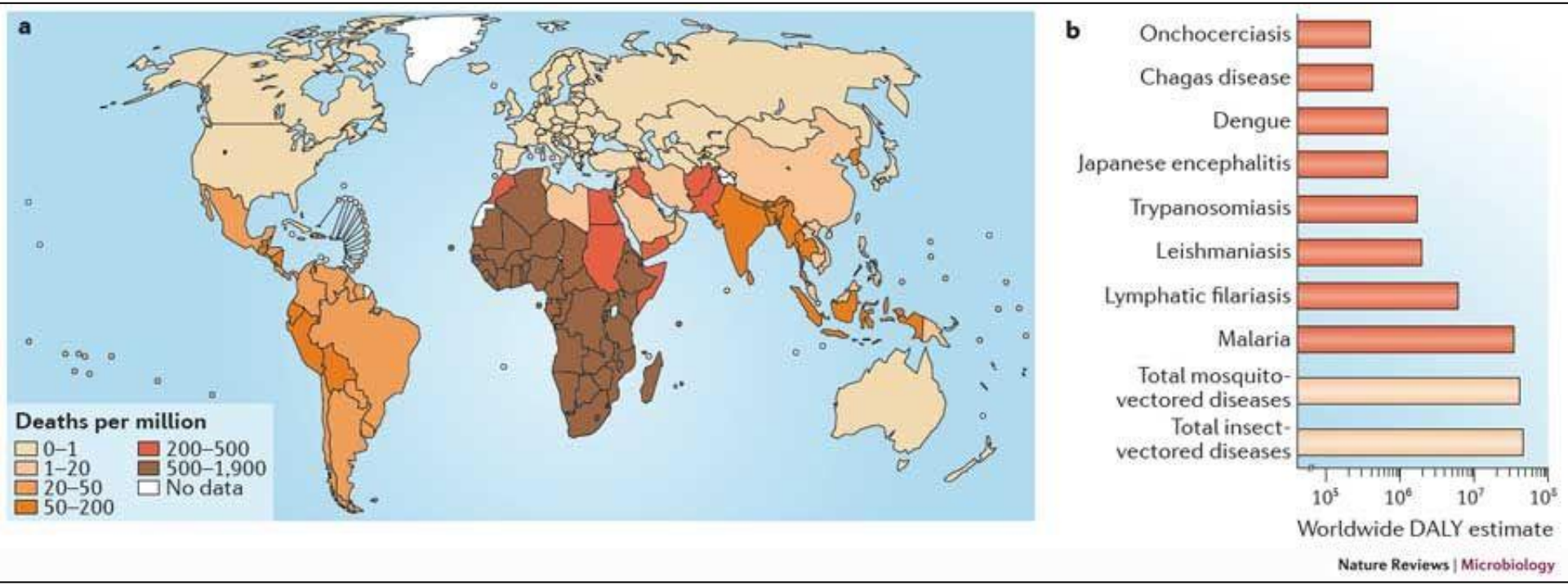
Vector-borne diseases and the host-vector-pathogen triad





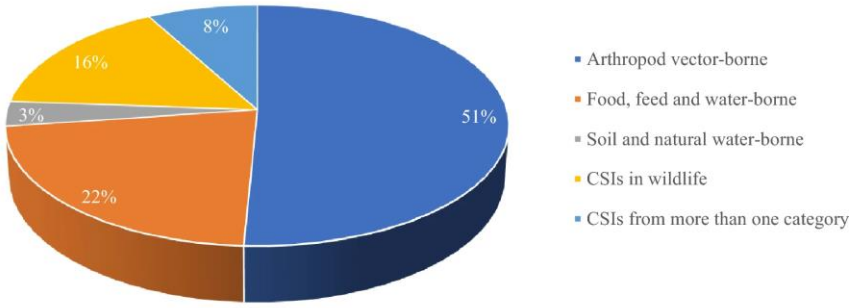


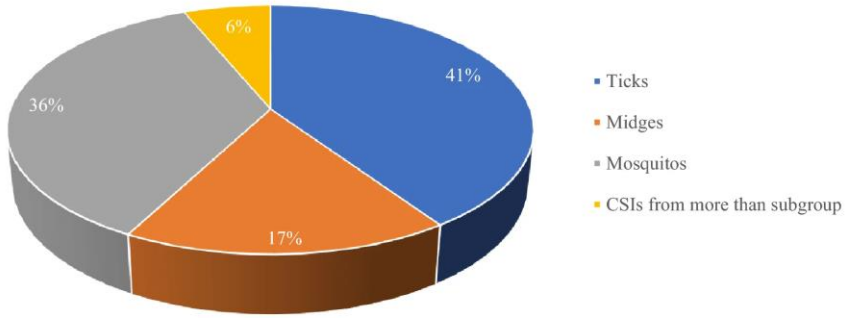
Vector-borne diseases are a global problem



- Vector-borne diseases account for 1/6 of the world's infection-associated DALY
- Malaria: 216 million cases per year
- Dengue: 50-100 million cases per year

Infectious diseases expected to invade the Eurasian Artic





- Arctic is warming
- Disease range expansion
- Meta-analysis: 37 CSIs
- Categories: vector, food, soil, contact, wildlife
- 51% in vector category
- 4 CSIs of concern: LB, TBE, BT, and fasciolosis

Omazic et al. 2019. Acta Veterinaria Scandinavica 61:53

What is Lyme disease and what causes it?

Lyme borreliosis symptoms in humans

Erythema migrans

Facial paralysis

Arthritis and joint pain

Borrelia burgdorferi causes Lyme disease

- Borrelia burgdorferi is a spirochete (cork screw shape)
- LD discovered in 1977 in Lyme, CT by Allen Steere
- Bb discovered in 1982 by Willy Burgdorfer in USA
- Bb belongs to Spirochaetes
- Spirochaetes cause Lyme borreliosis, leptospirosis, relapsing fever, and syphilis

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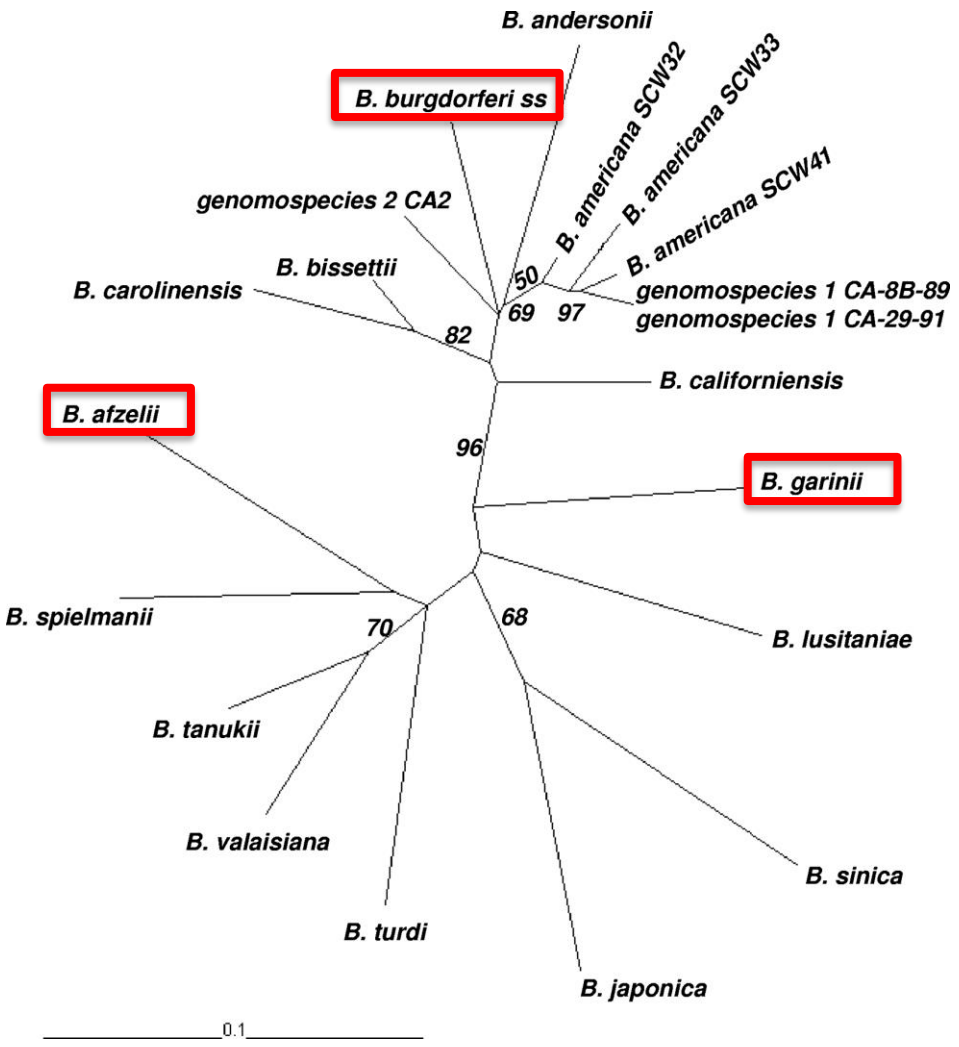
Diversity of *Borrelia burgdorferi* sensu lato

