

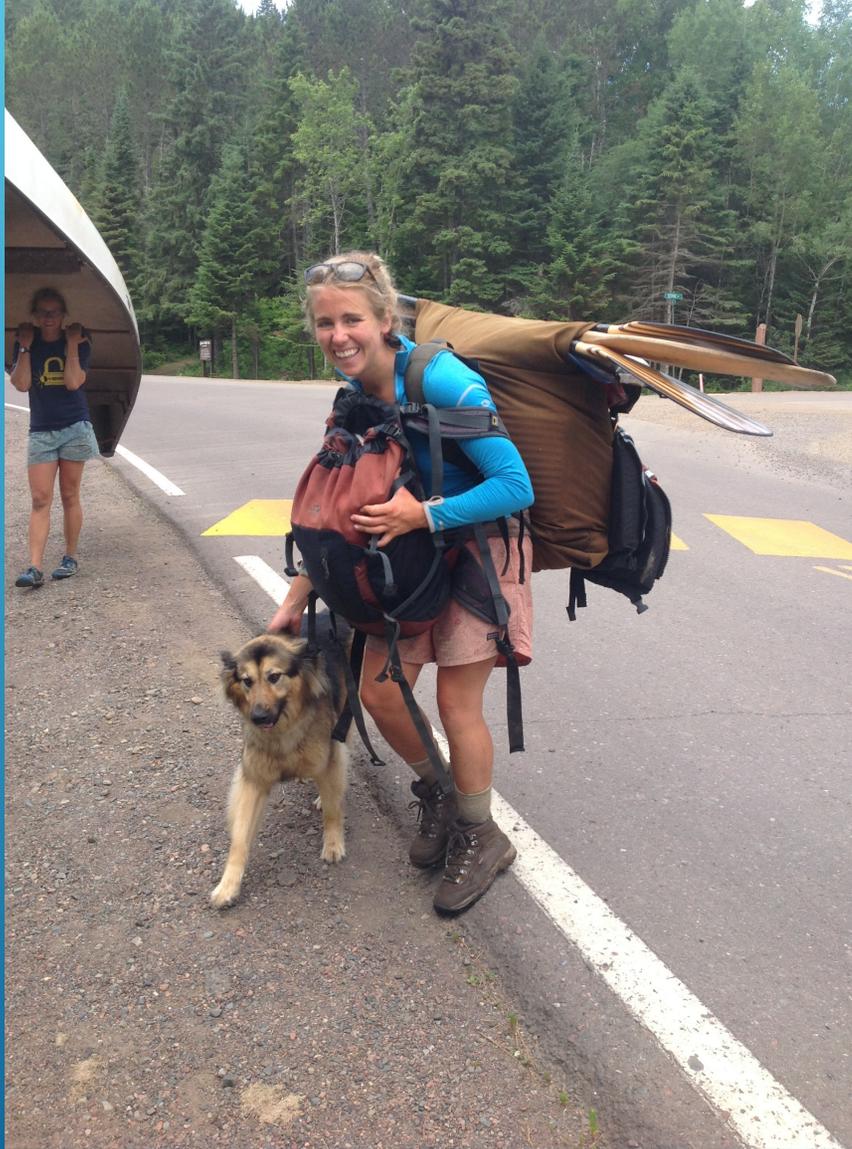
# INTRODUCTION TO LYME DISEASE

By: Andrew Pugliese, MS.M.D.

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# LEARNING OBJECTIVES

- Discuss an overview of Lyme Disease to include history, concerns and controversies
  - Review diagnostic dilemmas involving Lyme Disease
  - Articulate treatment options for Lyme disease including choice and length of antibiotic therapy, alternative therapies both good and bad.
  - Formulate post Lyme Disease Treatment
  - Describe other chronic zoonotic illnesses both especially with concerns tourism and lifestyles plus new challenges including zika and chikungunya.
- 



# CASE 1

- 24 year old college graduate working at REI and taking Outward Bound courses.
- Presents to medical clinic May 1989 with myalgias, migratory arthritis for several weeks.
- Responds well to oral doxycycline

# HISTORY OF LYME DISEASE

- ▶ The original descriptions of the dermatologic manifestations of Lyme disease date back to 1883 in Europe, when a German physician, Alfred Buchwald, described what is now termed acrodermatitis chronica atrophicans (ACA).

# HISTORY OF LYME DISEASE

- ▶ In 1912, the Swedish dermatologist Arvid Afzelius described the rash, then called erythema chronicum migrans, which currently is referred to simply as erythema migrans (EM).

# HISTORY OF LYME DISEASE

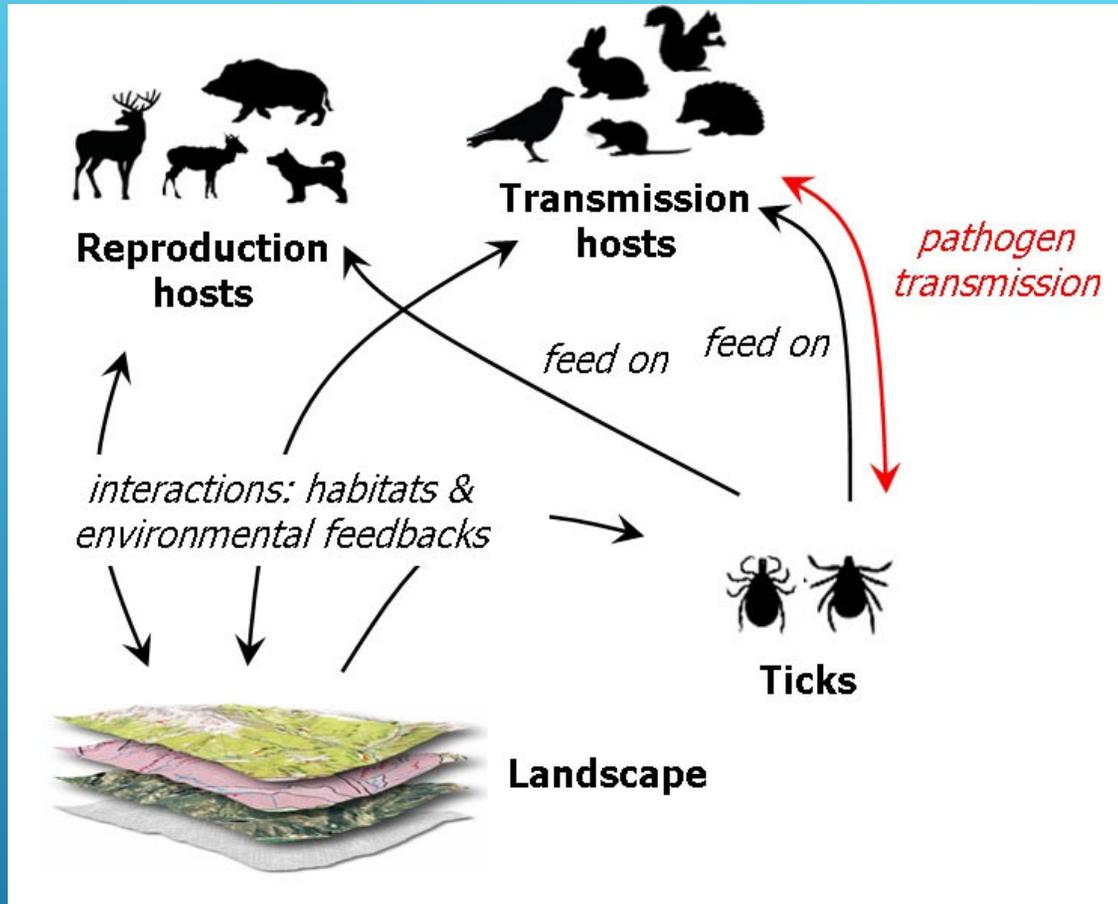
- ▶ In the 1920s, Garin and Bujadoux described a patient with meningoencephalitis, painful sensory radiculitis, and erythema migrans following a tick bite, which they attributed to a spirochetal infection.

# HISTORY OF LYME DISEASE

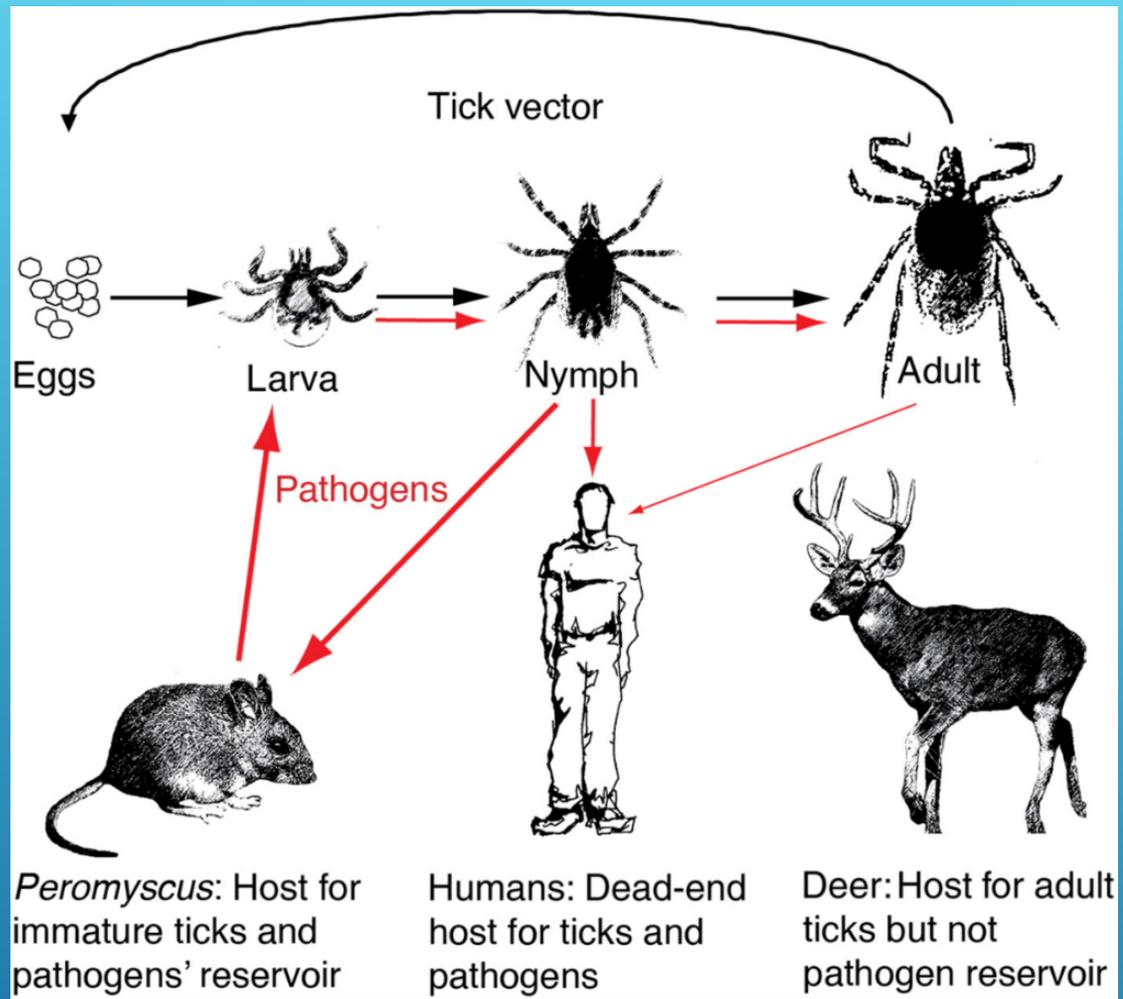
- ▶ By the mid 1930s, neurologic manifestations associated with Ixodes ticks (also known as deer ticks) were recognized and were known as tick-borne meningoencephalitis

# HISTORY OF LYME DISEASE IN THE US

- ▶ Infections are most common in the spring and early summer. **Lyme disease** was diagnosed as a separate condition for the first time in 1975 in Old **Lyme**, Connecticut. It was originally mistaken for juvenile rheumatoid arthritis.