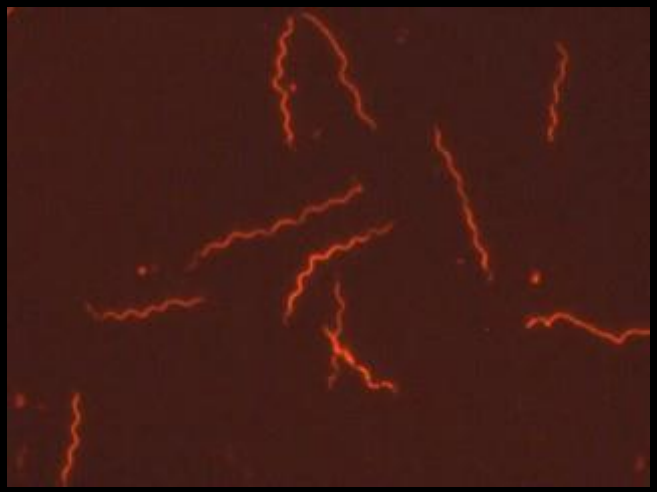


Rudenko N et al. J. Clin. Microbiol. 2009;47:3875-3880

Endemic Lyme disease system

Ixodes scapularis

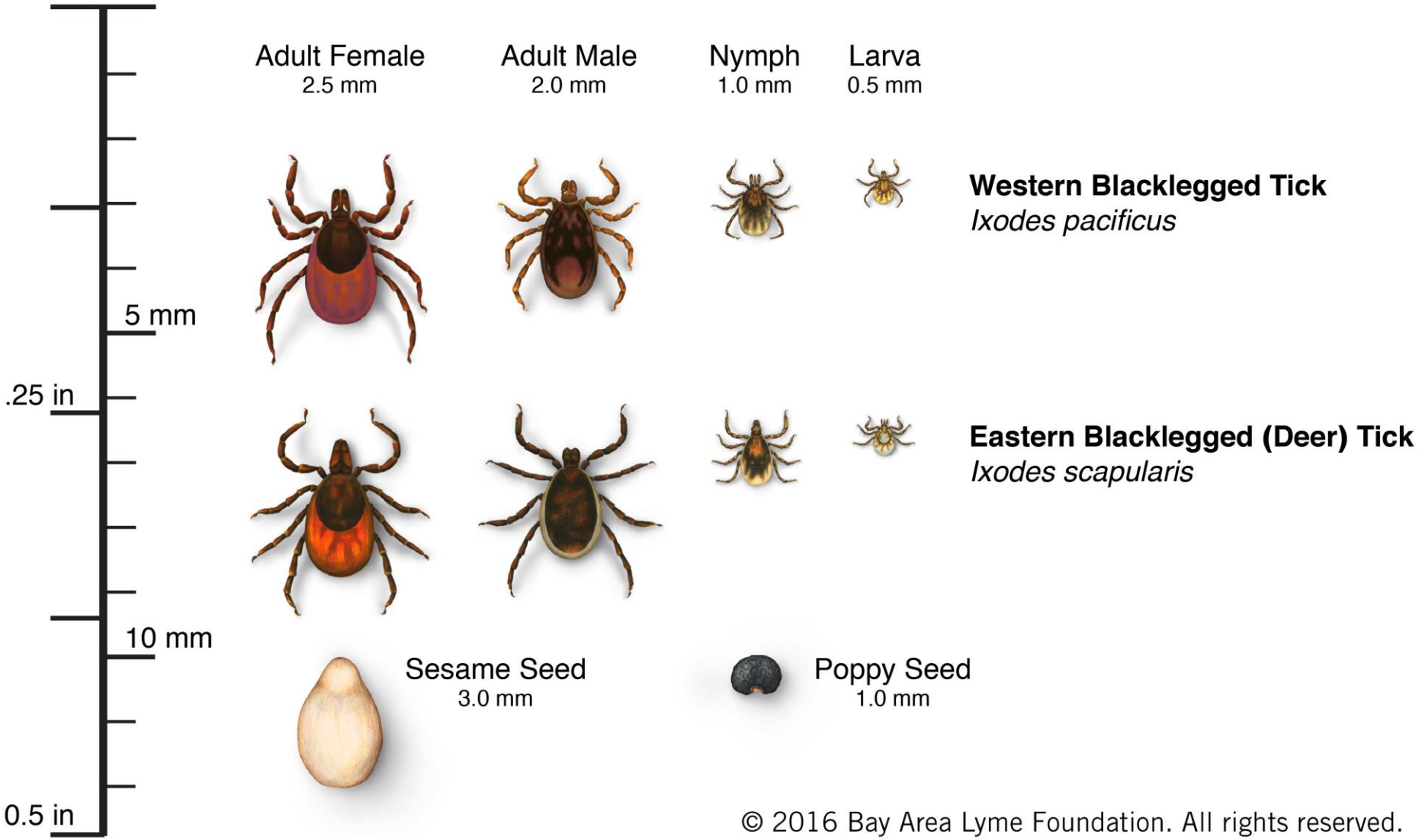
Peromyscus leucopus



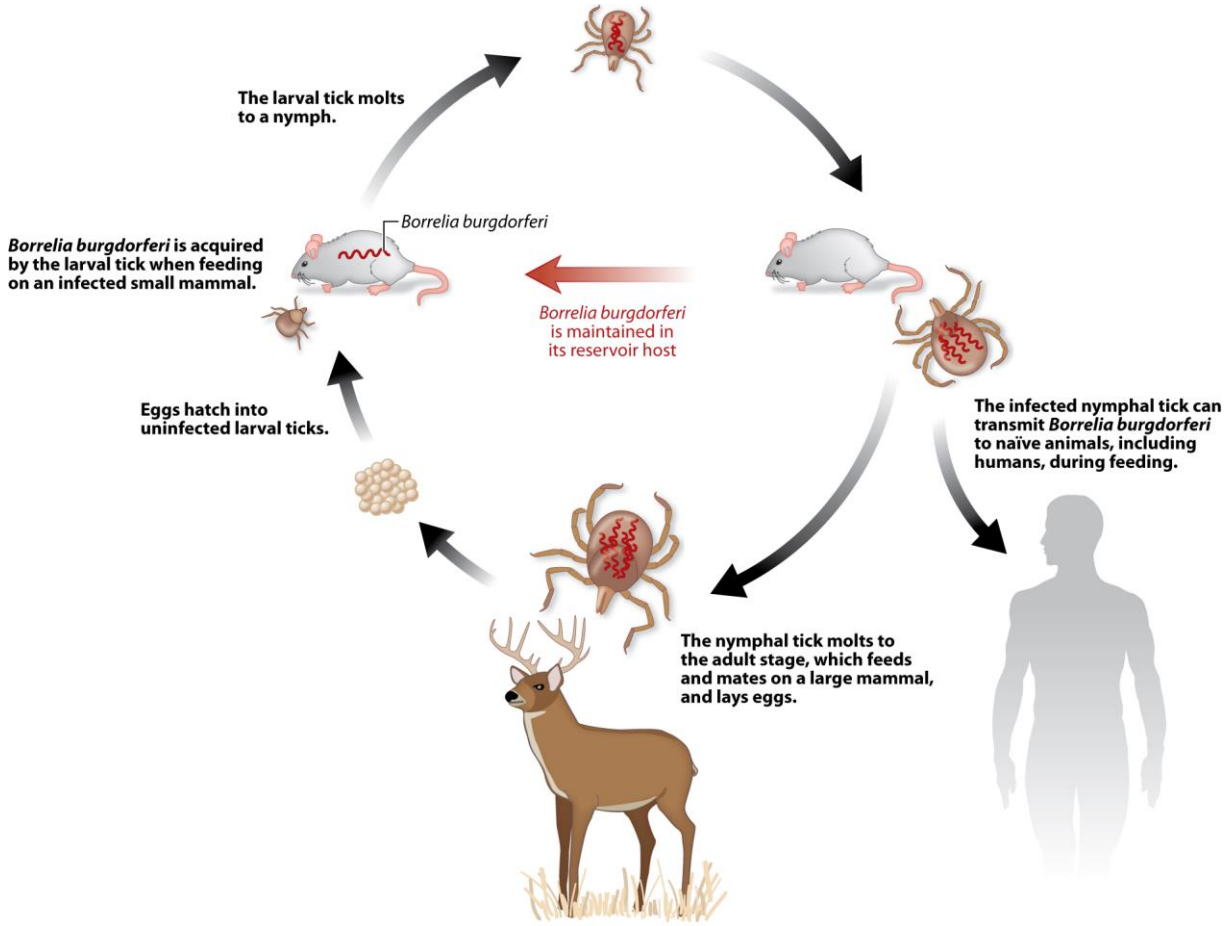
Borrelia burgdorferi sensu lato

Turdus migratorius

Vectors of Lyme disease



The life cycle of Lyme disease

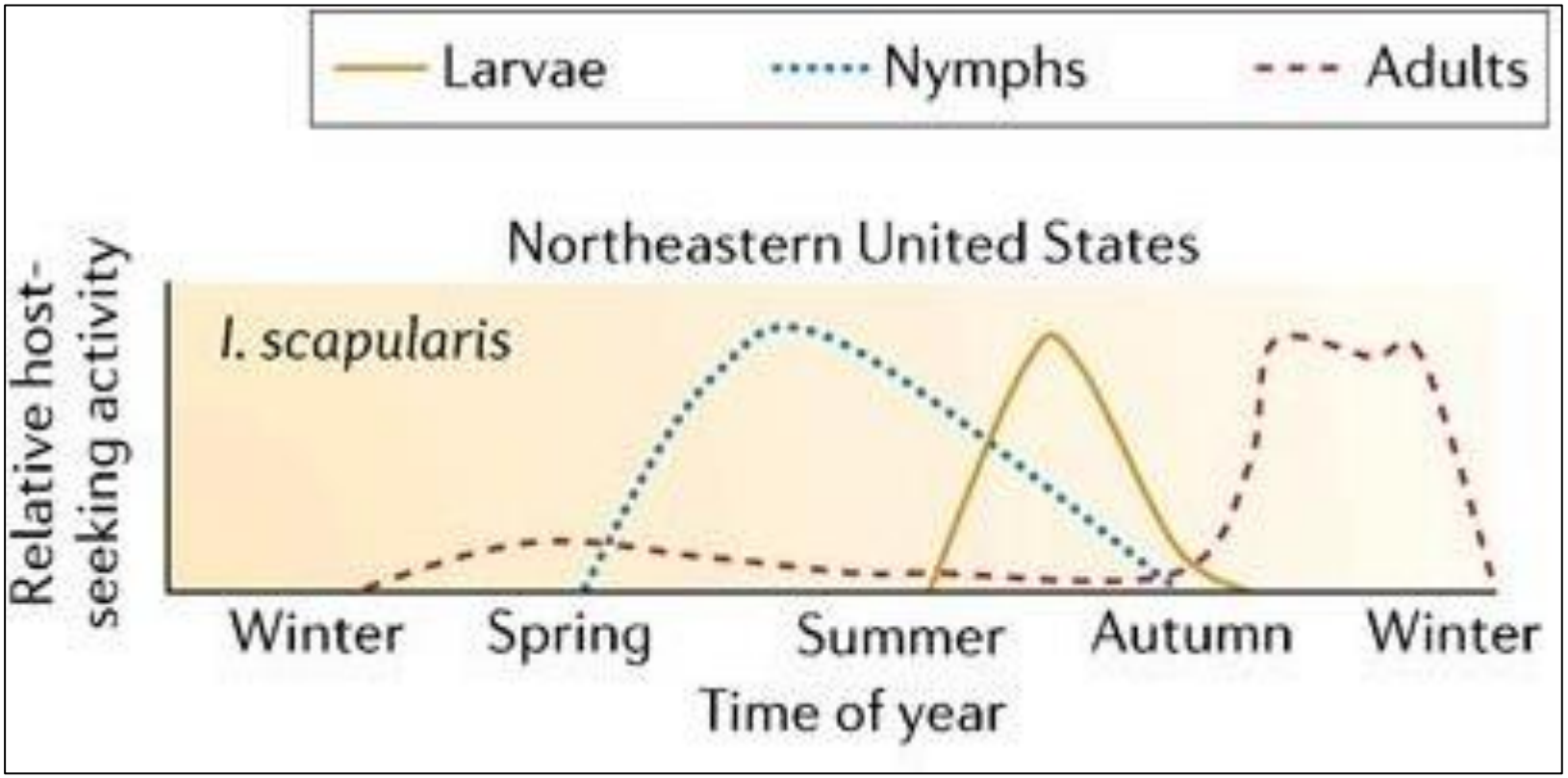


Brisson D, et al. 2012.
Annu. Rev. Genet. 46:515–36

Will vaccination of humans influence the Lyme disease risk?

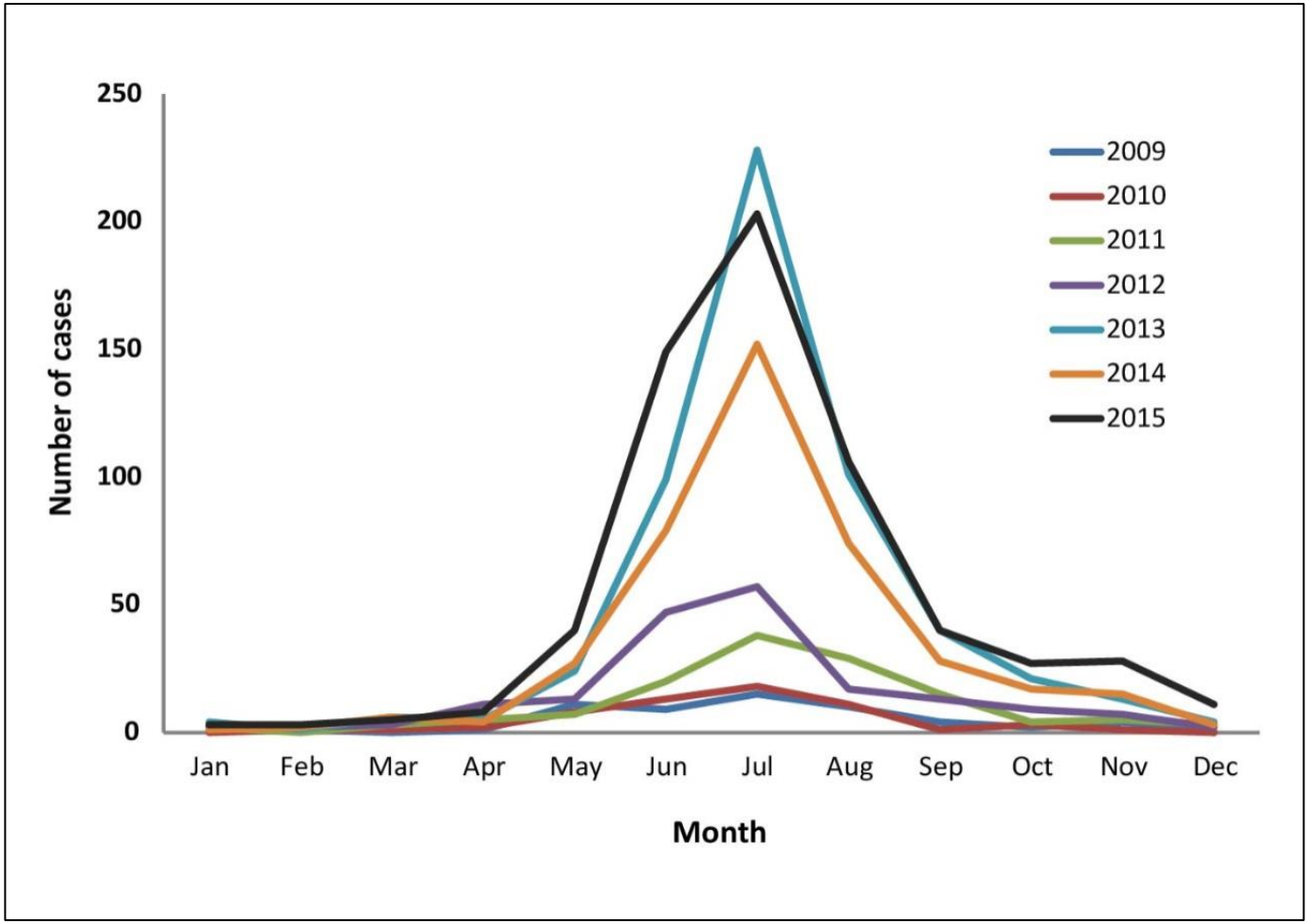
How is vaccination against Lyme disease fundamentally different compared to vaccination against COVID-19?

Seasonal activity of *I. scapularis* in USA



Kurtenbach et al. Nat Rev Microbiol. 4:660-669.

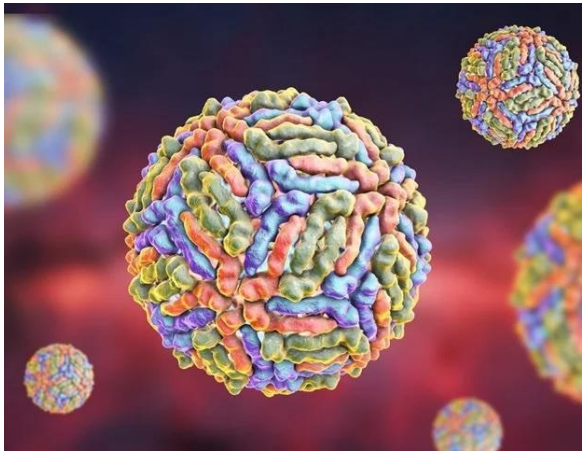
Month of Lyme disease illness onset for locally-acquired infection: Canada, 2009–2015 (n = 2,010)



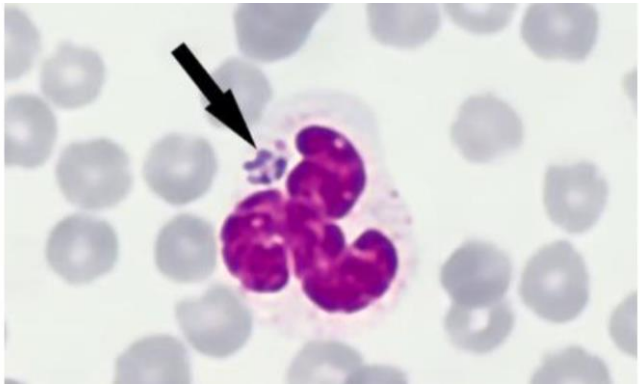
Gasmi et al. 2017. CCDR. 43(10):194-199.