# LIFE CYCLE OF LYME DISEASE



# LIFE CYCLE OF LYME DISEASE

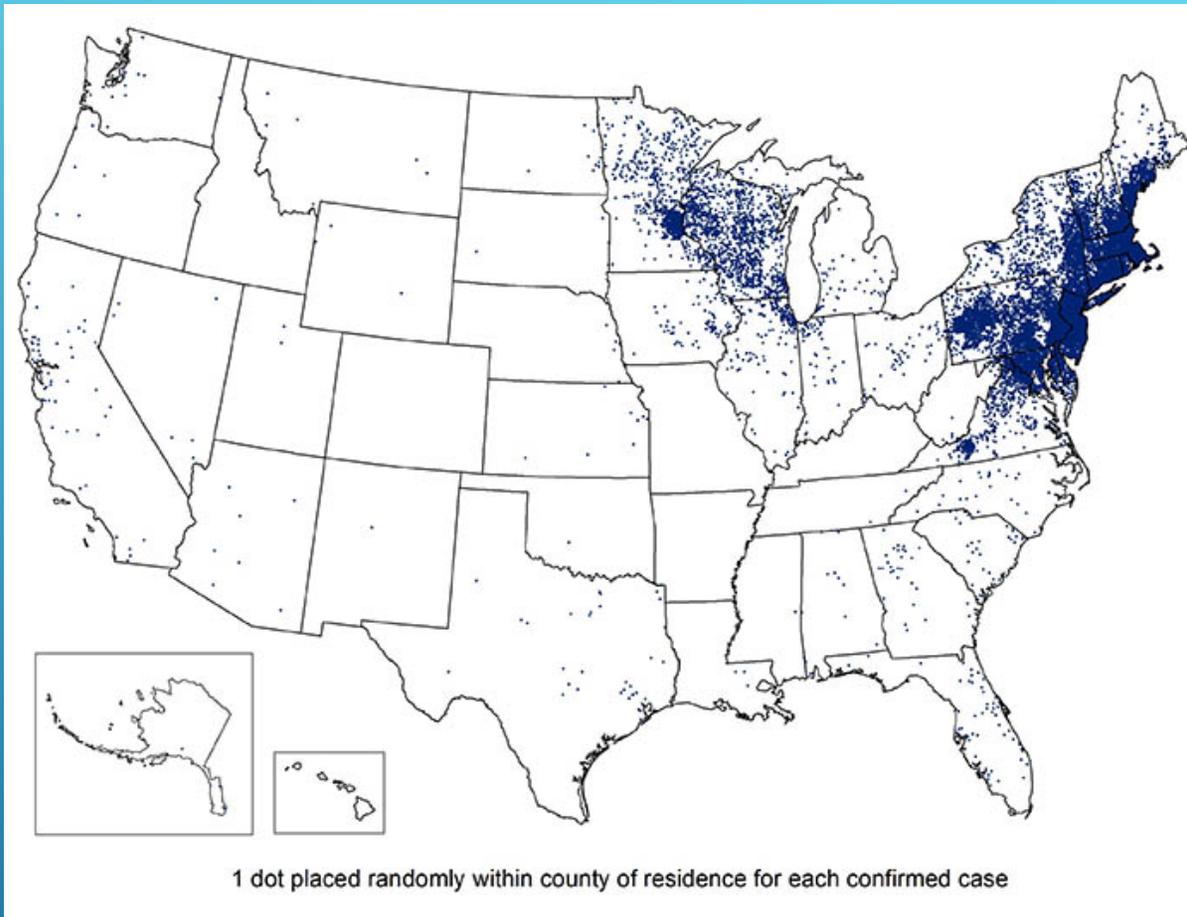
# CASE 2



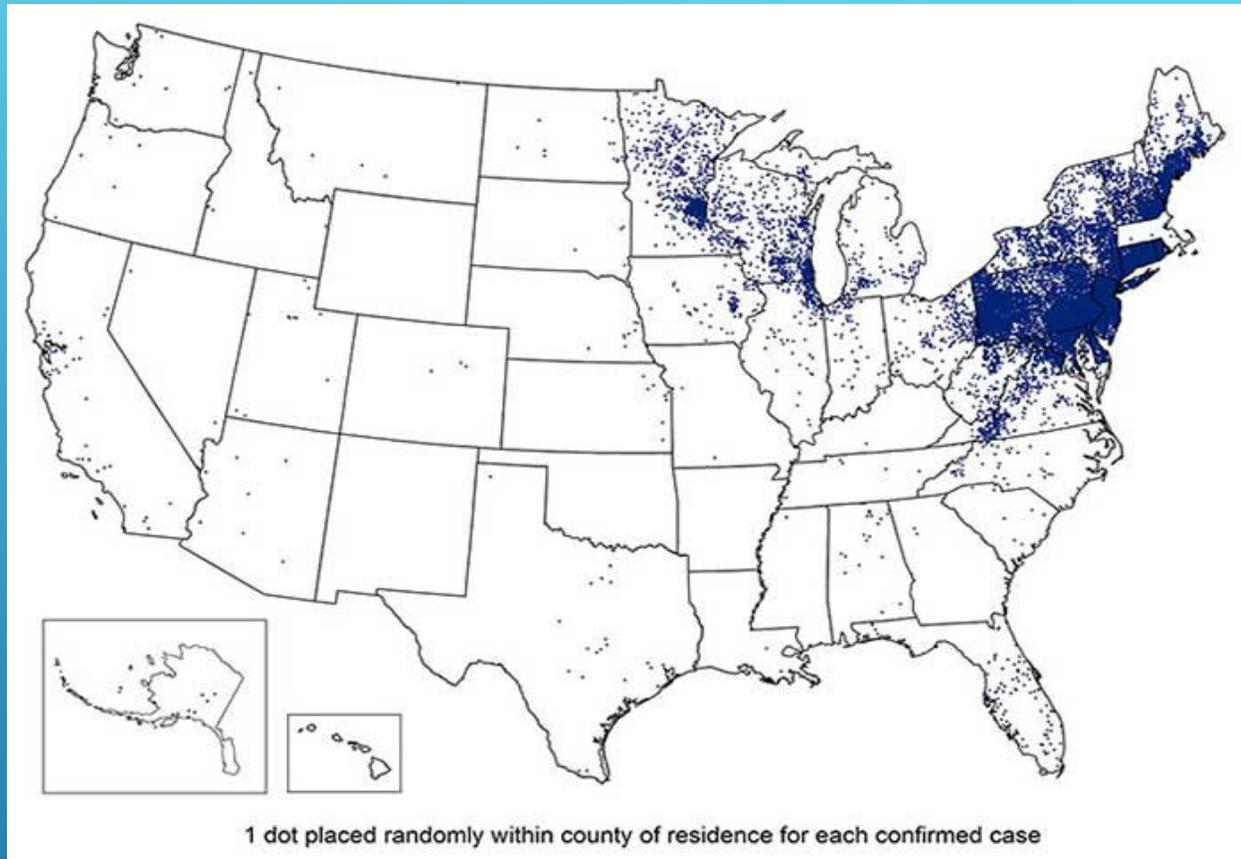
- 56 year old female, Upstate NY, February 2013, several days of myalgias and arthralgias when her husband notices a rash on her torso.
- Dead of winter
- No outdoor exposure
- Culprit?



# WHITE FOOTED MOUSE

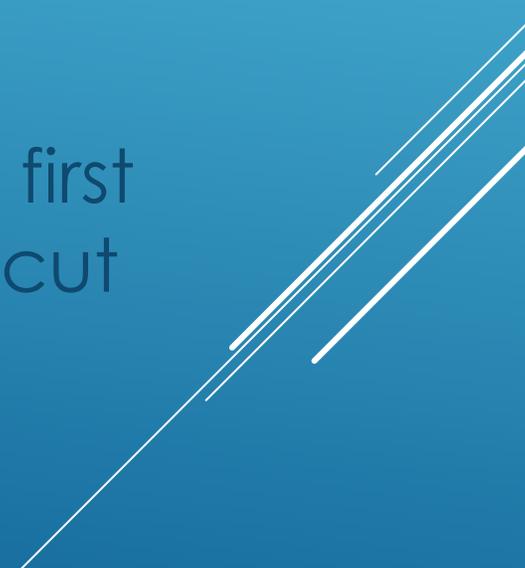


# DISTRIBUTION OF LYME DISEASE 2012



# DISTRIBUTION OF LYME DISEASE 2018

# CONTROVERSIES IN LYME DISEASE

- ▶ The Yale School of Public Health
  - ▶ Lyme disease bacterium is ancient in North America, circulating silently in forests for at least 60,000 years—
  - ▶ Long before the disease was first described in Lyme, Connecticut
- 

# CONCERNS WITH LYME DISEASE

- ▶ **House of Representatives orders Pentagon to investigate whether ticks were once used as biological weapons**
  - ▶ *By Christina Maxouris, CNN*

# CDC PROVIDES ESTIMATE OF AMERICANS DIAGNOSED WITH LYME DISEASE EACH YEAR

- ▶ Each year, more than 30,000 cases of Lyme disease are reported to CDC
- ▶ Lyme disease is roughly 10 times higher than the yearly reported number

This supports the estimates published in the 90's

# THERE'S NO LYME DISEASE IN GEORGIA

- ▶ The prevalence of **Lyme disease in Georgia** and the Southeast is reported to be low. The **Georgia** Department of Public Health says that fewer than 10 cases are reported in the state each year.

# THERE'S NO LYME DISEASE IN GEORGIA

- ▶ **New study ranks Georgia third in nation for increases in Lyme disease**
  - ▶ New research shows Lyme disease has infected people in all 50 states.
  - ▶ A new study by a national health care company has ranked Georgia third in the nation for the most increases in Lyme disease between 2015 and 2017.
  - ▶ Arizona and Florida were No. 1 and 2, respectively, in the new Quest Diagnostics Health Trends report.
- 

# CASE 3

- February 1998 until October 1999, Federal Agent assigned to the Southeast Bomb Task Force (formed in response to the 1996 Atlanta Olympic Bombing and subsequent bombings in Atlanta and Birmingham).
- Spent hundreds of hours in the densely wooded, mountainous terrain of Western North Carolina searching for fugitive bomber.
- Assignments included grid searches in national forests and canvassing areas on and adjacent to the Appalachian Trail.



# MISDIAGNOSES:

- ▶ Prior to 1998, no significant medical history.
- ▶ Presented to family doctor on April 18, 1998 with a persistent, EM typical rash in left groin. Diagnosis missed.
- ▶ Patient's symptoms worsened from 1999-2005 including:
  - Sore/swollen throat, nausea, dizziness, progressive fatigue, chest pain, increasing joint pain, severe headaches, cognitive dysfunction, reduction in exercise tolerance, weakness
- ▶ Between 1999 and 2002 the patient saw his family physician who ran lots of tests, but no Lyme bloodwork.
- ▶ 2002 – referred to Infectious disease physician who diagnosed him with an unspecified viral infection and treated with 1 month of Levaquin with some relief, but ultimately symptoms returned.
- ▶ Sought second opinion of SWAT team doctor who ordered lots of diagnostic and neurological testing, but no Lyme test.
- ▶ Referred to Gastroenterologist and Cardiologist

# COMPLICATIONS:

- ▶ 2003: Referred to Chronic Fatigue Specialist – Diagnosed with Chronic Fatigue Syndrome and Dysautonomia.
- ▶ 2003: Internal medicine doctor finally performed the ELISA test – unfortunately, it was a false negative.
- ▶ Developed POTS and NMH – confined to bed for 2 years due to sensitivity to light and sound/total neurological overload
- ▶ July 2005: Finally tested positive for Lyme via Western Blot; also diagnosed with Borrelia
- ▶ July 2005: Immediately started IV antibiotics – Rocephin was causing gallbladder issues and the gallbladder had to be removed. PICC line was occluded after 3 months and had to be removed. Continued with oral antibiotics during that time, the disease did not worsen, but did not get better.
- ▶ July 2007: Patient started seeing me for the first time. Started 12-month course of IV Levaquin which had to be stopped after 8 months due to tendonitis.
- ▶ 2008-2011: Treated with oral antibiotics and hyperbaric oxygen therapy
- ▶ 2011-present: treated with antibiotic pulse therapy – Symptoms are finally improving after 22 years.

# LYME DISEASE PRESENTING AS CHRONIC FATIGUE SYNDROME

Chronic Fatigue Syndrome (CFS) by definition represents a diagnosis of exclusion.

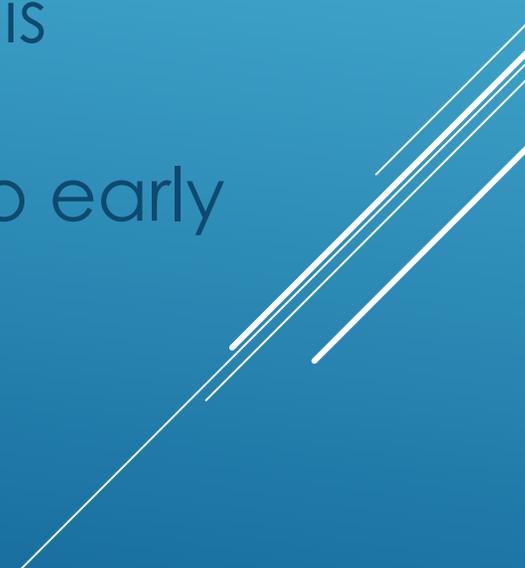
Late stage or “Chronic Lyme: infection with or without “co-infections” is a difficult diagnosis to establish.

The symptom complex of both conditions can be very similar.

*Source: Journal of Chronic Fatigue Syndrome. 2007  
Vol 13 Issue 4 pp:67-75*

# LYME DISEASE: THE LATEST GREAT IMITATOR.

PEDIATR INFECT DIS J. 1988 JUN;7(6):402-9.