Ixodes scapularis transmits other tick-borne pathogens

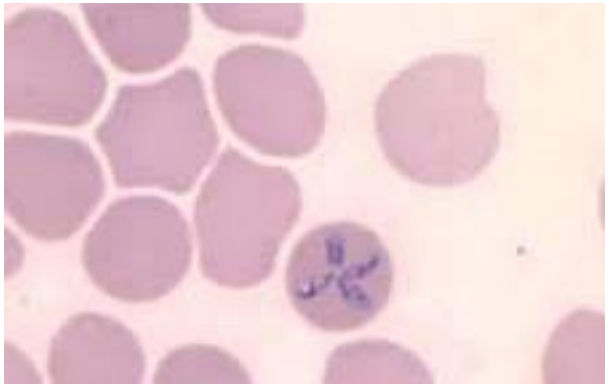
Ixodes scapularis



Powassan virus



Anaplasma phagocytophilum



Babesia microti

Diagnosis of Lyme disease

- Erythema migrans lesion is highly diagnostic
- *B. burgdorferi* has low abundance in human tissues
- PCR or culture of human tissues has low sensitivity
- Diagnostic tests are based on serology
- Two-tiered testing: ELISA + Western Blot

Limitations of antibody-based methods

- Antibodies take time to develop (2 to 4 weeks)
- Serological tests unreliable for early LD (4 weeks)
- Endemic areas: people can get Lyme disease repeatedly
- Antibodies indicate exposure: no distinction between past and present infection
- Need diagnostic tests that show active infection

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Post-treatment Lyme disease syndrome

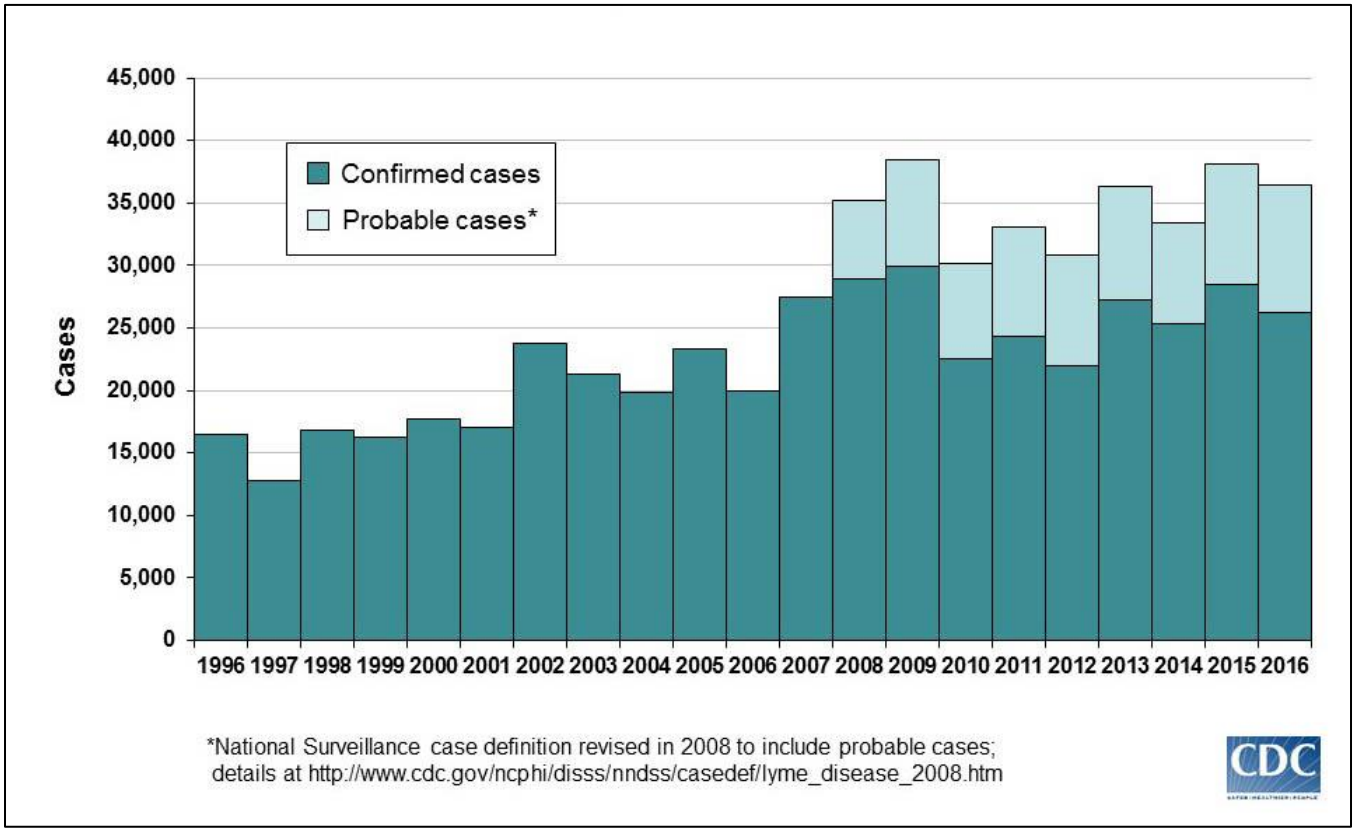
- Lyme disease treatment: antibiotics for 3 – 4 weeks
- Most patients make complete recovery
- Post-treatment Lyme disease syndrome (PTLDS): some patients (10-20%) have symptoms that last months to years after antibiotic treatment
- Symptoms include arthritis, cognitive defects, fatigue
- Cause of symptoms is not known. Researchers believe that bacterium can induce a dysregulated immune system
- Some patient groups believe that patients with PTLDS are still infected and need more antibiotics

Summary 1

- Lyme disease is a tick-borne disease
- Spirochete *B. burgdorferi* causes Lyme disease
- Blacklegged tick transmits many other tick-borne pathogens
- Diagnosis depends on clinical symptoms and serology
- Antibiotic treatment is generally effective
- Some individuals suffer from PTLDS
- Vaccination of humans will have no impact on the epidemiology of *B. burgdorferi*
- No herd immunity! Vaccination protects individual but does not decrease risk for unvaccinated individuals

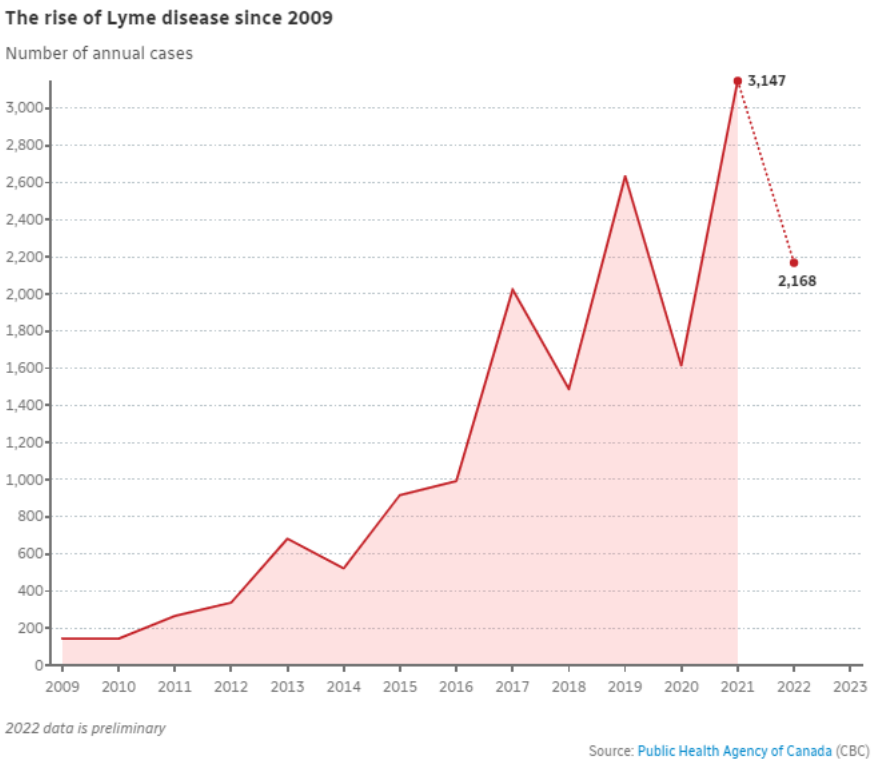
Incidence of Lyme disease is increasing in both Canada and the United States

Lyme disease is increasing in the USA



- Reported LD cases: 15,000 in 1996 and 35,000 in 2016
- LD is greatly underreported by doctors in USA
- Studies of insurance claims suggest 476,000 cases per year

Lyme disease is increasing in Canada

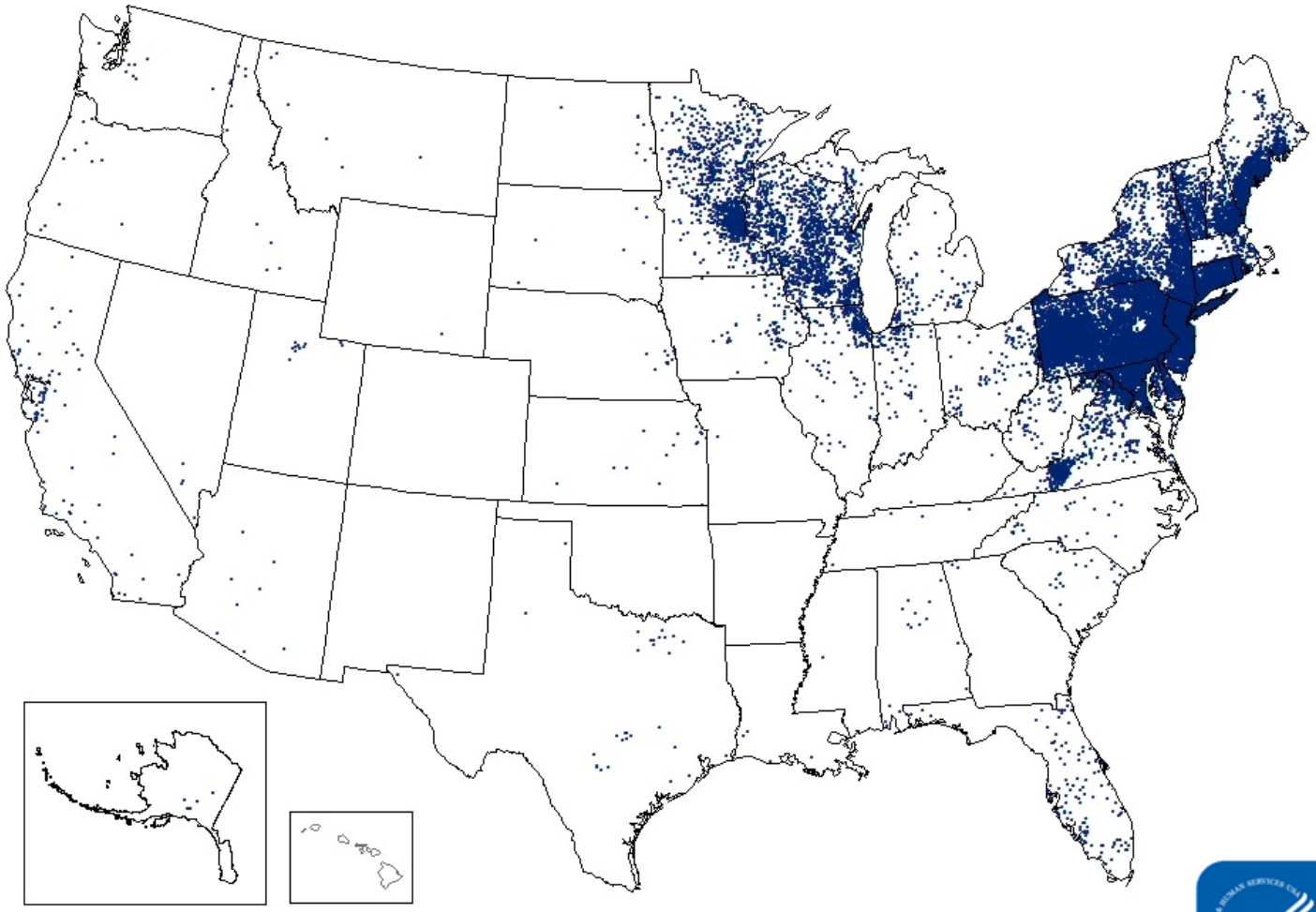


- In 2009, Canada had less than 200 cases of Lyme disease
- In 2021, Canada had > 3000 cases of Lyme disease
- Annual case-load has increased 15-fold over a 12-year period