- ▶ Like its counterpart syphilis, it causes multisystem disease.
  - ▶ The prompt recognition of this disease and its diverse manifestations should lead to early treatment and resolution.
- 

# LYME DISEASE ASSOCIATED WITH SUDDEN SENSORINEURAL HEARING LOSS: CASE REPORT AND LITERATURE REVIEW

Sudden sensorineural hearing loss, followed  
by a facial paralysis

Lyme disease confirmed by positive  
serology and a positive immunoblot.

Treated with ceftriaxone, recovery of the  
facial paralysis, no recovery of the hearing  
loss was observed.

Otol Neurotol. 2013 Jul;34(5):832-7.

## LYME DISEASE ASSOCIATED SENSORINEURAL CONTINUED:

- ▶ A systematic literature search, suggests active Lyme disease as a cause in patients with sudden sensorineural hearing loss.
- ▶ Significantly higher incidence of confirmed positive serology for *Borrelia burgdorferi* as compared to the general local population.
- ▶ Otol Neurotol. 2013 Jul;34(5):832-7.

# LYME DISEASE SENSORINEURAL HEARING LOSS CONTINUED:

- ▶ Literature suggests that sudden sensorineural hearing loss may coincide with *Borrelia burgdorferi* infection.
- ▶ Sudden deafness seems to be depending on the country and on the tests used to confirm Lyme disease.
- ▶ Otol Neurotol. 2013 Jul;34(5):832-7.

# WHY IS LYME DISEASE SPREADING

- ▶ While the exact reasons are unclear.
  - ▶ A number of factors may contribute.
  - ▶ Changes in land use patterns
  - ▶ Suburban development in these areas has increased, ticks, deer, and tick hosts such as mice and chipmunks are in close contact.
- 

# ACRODERMATITIS CHRONICA ATROPHICANS

- ▶ Acrodermatitis chronica atrophicans (ACA) has hitherto mainly been described in.
- ▶ In recent years, ACA in connection with Lyme disease rarely has been described in US
- ▶ (Lavoie et al. 1986; Kaufman et al. 1989).  
Aspects of Lyme Borreliosis pp 193-204

# LYME CONTROVERSIES

- ▶ **Mass. Lawmakers Override Veto On Long-Term Antibiotics For Lyme**
- ▶ Massachusetts Senate voted 37-1 to override Gov. Charlie Baker's veto of a bill requiring health insurers to cover long-term antibiotic treatment for Lyme disease.

# CELEBRITIES WITH LYME DISEASE

- ▶ Justin Bieber
- ▶ Ben Stiller
- ▶ Alec Baldwin
- ▶ Yolanda Hadid
- ▶ Bella Hadid
- ▶ Kris Kristofferson
- ▶ Kathleen Hanna
- ▶ Thalia Mottola
- ▶ Daryl Hall
- ▶ Jamie Lynn-Siegler
- ▶ Debbie Gibson
- ▶ Ally Hilfiger
- ▶ Kelly Osbourne
- ▶ Shania Twain
- ▶ Avril Lavigne



# CELEBRITIES WITH LYME DISEASE



## CURSE OF OAK ISLAND SEASON 5, 2017

Several days of low grade fever associated with myalgias, arthralgias and brain fog.

Diagnosed at Urgent Care and treated successfully with doxycycline.

# UNDER-DETECTION OF LYME DISEASE IN CANADA

HEALTHCARE (BASEL). 2018 DEC; 6(4): 125.

- ▶ Through analysis of published literature and public health databases
  - ▶ Suggests that many cases of Lyme disease in Canada are, and have been, undetected, unreported, and hence potentially untreated.
  - ▶ Development and use of improved methodologies of laboratory testing, is urgently needed.
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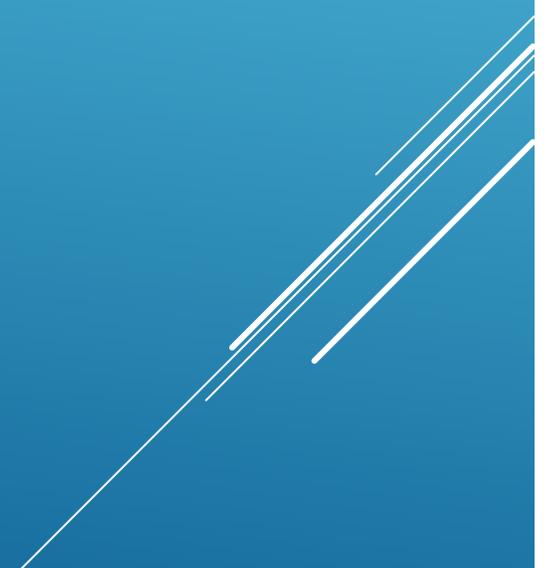
# UNDER-DETECTION OF LYME DISEASE IN CANADA

HEALTHCARE (BASEL). 2018 DEC; 6(4): 125.

- ▶ Under-estimation of the problem likely results in inadequate allocation of health care and research resources.
  - ▶ Significant health, social and economic costs.
  - ▶ Personal suffering for those who truly have Lyme disease.
- 

# LYME DISEASE

Understanding the challenges  
of *Borrelia burgdorferi* as a  
disease



# STAGES OF LYME DISEASE

- ▶ Early Local – Days to Weeks
  - ▶ Early Disseminated -- Weeks to Months
  - ▶ Late Disseminated – Months to Years
- 

# DIAGNOSING LYME DISEASE

- ▶ Problem: Very difficult to culture *Borrelia*. Without the ability to culture organism makes it difficult to determine how accurate serologic testing actually is.

# SERONEGATIVE CHRONIC LYME DISEASE

- ▶ Chronic Lyme disease cannot be excluded by the absence of antibodies against *B. burgdorferi*.
  - ▶ There is evidence of infection in seronegative patients with clinical indications of chronic Lyme disease.
  - ▶ (N Engl J Med 1988; 319:1441–6.)
- 
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**Table 1. Characteristics of Patients Seropositive and Seronegative for Chronic Lyme Disease.**

	SEROPOSITIVE PATIENTS (N = 18)	SERONEGATIVE PATIENTS (N = 17)
Mean age (yr)	36.6 (16–72)	38.0 (10–65)
Sex (M/F)	9/9	11/6
History of ECM	14	15
Initial influenza-like illness	17	17
Initial treatment		
Tetracycline	1	12
Penicillin	1	4
Cephalexin	1	—
Erythromycin	—	1
Duration of illness (mo)*	8.4±2.5 (1–24)	17.6±5.4 (8–72)
Clinical manifestations		
Arthritis	15	12†
Peripheral neuropathy	7	9
Symptoms‡	18	17

\*Period (mean ±SD) from initial illness to diagnosis of chronic Lyme disease.