Geographic distribution of Lyme disease in the USA and Canada

Reported Cases of Lyme Disease–United States, 2016

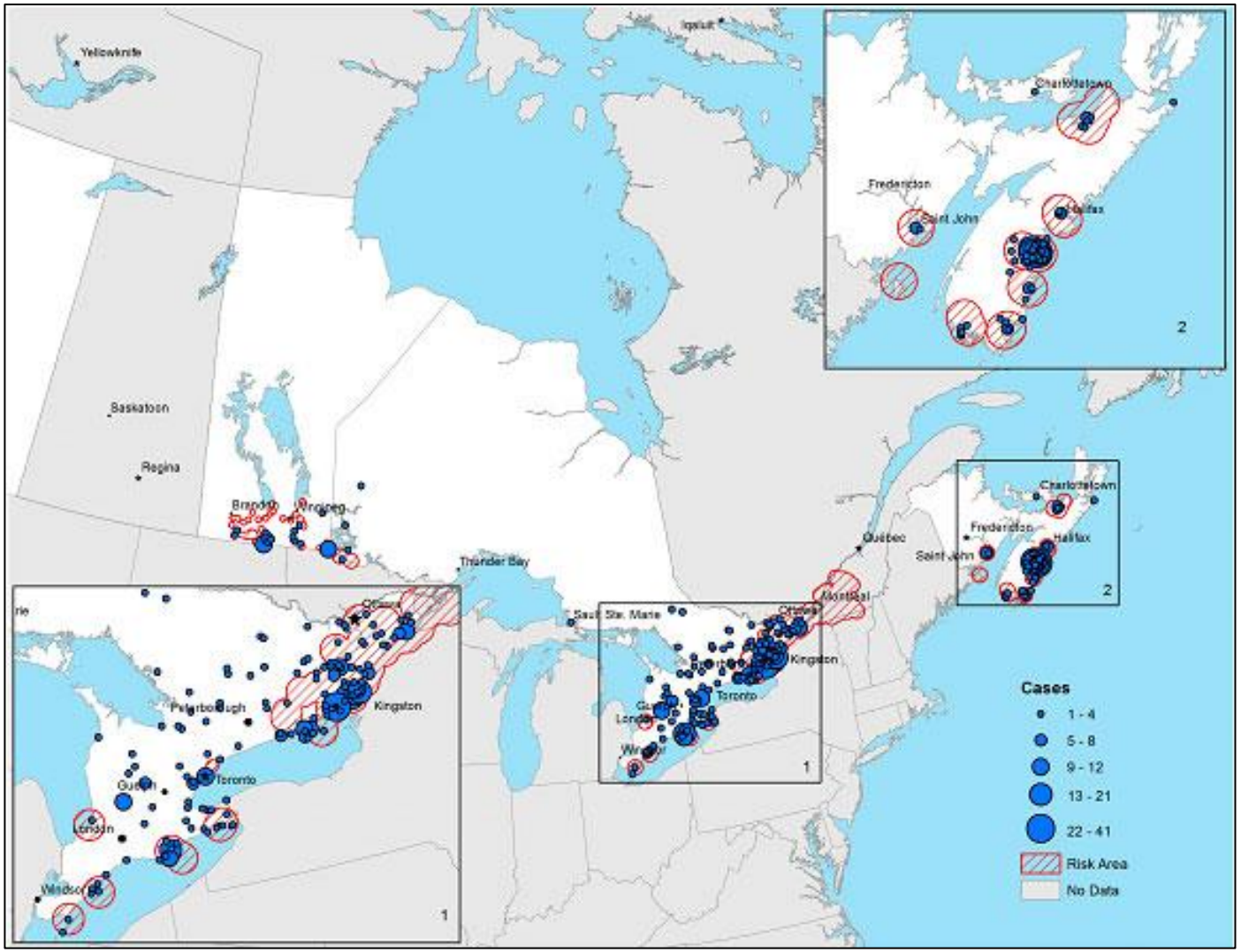
Each dot represents one case of Lyme disease and is placed randomly in the patient's county of residence. The presence of a dot in a state does not necessarily mean that Lyme disease was acquired in that state. People travel between states, and the place of residence is sometimes different from the place where the patient became infected.



National Center for Emerging and Zoonotic Infectious Diseases

Division of Vector-borne Diseases | Bacterial Diseases Branch

Map of Lyme disease in Canada

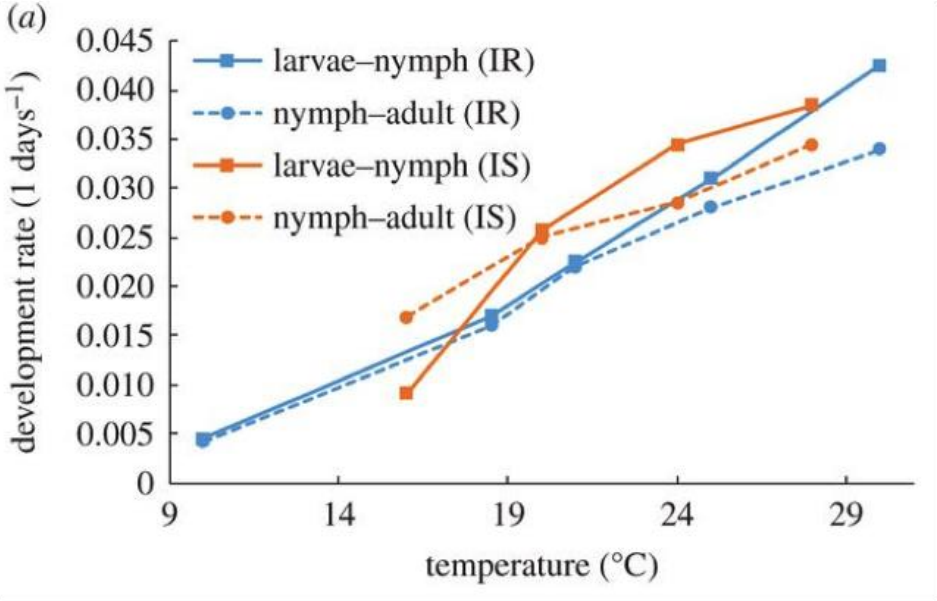


Gasmi et al. 2017. CCDR. 43(10):194-199.

Geographic distribution of Lyme disease depends on geographic range of tick vector and competent vertebrate reservoir hosts

Tick development versus temperature

- Tick development rates are highly sensitive to temperature
- Microclimate influences tick development, tick survival, and host searching activity
- If mean temperature is too low, ticks will not complete their inter-stage development in time and cannot establish viable populations
- Inter-stage development rates of Ixodes ricinus (IR = blue) and Ixodes scapularis (IS = orange) at different temperatures
- Temperature determines the northern range limit of *I. scapularis* populations



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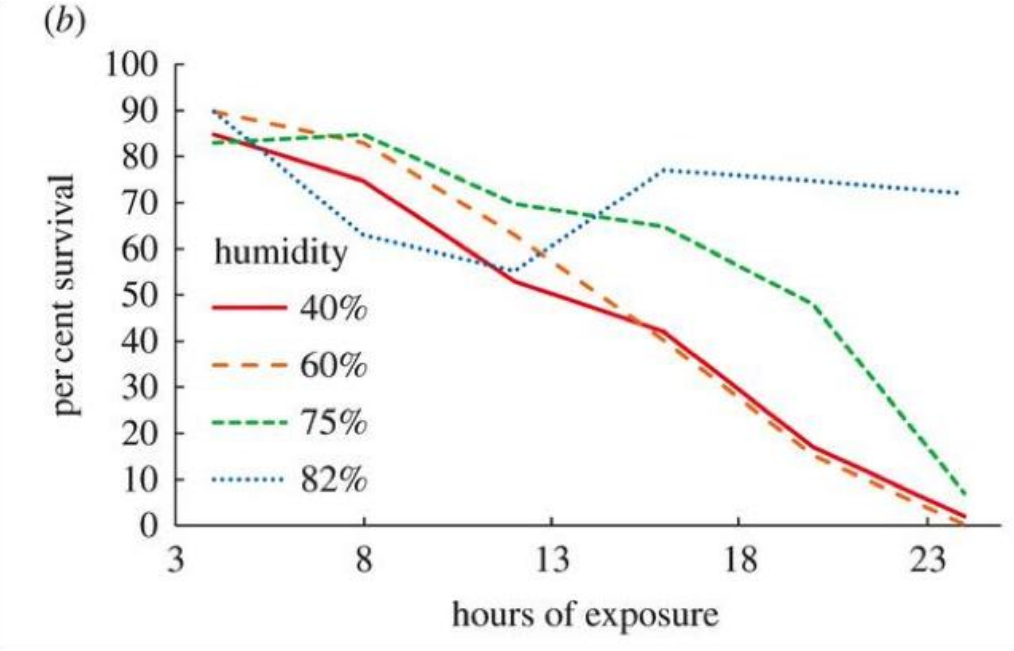
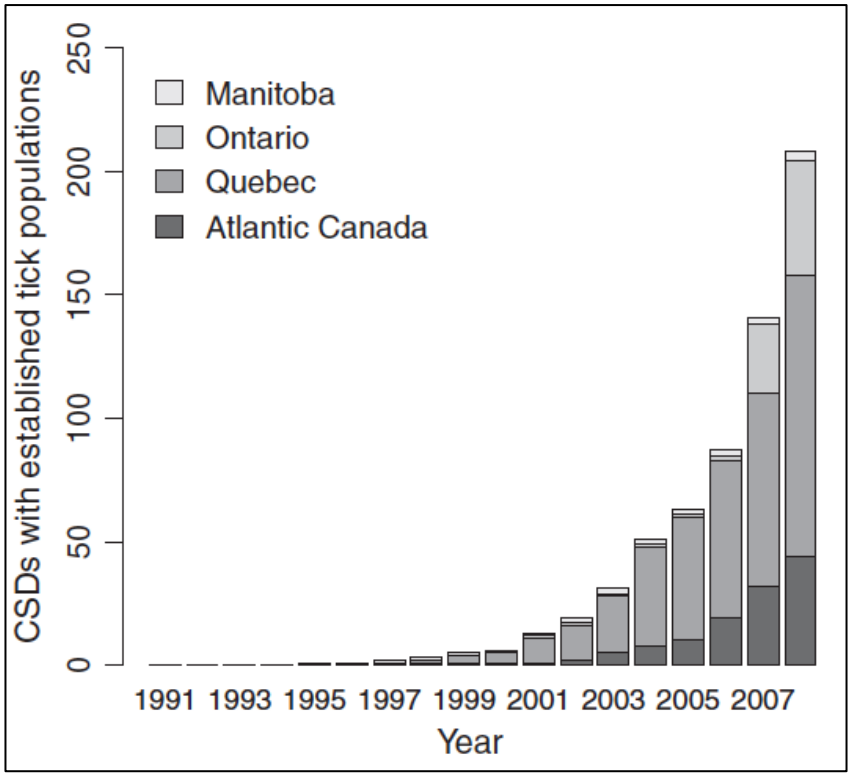
Tick survival versus humidity

- Tick development rates are highly sensitive to humidity
- Survival of nymphal Ixodes scapularis ticks after 4–24 h exposure to four different humidity treatments
- At 82% humidity, most of the ticks are still alive after 23 hours
- Below 75% humidity, all of the ticks are dead after 24 hours
- Sensitivity to desiccation explains why blacklegged ticks are rare in American Midwest and Alberta and Saskatchewan



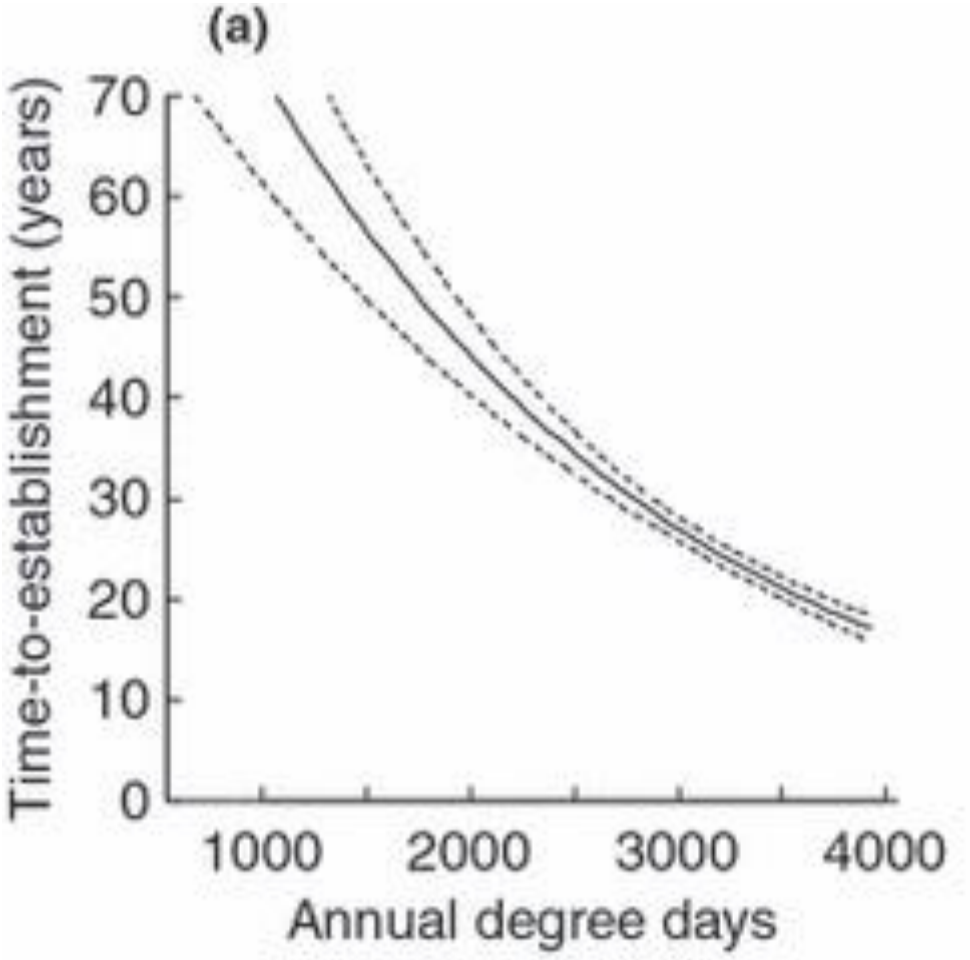
Climate change is driving the geographic expansion of *Ixodes scapularis*, which is increasing the incidence of Lyme disease in Canada

Number of CSDs with ticks over time



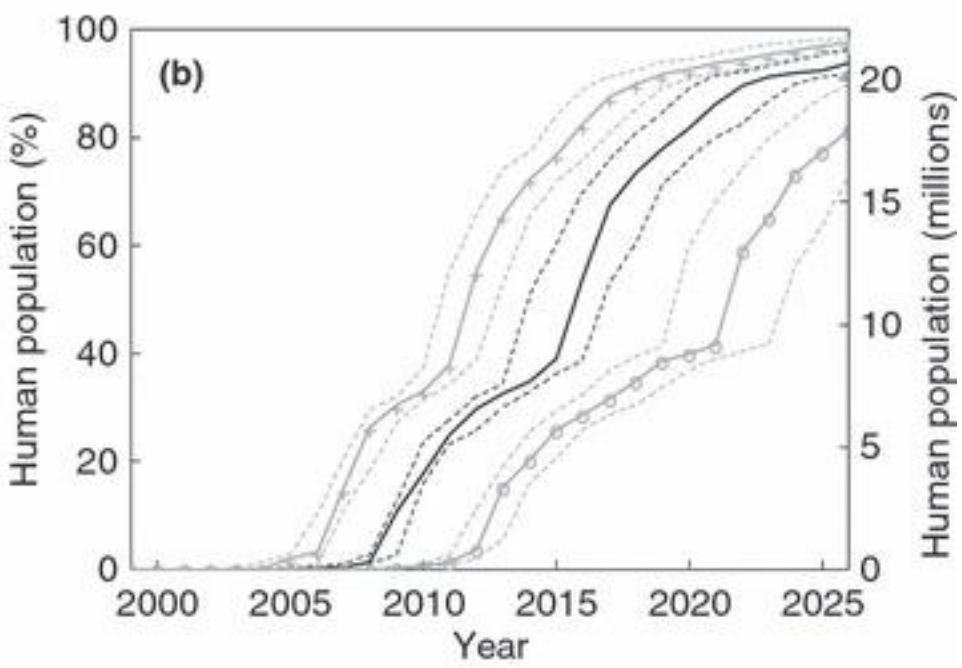
- Active surveillance determines established tick populations
- Number of census sub-divisions with established tick populations has increased from 1 in 1995 to >200 in 2008
- Blacklegged ticks have expanded their geographic range into southern Canada

Degree days predict establishment of *Ixodes scapularis* populations



- Degree days (DD) are best predictor of time-to-establishment (TTE) of tick populations in Canada
- DD is sum of days with temperature > 0 ºC
- Locations with high DD have shorter TTE
- Tick populations establish more quickly at warmer locations in Canada

Degree days predict establishment of *Ixodes scapularis* populations



- Ticks moving north at rate of 46 km per year
- In 2000, 0% of humans in eastern Canada live in areas with established populations of blacklegged ticks
- In 2020, 82% of humans in easter Canada live in areas with established populations of blacklegged ticks

Migratory birds transport ticks

- Migratory birds are importing ticks into Canada from the USA
- Ticks attach to bird for days and move 100s of kms
- Birds disperse 50 to 175 million blacklegged ticks into Canada each spring
- Climate change and warmer conditions now allows these tick populations to establish

Summary 2

- Incidence of Lyme disease has increased dramatically in Canada over the last 20 years
- Blacklegged tick is sensitive to temperature and humidity
- Surveillance shows rapid northwards expansion of geographic range of black legged tick
- Sensitivity to desiccation ~ absence from Midwest
- Climate change drove range expansion of black legged tick
- Migratory birds import ticks from USA into Canada
- Canada will become epicenter of Lyme disease in North America

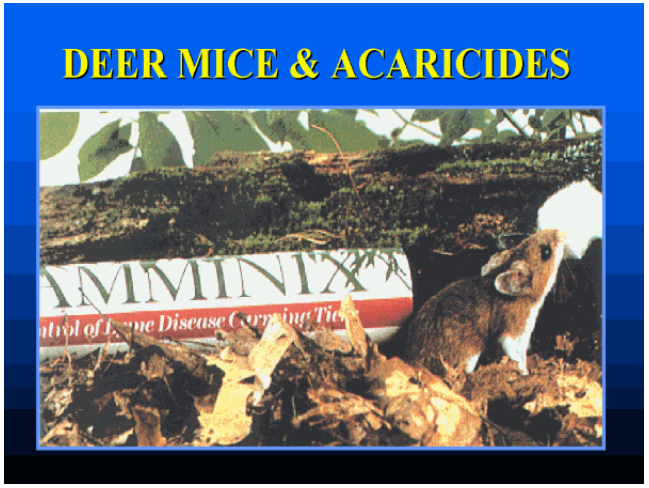
How can we prevent Lyme disease?

Strategies to reduce the risk of Lyme borreliosis

Personal Protective Clothing

Culling deer

Acaricides



Reservoir-host targeted methods

Lyme disease vaccines

- Need for Lyme disease vaccines
- High incidence: 476,000 cases of LD per year in USA
- Patients can remain sick for life (PTLDS)
- 1998, FDA approved LYMErix vaccine
- 2002, vaccine removed due to poor sales
- Why did LYMErix fail?

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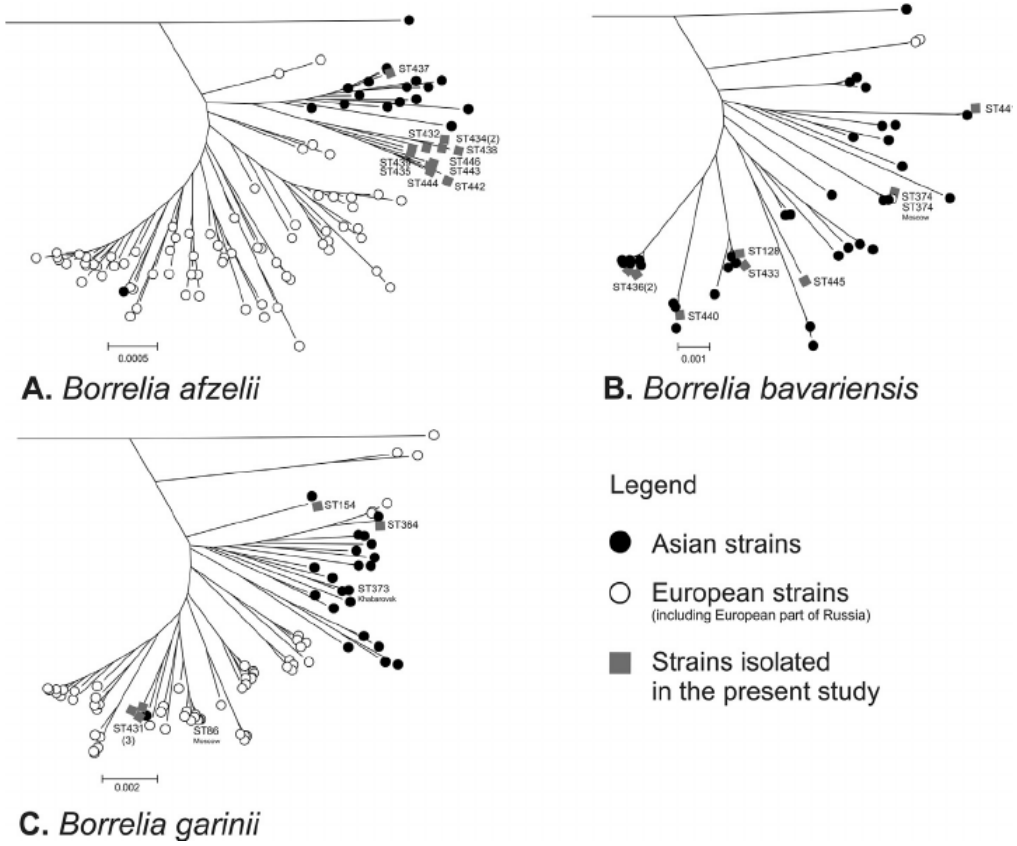
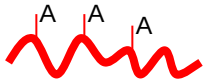
Strain diversity within *Borrelia* species

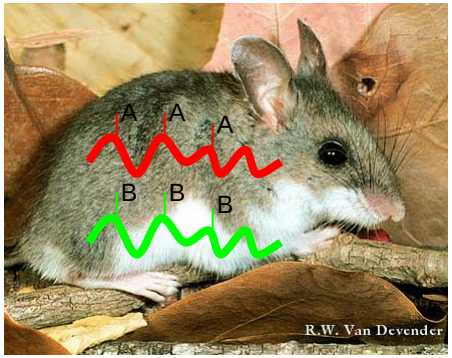


Mukhacheva & Kovalev. 2013. TTBD 4(4): 275-279

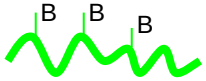
Vertebrate hosts and ticks are often co-infected with multiple strains of the same Bbsl genospecies

B. burdorferi
strain A



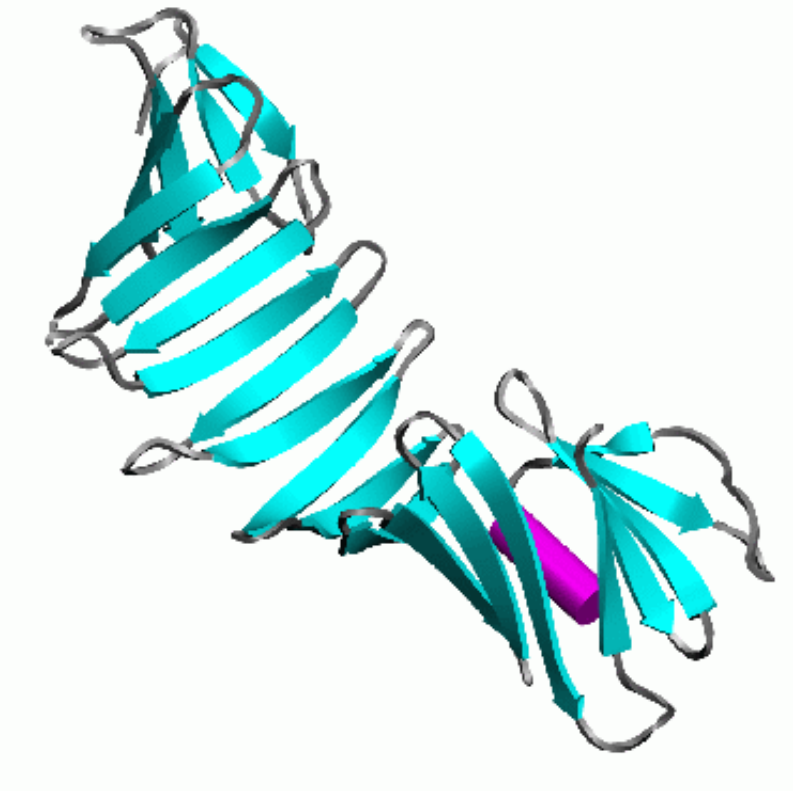


B. burdorferi
strain B

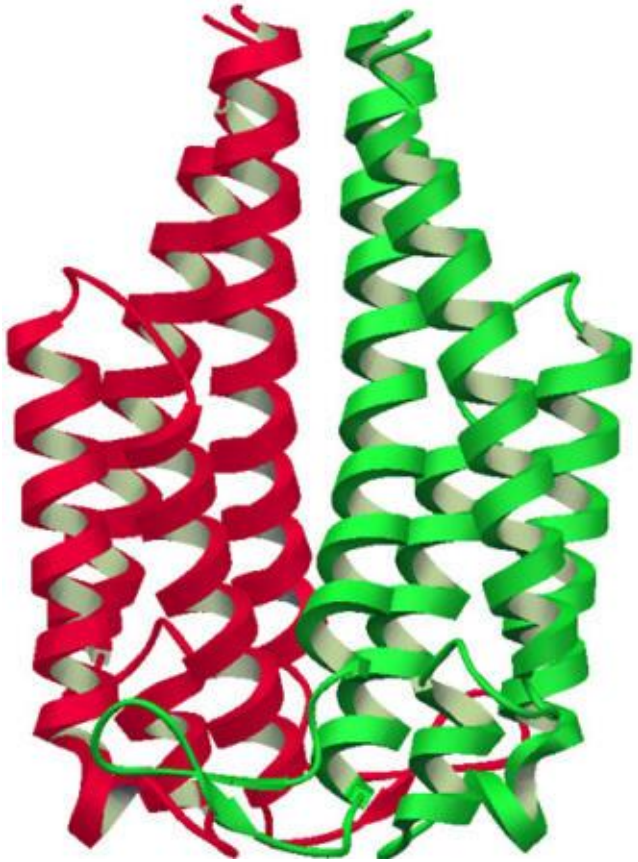


- Co-infection (or mixed infections) is when host carries multiple pathogen strains
- White-footed mouse carries two strains (red and green)
- Hosts can be sequentially infected with antigenically distinct strains
- Some human patients have had Lyme disease multiple times
- Presence of multiple genospecies and strains complicates vaccine development