†Three other patients had a history of arthritis.

‡Includes headaches, fatigue, arthralgia, and cognitive dysfunction.

# SERONEGATIVE CHRONIC LYME DISEASE

# CLINICAL ADVISOR

## MAY 19<sup>TH</sup> 2007

- ▶ The CDC is aware of the insensitivity of the tests for Lyme disease.

Encourages clinicians to use judgment rather than a test result to make the diagnosis

([www.cdc.gov/ncidod/dvbid/lyme/ld\\_humandisease\\_diagnosis.htm](http://www.cdc.gov/ncidod/dvbid/lyme/ld_humandisease_diagnosis.htm). Accessed April 5, 2007).

# CLINICAL ADVISOR

## MAY 19<sup>TH</sup> 2007

- ▶ Since a screening test should have at least 90% sensitivity,
  - ▶ 65% sensitivity of the commercial Lyme ELISA should lead to its reconsideration as an acceptable screening tool.
- 

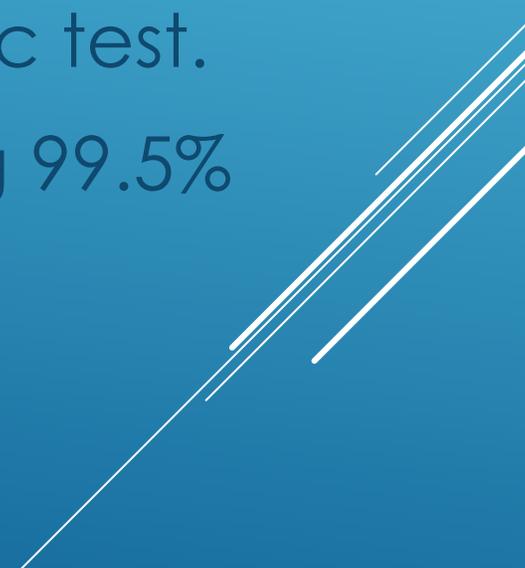
# CLINICAL ADVISOR

## MAY 19<sup>TH</sup>, 2007

- ▶ While the CDC has published strict criteria for positivity on the Western blot to make a more exclusive cohort for epidemiologic purposes,
  - ▶ Never intended for these criteria to be used for diagnosis.
- 

# LYME WARS: LET'S TACKLE THE TESTING

BMJ.2007;335:1008

- ▶ Two-tier approach in Lyme disease patients tested at least 4 to 6 weeks after infection is only 44% to 56%,
  - ▶ Inadequate for a clinical diagnostic test.
  - ▶ Comparison, HIV diagnostic testing 99.5% sensitive
- 

# DEVELOPMENT OF A METABOLIC BIOSIGNATURE FOR DETECTION OF EARLY LYME DISEASE.

*CLIN INFECT DIS. 2015 JUN 15;60(12):1767-75. DOI: 10.1093*

- ▶ Early Lyme disease patients often present to the clinic prior to developing a detectable antibody response.
  - ▶ Thus, existing 2-tier serology-based assays yield low sensitivities (29%-40%) for early infection.
  - ▶ Underscores the need for new diagnostic approaches.
- 

## DEVELOPMENT OF A METABOLIC BIOSIGNATURE FOR DETECTION OF EARLY LYME DISEASE. CONTINUED

- ▶ Metabolic profiling for early Lyme disease can achieve significantly greater ( $P < .0001$ ) diagnostic sensitivity than current 2-tier serology, while retaining high specificity.

# LATE DISSEMINATED LYME DISEASE:

ASSOCIATED PATHOLOGY AND SPIROCHETE PERSISTENCE POSTTREATMENT IN RHESUS MACAQUES

NICHOLAS A. CROSSLAND\*† XAVIER ALVAREZ‡ MONICA E. EMBERS\*†

- ▶ Rare morphologically intact spirochetes were observed in the brains of two treated rhesus macaques.
  - ▶ Chronic Lyme disease symptoms can be attributable to residual inflammation in and around tissues.
- 

# CHRONIC INFECTIONS DUE TO LYME DISEASE

The presence of coinfecting organisms enhance the symptoms and exacerbate the severity of Lyme disease.

Recognition of chronic coinfections supports the concept of unresolved illness due to persistent infection with the Lyme spirochete.

- ▶ *Lyme disease: the next decade*
- ▶ *Raphael B Stricker and Lorraine Johnson*
- ▶ *Infect Drug Resist.* 2011; 4: 1–9.

# CELL WALL DEFICIENT BORRELIA

- ▶ Recent studies have suggested a link between CWD borrelia and neurodegenerative diseases.
- ▶ Resistance of cystic forms to antibiotic therapy has been documented.
- ▶
- ▶ Lyme disease: the next decade. Infect Drug Resist. 2011; 4: 1–9.

# DESTRUCTION OF SPIROCHETE *BORRELIA BURGENDORFERI* ROUND-BODY PROPAGULES (RBS) BY THE ANTIBIOTIC TIGECYCLINE.

- ▶ Recent advances in understanding molecular mechanisms of CWD bacterial formation has offered a glimpse at new treatment approaches to chronic Lyme disease.
- ▶ Proc Natl Acad Sci U S A. 2009;106:18656–18661.

# LYME DISEASE: THE NEXT DECADE

- ▶ Currently the only antibiotic that reliably targets the cyst form of *B. burgdorferi* is metronidazole or its derivatives.
- ▶ Other agents have yielded negative or conflicting treatment results with cysts.
- ▶ Infect Drug Resist. 2011; 4: 1–9.

PLAQUES OF ALZHEIMER'S DISEASE ORIGINATE FROM CYSTS OF *BORRELIA BURGENDORFERI*, THE LYME DISEASE SPIROCHETE.