Borrelia outer surface proteins A and C

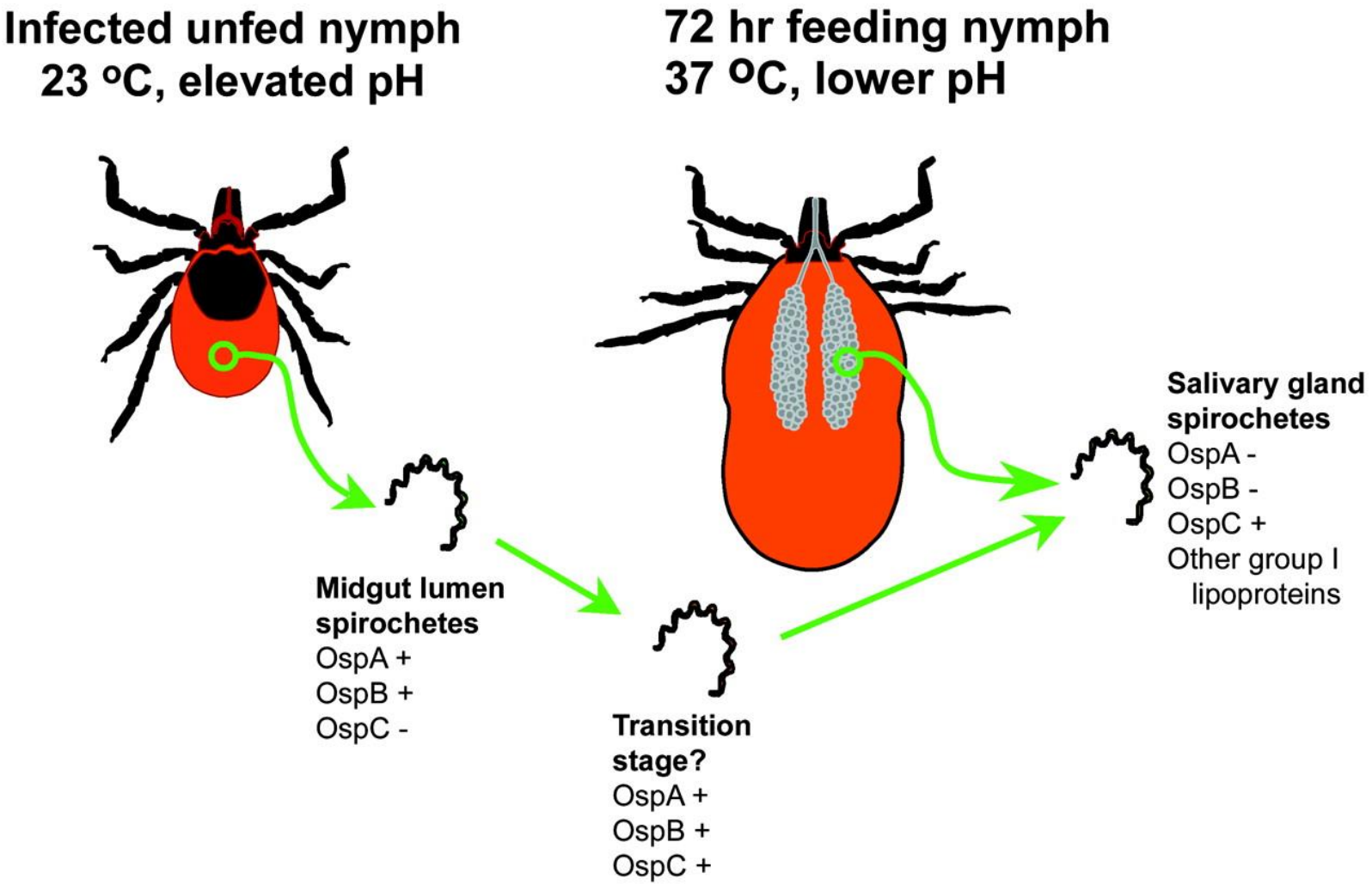


OspA attaches *Borrelia* to tick midgut



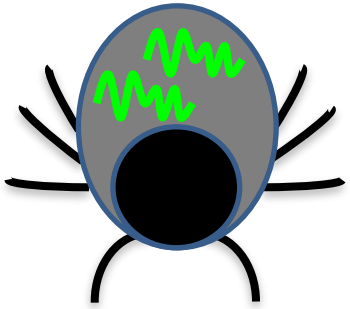
OspC facilitates *Borrelia* invasion of vertebrate host

Borrelia gene expression

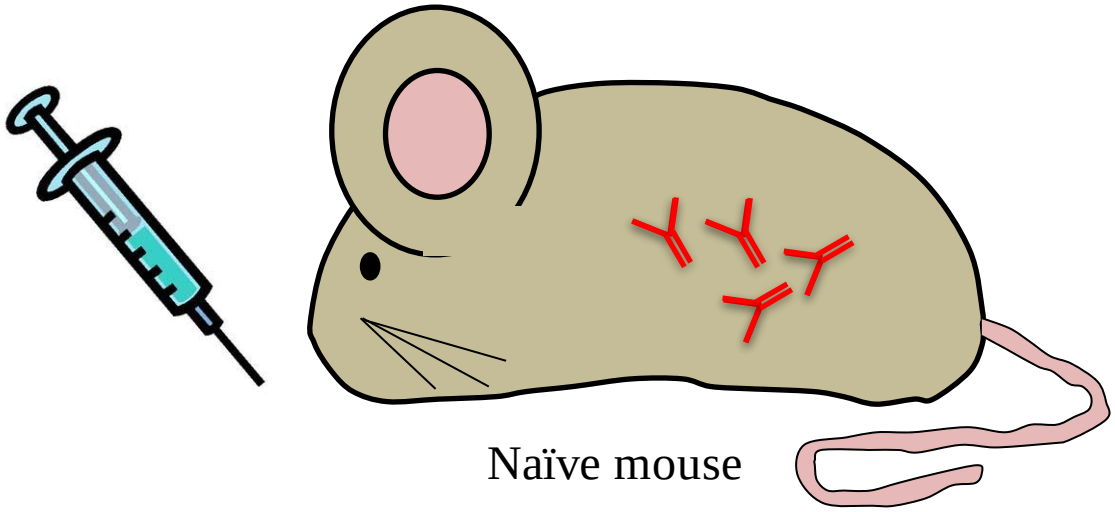


Templeton T J J Exp Med 2004;199:603-606

ospA-Lyme disease vaccine prevents tick-to-mouse transmission of *B. burgdorferi*



Borrelia burgdorferi-
Infected tick



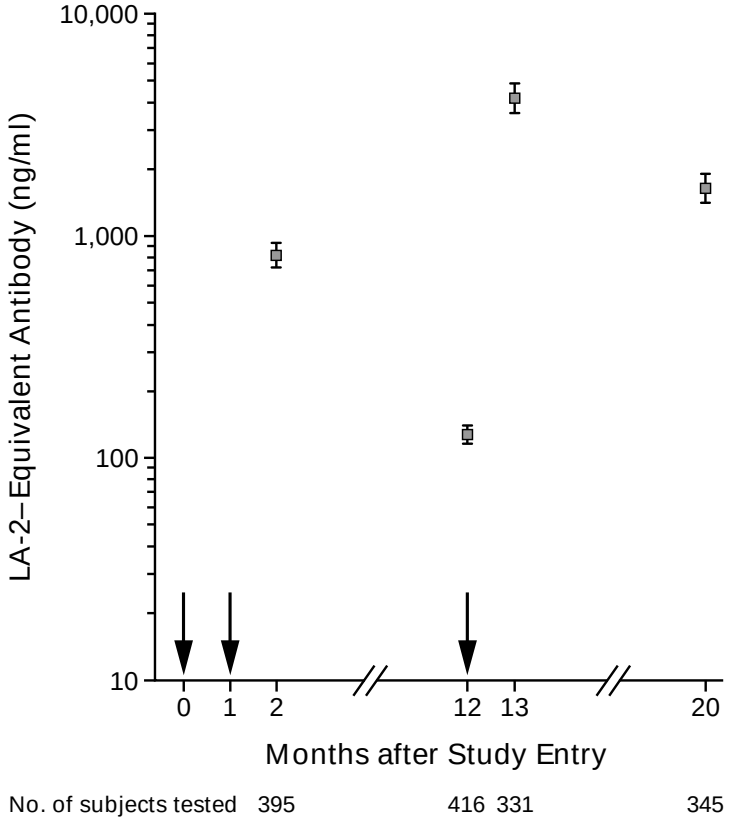
Naïve mouse

- **What is a potential problem with this vaccine?**

OspA Vaccine Trials

- Two OspA vaccine trials were published in 1998
- SmithKline Beecham with Lymerix vaccine and PasteurMerieux Connaught with ImuLyme
- Both trials had ~5,000 vaccinated and ~5,000 placebo
- Immunization schedule: 0, 1, and 12 months
- Strict case definition of LD: clinical symptoms and lab tests
- Lymerix efficacy 49% in year 1, 75% in year 2
- **Is efficacy good? Why is efficacy higher in year 2?**

Antibodies to OspA wane over time

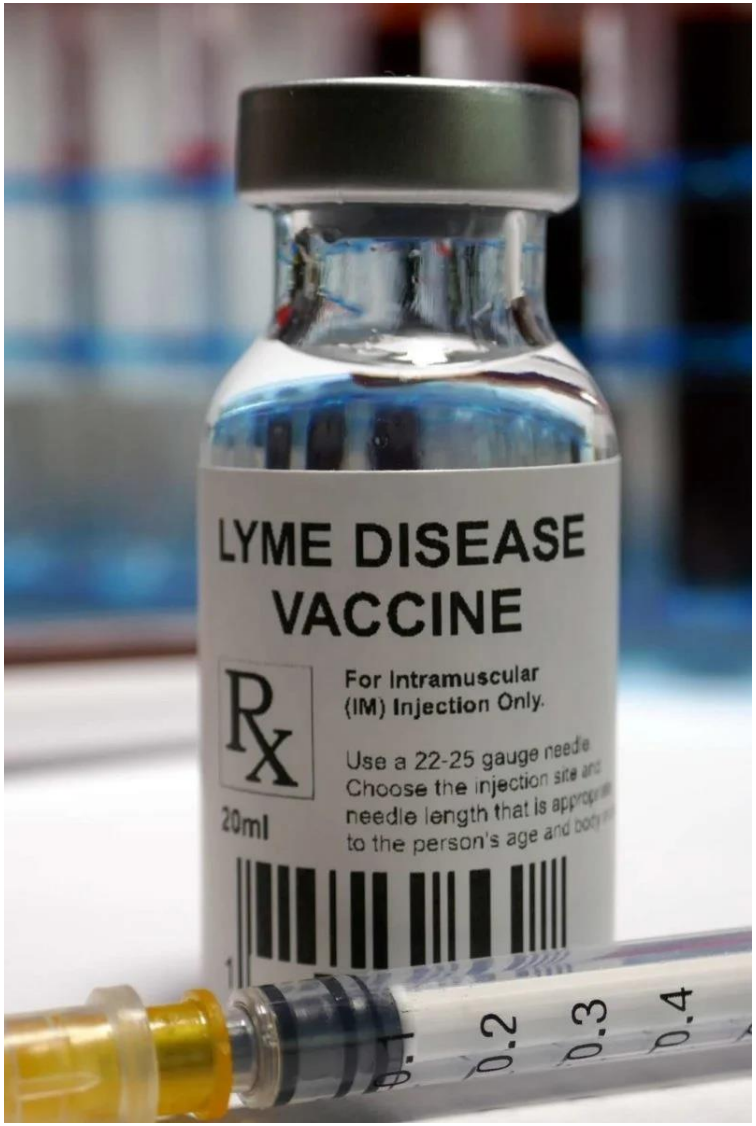


- Month 2, Ab titre is 816 ng/mL
- Month 10, Ab titre declined
- Month 13, Ab titre is 4127 ng/mL
- Month 20, Ab titre higher than month 2
- Ab titre determines protection

OspA vaccine safety

- Both OspA vaccines were found to be safe
- As expected, short-term adverse effects were more common in vaccinated group compared to placebo group
- Mild, self-limited effects (first 7 days): pain or tenderness at injection site and local muscle pain
- Lymerix: No difference in type or frequency of symptoms between vaccine and placebo at 30 days after injections
- ImuLyme: No difference in severe effects between vaccine and placebo at 7 days after first or second immunization
- **Can clinical trials rule out rare adverse effects (1/10,000?)**

Limitations of Lymerix vaccine



- Efficacy of 80%
- 3 shots over 1 year
- Not tested in children
- Only protects against Bbss
- Waning immunity and need for boosters unknown
- Human behaviour and risk for other TBPs

Failure of Lymerix vaccine

- Costs about $500 million to license a vaccine
- FDA approved licensure for LYMErix vaccine in 1998
- In 1998, SmithKline Beecham (SKB) marketed LYMErix
- Some individuals claimed vaccine gave them arthritis
- Media gave extensive coverage to ‘vaccine victims’
- Dec 1999: Class action lawsuit against SKB
- Poor press: vaccine sales dropped dramatically in 2001
- Feb 2002: SKB withdrew LYMErix from market

12:50 PM

Testimony of vaccine recipient

- "*This vaccine is not causing just some minor joint pain, it is destroying lives. It is destroying the lives of our most healthiest population. They thought they were protecting themselves from a horrible disease. Instead, they've gotten an even worse disease, one that cannot be treated or cured.*"

- Jenny Marra, a nurse vaccinated with LYMErix in 1998

- Suffered crippling joint and muscle pain, fatigue, and periods of paralysis since receiving second vaccine dose

Lyme disease vaccines for dogs

- Lyme disease vaccines are available for dogs
- Merck Nobivac Lyme based on OspA and OspC
- Zoetis Vanguard crLyme based on OspA and OspC
- 2 doses 3 weeks apart, 12 to 15 months of immunity

Public Health Fiasco

- Plotkin (2011) gave 4 reasons for Lymerix failure
- Weak recommendation from the CDC: “Vaccination may be considered for high-risk groups”
- Reports that Lymerix caused rheumatic side effects
- Unenthusiastic response of opinion leaders in FDA: “Not something I would push tomorrow” and “This is a vaccine for yuppies”.
- Educate physicians rather than targeting public

New Lyme disease vaccines

- Pfizer and Valneva are developing a new Lyme disease vaccine called VLA15
- Fusion protein of OspA from 4 genospecies: *Bbss*, *B. afzelii*, *B. garinii*, and *B. bavariensis*
- Removed OspA epitope that exhibits cross-reactivity with human leukocyte function associated antigen 1 (hLFA-1)
- Phase 3 study of VLA15 started in August 2022
- VLA15 has similar limitations as Lymerix

Appetite for Lyme disease vaccines

- Surveys of interest in vaccine in LD-endemic areas
- 64% willing, 30% uncertain, 7% not willing
- 18% had LD diagnosis; 86% concerned about future LD
- 94% believe that recommended vaccines benefit people
- Concerns include safety (71%) and cost (63%)
- 89% said positive recommendation from HCP would influence their willingness to be vaccinated

Summary 3

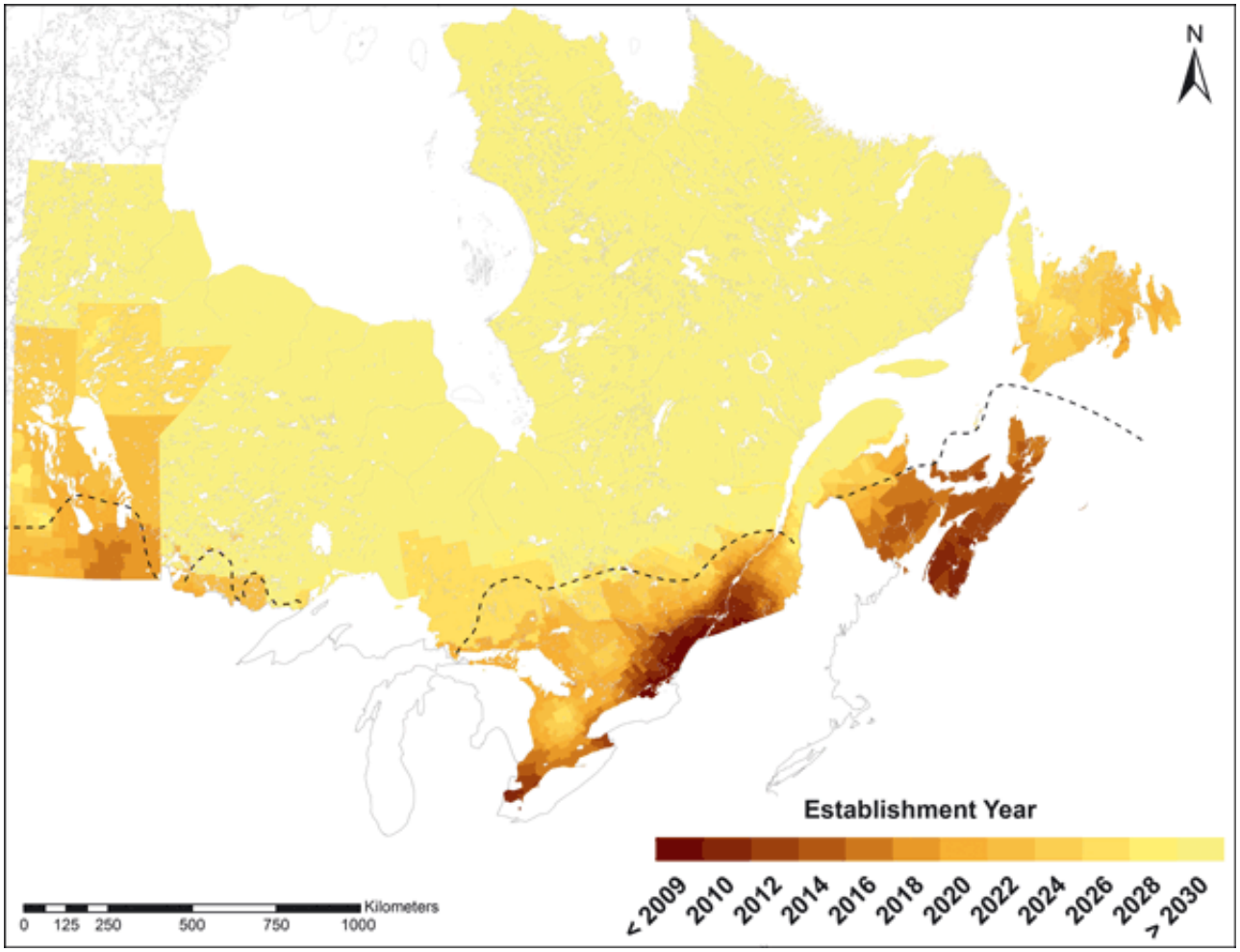
- OspA-based vaccines protect against Lyme disease
- Lymerix had several limitations
- Public perception that vaccine was not safe resulted in poor sales
- Autopsy on what went wrong
- New vaccines have solved some problems but share many of the same limitations as the old vaccines
- Whether new vaccines will succeed remains to be seen
- Surveys of endemic areas found interest in vaccines

Thank you for your attention

OspA and hLFA-1

- Portion of OspA resembled hLFA-1; human protein involved in immune response
- Molecular mimicry: Host antibodies developed against OspA cross-react with host antigen hLFA-1
- Patients with treatment-resistant Lyme arthritis have antibodies to OspA and hLFA-1
- Infection with Bbss -> antibodies to OspA -> cross-react with hLFA-1 -> treatment-resistant Lyme arthritis
- Could vaccination with OspA result in arthritis?

Projected range expansion of *I. scapularis* in Canada



Ogden et al. 2005. Int Journal Parasit 35:375-89

LYME DISEASE
-is your dog protected?

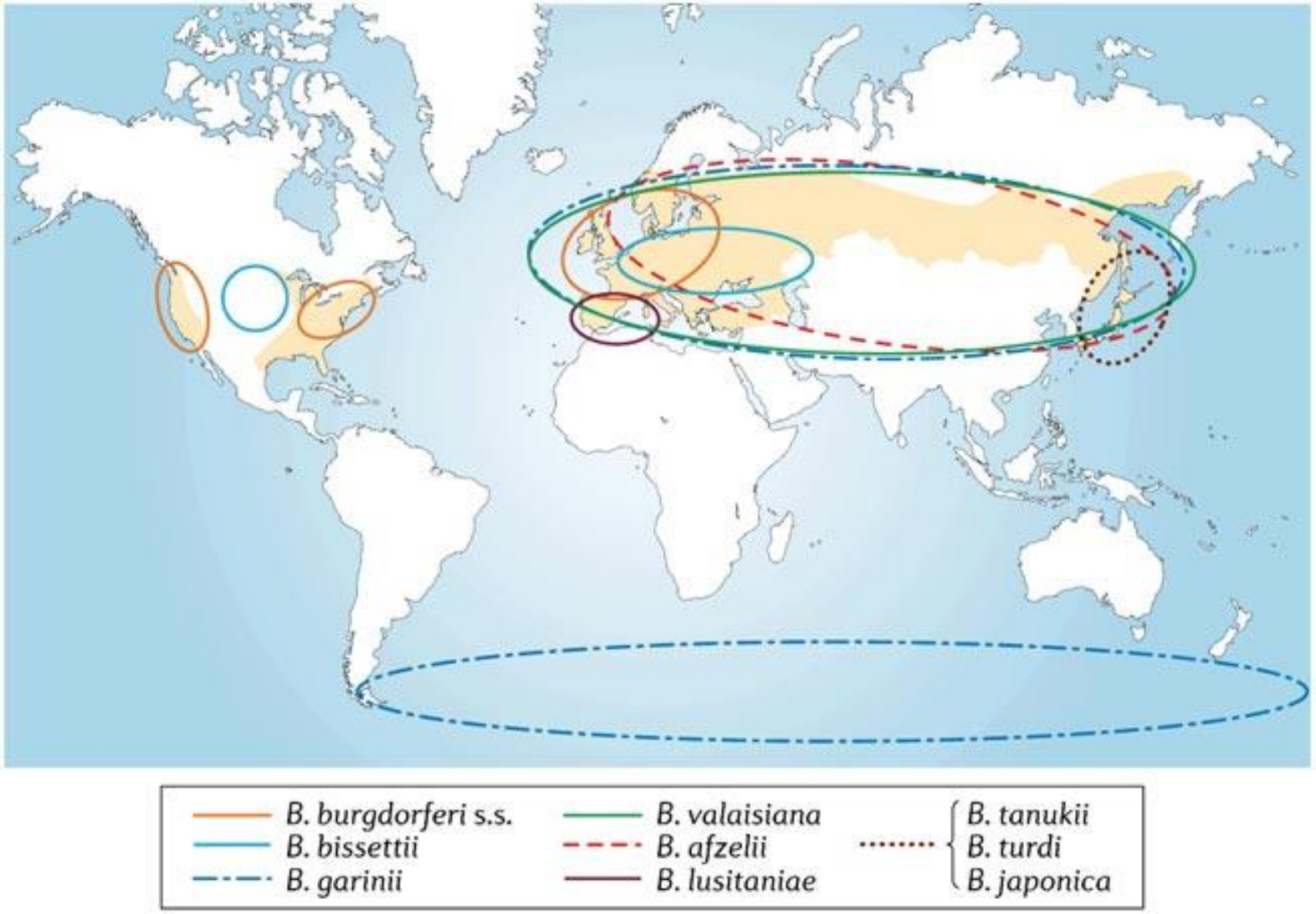
Lyme disease is transmitted to people and pets by tick bites, and infection can cause serious illness