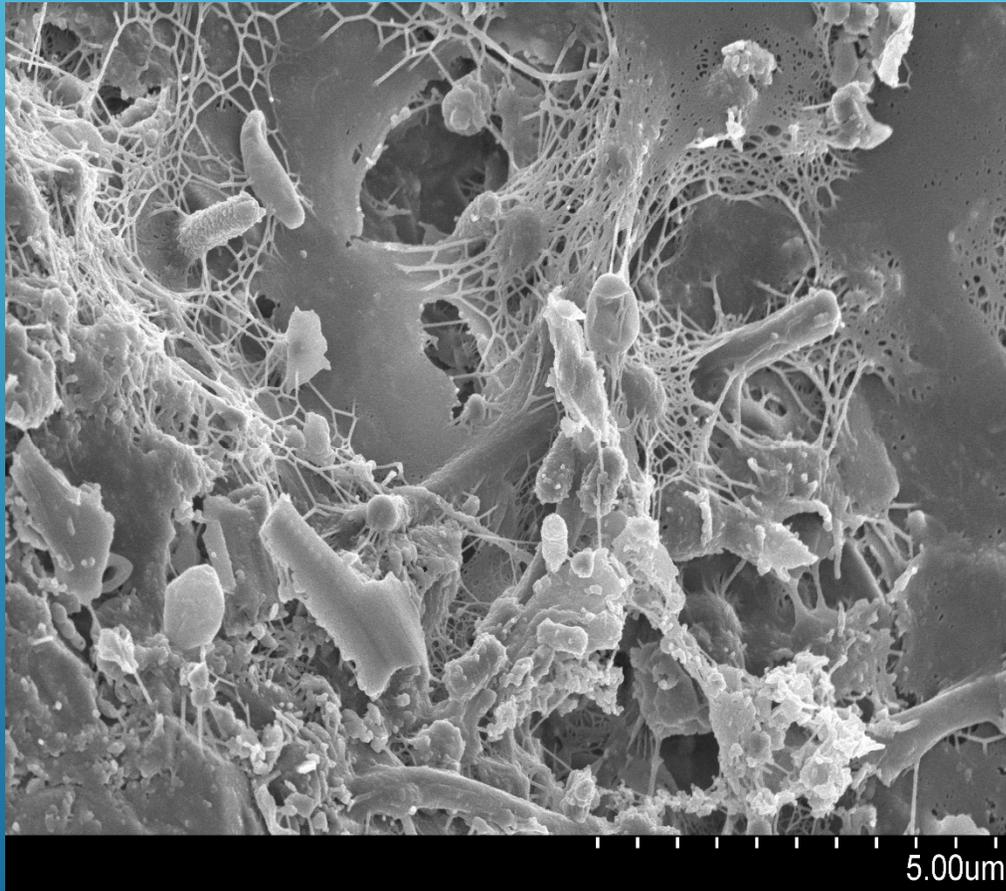
- ▶ Given the potential importance of CWD forms in persistent *B. burgdorferi* infection.
- ▶ Newer antibiotics are desperately needed to eradicate chronic infection in Lyme disease.
- ▶ Med Hypotheses. 2006;67:592–600

## BIOFILM AND CHRONIC LYME DISEASE.

Biofilms are responsible for a number of chronic infections.

These adherent polysaccharide-based matrices protect bacteria from the hostile host environment and facilitate persistent infection.

Microbiol Mol Biol Rev. 2000;64:847-867.

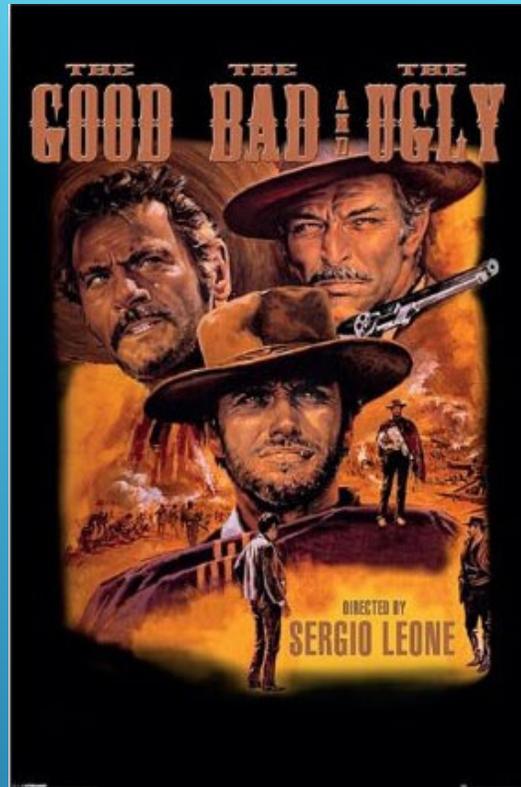


# BIOFILMS OF *BORRELIA BURGENDORFERI* IN CHRONIC CUTANEOUS BORRELIOSIS.

- ▶ Combinations of borrelial cysts and putative biofilms have also been noted in patient skin biopsies
  - ▶ Am J Clin Pathol. 2008;129:989–990.
- 

# THE GENOMICS AND PROTEOMICS OF BIOFILM FORMATION PROCESS

- ▶ To date no antibiotic treatment exists for biofilm formation.
  - ▶ Development of 'designer' antibiotics that interfere with biofilm formation.
  - ▶ Genome Biol. 2003;4:219.
- 



# TREATMENT OF LYME DISEASE THE GOOD, THE BAD AND THE UGLY



**THE BAD**

IDSA Protocols for Treating Lyme Disease

# IDSA GUIDELINES

## Early Lyme Disease

- ▶ Administration of doxycycline in a dosage of 100 mg or amoxicillin 500 mg for 14 to 21 days.
  - ▶ Ridged.
- 
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# IDSA GUIDELINES

## Late Lyme Disease

- ▶ Patients with late neurologic disease affecting the central nervous system should be treated with IV ceftriaxone for two to four weeks.
  - ▶ Alternative parenteral therapy cefotaxime or penicillin G.
  - ▶ Same for children.
- 
- A decorative graphic consisting of several parallel white lines of varying lengths, slanted upwards from left to right, located in the bottom right corner of the slide.

# IDSA GUIDELINES

## Late Lyme Disease

- ▶ Lyme arthritis can usually be treated successfully with oral or IV antimicrobial agents, given for 28 days.
- ▶ The IDSA panel recommends amoxicillin for all children and doxycycline for children eight years and older.
- ▶ Compared with IV antibiotics, oral therapy safer, cheaper.

# IDSA GUIDELINES

## **Chronic Lyme Disease or Post-Lyme Disease Syndrome**

- ▶ IDSA panel reports that there is insufficient evidence to regard “chronic Lyme disease” as a separate diagnostic entity.