A VACCINE FOR DOGS IS NOW AVAILABLE

Brought to you by

Merilym3

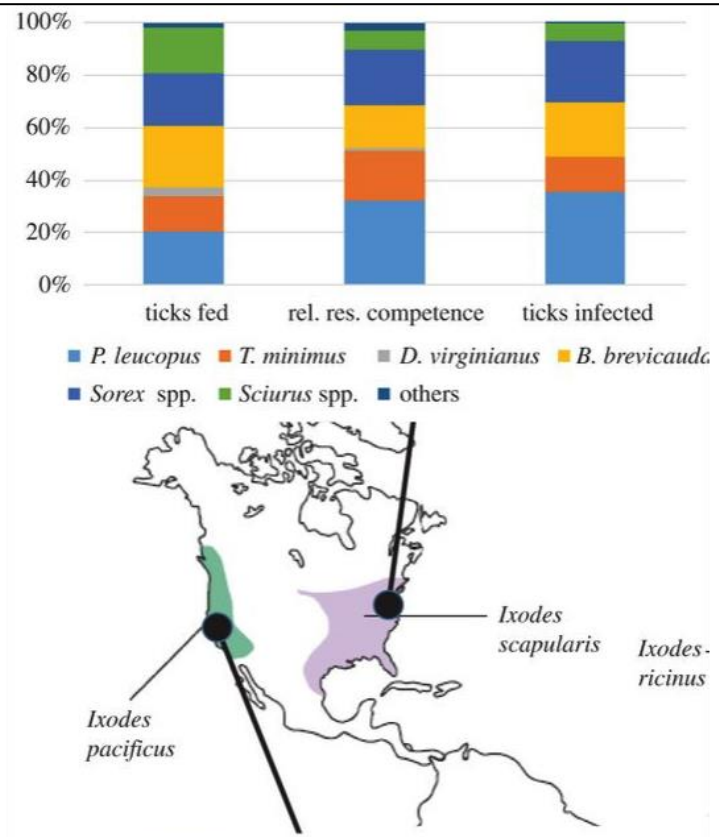
Global distribution of Lyme disease



Nature Reviews | Microbiology

Host community and *Borrelia* transmission

Western fence lizard



White-footed mouse

Lyme disease is increasing in Canada

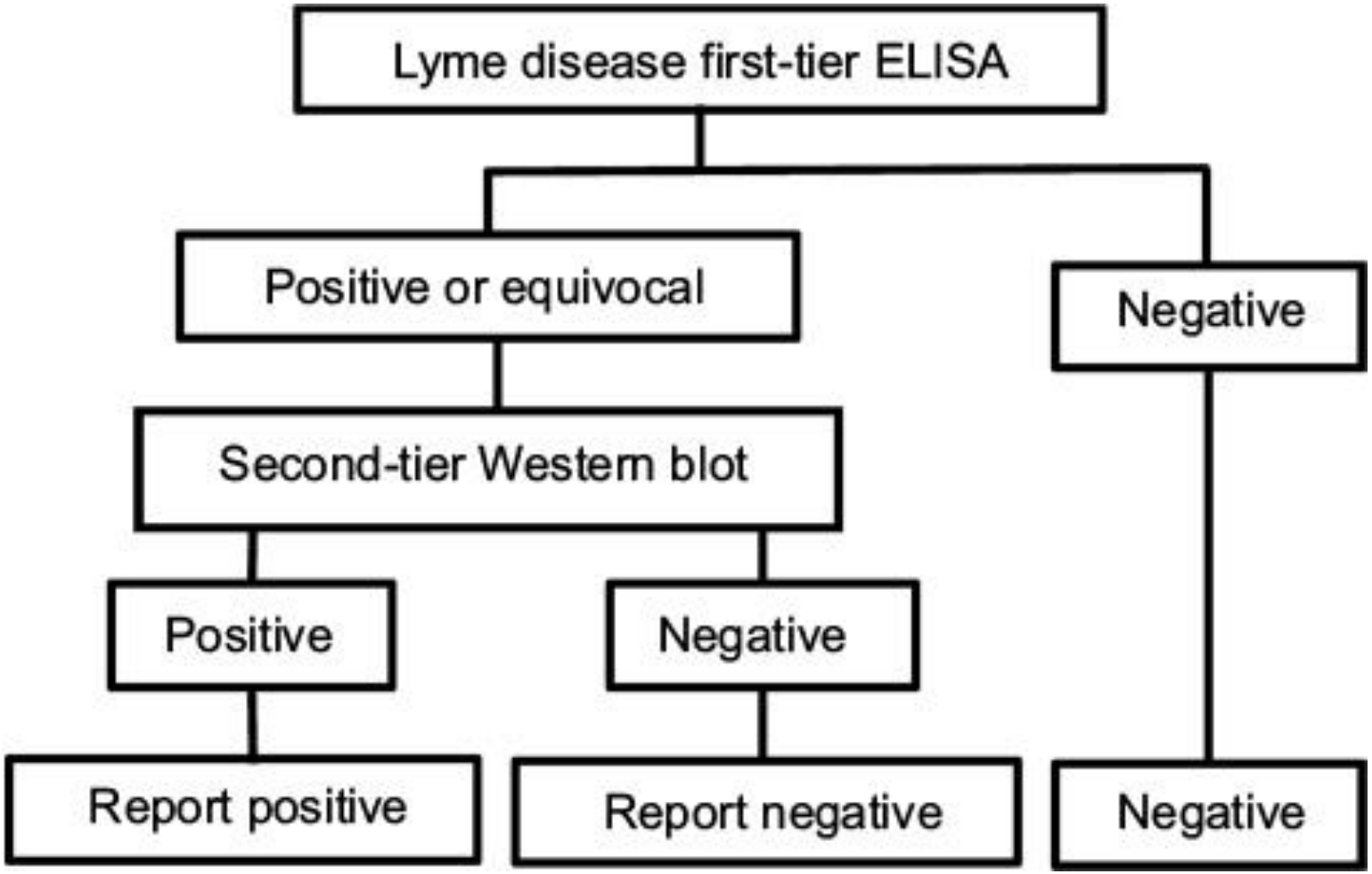
Table 3: Classification (confirmed and probable) of all reported Lyme disease cases and cases acquired in Canada*, 2009–2015

Classification	Number (percentage of cases)							
Year	2009	2010	2011	2012	2013	2014	2015	Total
Lyme disease cases reported in Canada (n=3,012)								
Confirmed	115 (79.9%)	109 (76.2%)	195 (73.3%)	232 (68.6%)	485 (71.1%)	334 (64.0%)	651 (71.0%)	2,121 (70.4%)
Probable	29 (20.1%)	34 (23.8%)	71 (26.7%)	106 (31.4%)	197 (28.9%)	188 (36.0%)	266 (29.0%)	891 (29.6%)
Total	144	143	266	338	682	522	917	3,012
Lyme disease cases acquired in Canada (n=2,015)								
Confirmed	56 (70.9%)	56 (65.1%)	96 (60.0%)	129 (58.1%)	286 (61.1%)	198 (59.5%)	467 (70.0%)	1,288 (63.9%)
Probable	23 (29.1%)	30 (34.9%)	64 (40.0%)	93 (41.9%)	182 (38.9%)	135 (40.5%)	200 (30.0%)	727 (36.1%)
Total	79	86	160	222	468	333	667	2,015

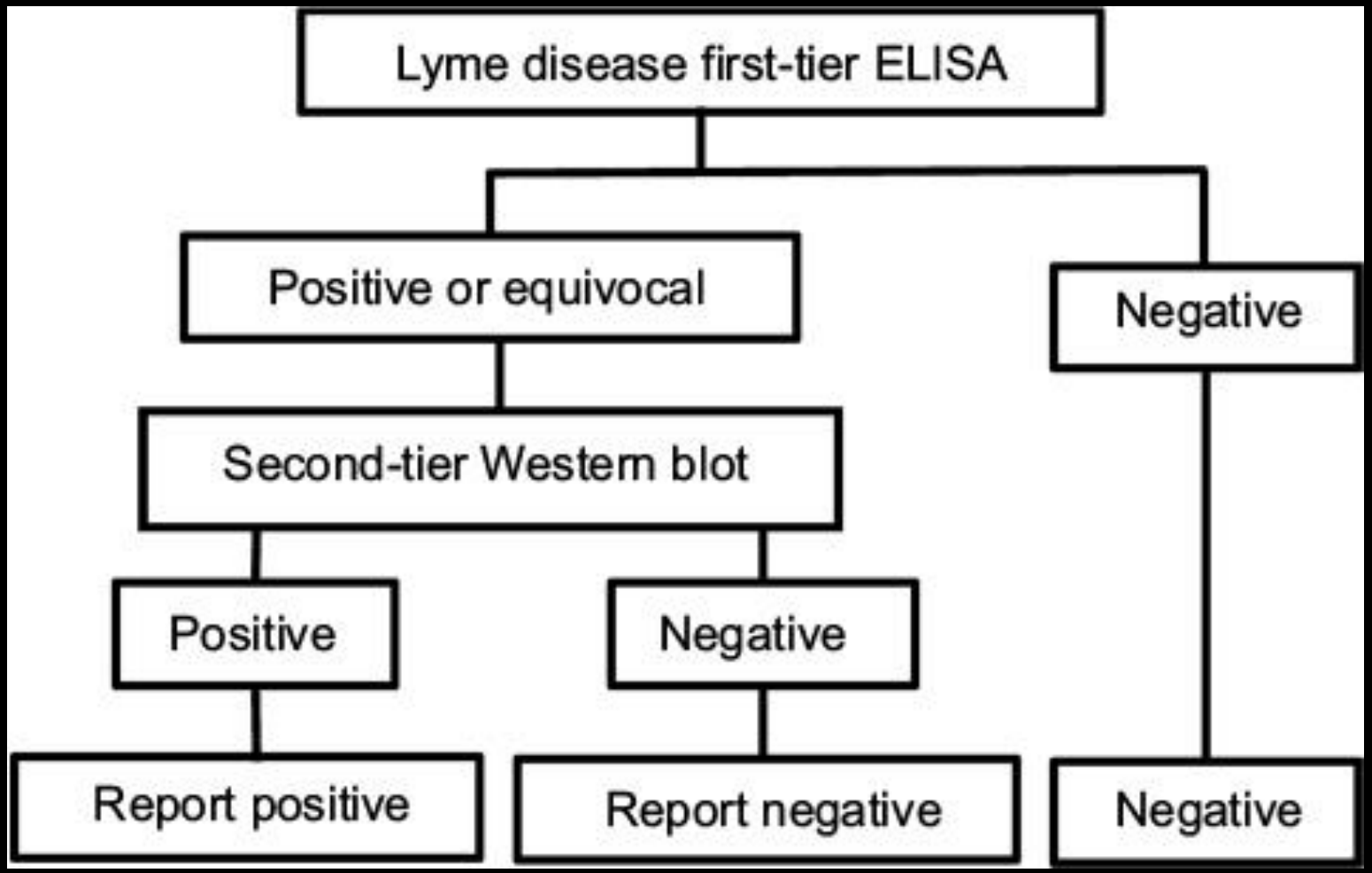
Gasmi et al. 2017. CCDR. 43(10):194-199.

Other tick species in Canada

(1) Black-legged tick (*Ixodes scapularis*), (2) Groundhog tick (*Ixodes cookei*), (3) American dog tick (*Dermacentor variabilis*), (4) Lone star tick (*Amblyomma americanum*), (5) Brown dog tick (*Rhipicephalus sanguineus*) (6) Rabbit tick (*Haemaphysalis leporispalustris*)

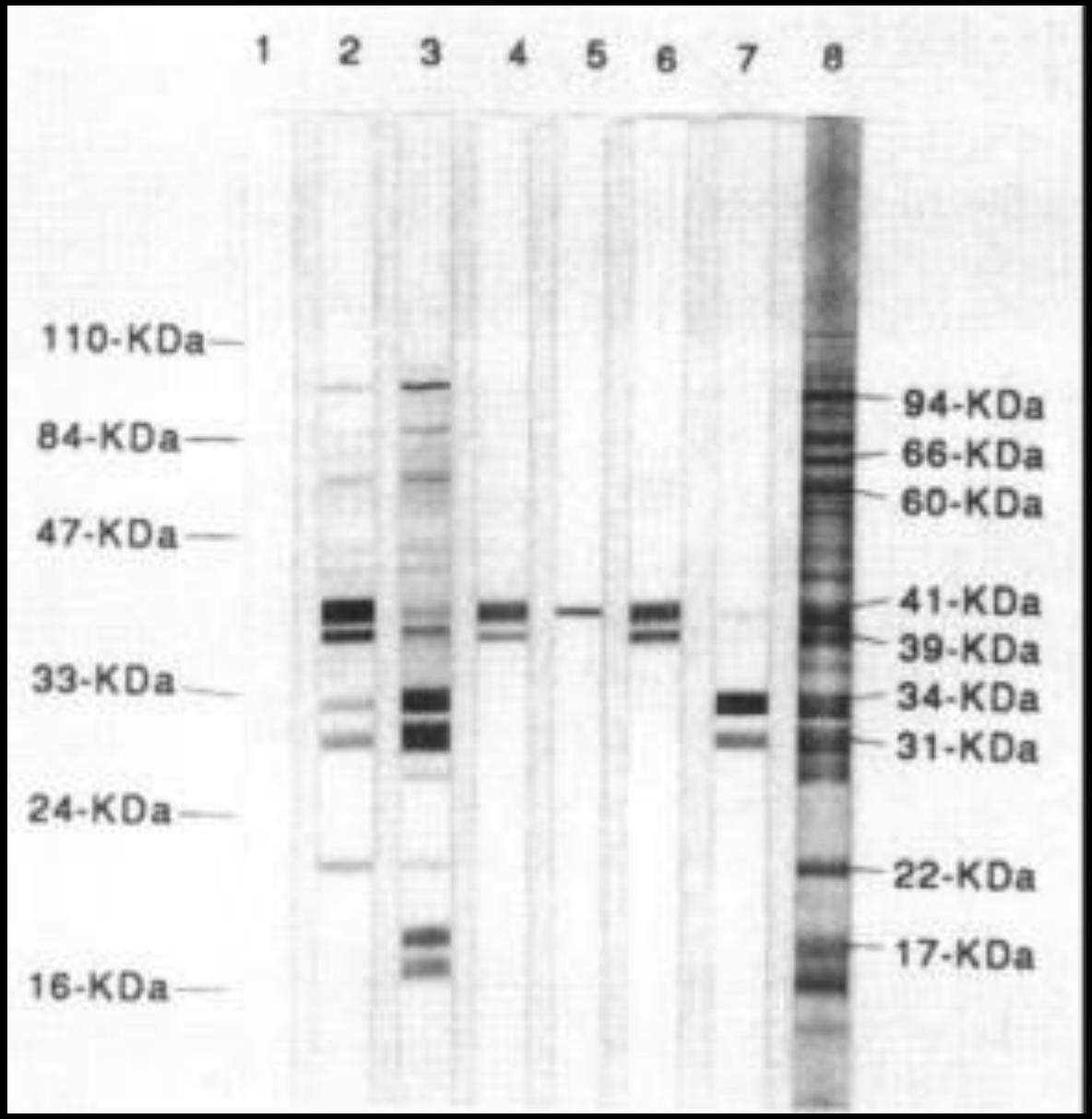

Lyme disease first-tier ELISA
Positive or equivocal
Negative
Second-tier Western blot
Positive
Negative
Report positive
Report negative
Negative

Two-tiered immunological testing



Public Health Agency of Canada and the CDC

Western blot



Conclusions on Lyme disease in Canada

- Lyme disease has increased rapidly in Canada
- Range expansion of *Ixodes scapularis* is responsible
- Encourage use of personal protective measures
- Active research to improve diagnostics
- Valneva is working on a new Lyme disease vaccine

Biggest threat: hysteria and false information

Overlap between LD and other diseases