# THE INFECTIOUS DISEASES SOCIETY OF AMERICA LYME GUIDELINES: A CAUTIONARY TALE ABOUT DEVELOPMENT OF CLINICAL PRACTICE GUIDELINES

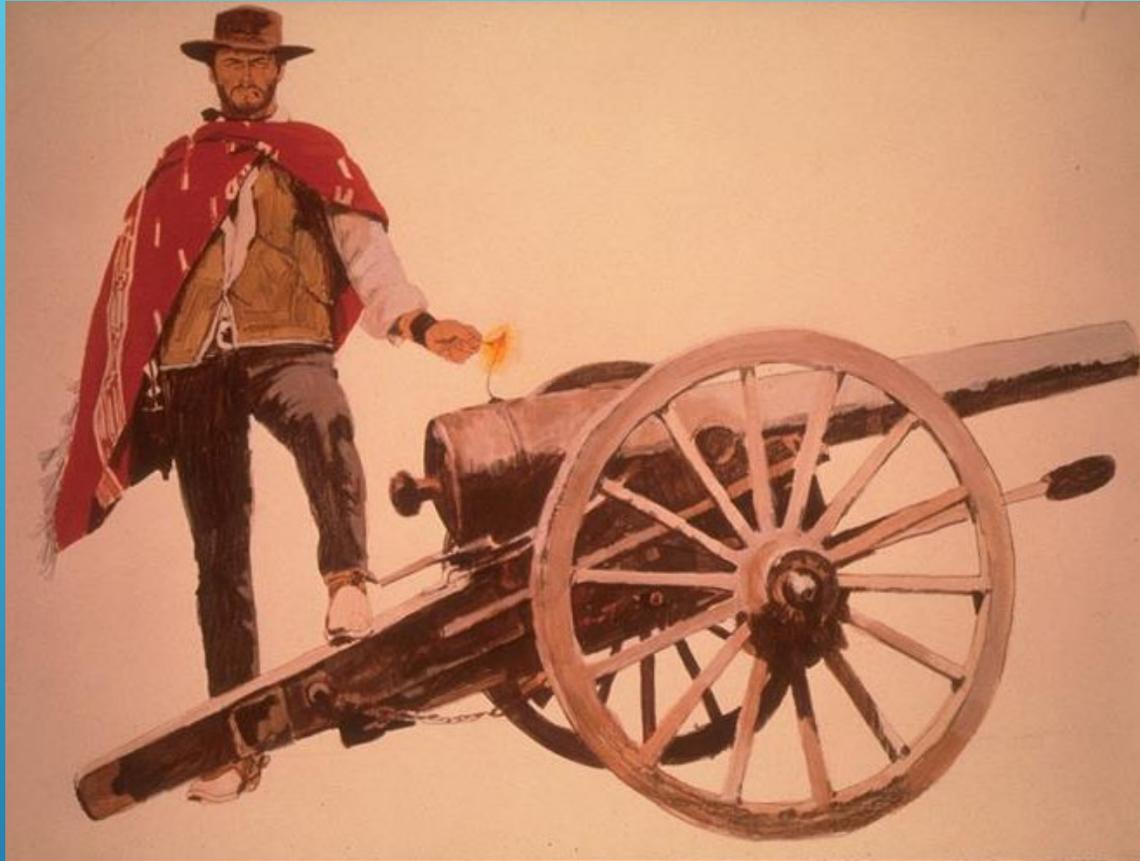
- ▶ The review panel held a hearing in July 2009
  - ▶ 300 peer-reviewed articles and 1600 pages of analysis
  - ▶ Persistent infection despite short-course antibiotic therapy of 2 to 4 weeks.
  - ▶ Philos Ethics Humanit Med. 2010;5:9.
- 

# FINAL REPORT OF THE LYME DISEASE REVIEW PANEL OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA: A PYRRHIC VICTORY?

- ▶ Despite this extensive evidence, the IDSA review panel voted unanimously to uphold the flawed Lyme guidelines.
- ▶ Seven of the eight members of the review panel were members of IDSA.
- ▶ Clin Infect Dis. 2010;51:1108–1109.

# OFFICIAL WORD ON IDSA GUIDELINES' REMOVAL FROM NGC

- ▶ In summary, the IDSA Guidelines were removed because they no longer met the NGC inclusion.”
- ▶ NGC indicates no update within 5 years are removed annually. The date of IDSA's Guidelines was 2006.
- ▶ Lyme Disease Association February 19, 2016



## THE GOOD

ILADS Protocols, Pulse therapy, Adjunct therapies, PTLDS, CIRS

# ILADS GUIDELINES

- ▶ The optimal treatment regimen for the management of known tick bites, has not yet been determined.
  - ▶ Accordingly, it is too early to standardize restrictive protocols.
  - ▶ Fluid
- 

# ILADS GUIDELINES

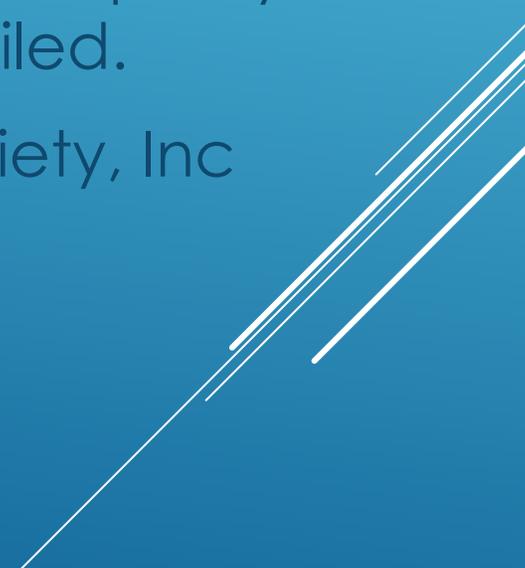
## Treatment Guidelines

- ▶ Given the low success rates in trials treating EM rashes for 20 or fewer days, ILADS recommends that patients receive 4-6 weeks of doxycycline, amoxicillin or cefuroxime.
- ▶ Persistent symptoms and signs of Lyme disease be evaluated for other potential causes before instituting additional antibiotic therapy.
- ▶ ILADS recommends antibiotic retreatment when a chronic Lyme infection is judged to be a possible cause.

# ILADS GUIDELINES

- ▶ Clinical Judgment and Shared Decision-Making
  - ▶ Clinical judgment is crucial to the provision of patient-centered care.
  - ▶ Patient goals and values regarding treatment options be identified and strongly considered during a shared decision-making process.
- 

# TREATMENT OF LYME DISEASE WITH HYPERBARIC OXYGEN THERAPY

- ▶ No cure is claimed by this treatment even though many who have completed the regimen remain essentially well or are much improved.
  - ▶ It is clear that this treatment improves the quality of life after all other treatments have failed.
  - ▶ Undersea and Hyperbaric Medical Society, Inc
- 

# ALTERNATIVES TO TREATMENT OF LYME DISEASE ARE NEEDED

- ▶ Multiple observations have given cause for the concern regarding the ability of antibiotics to completely eradicate *Borrelia* in an infection setting.
  - ▶ Alternatives to treat Lyme disease, and one such approach is bacteriophage (phage) therapy
- 

# METAMORPHOSES OF LYME DISEASE SPIROCHETES: PHENOMENON OF *BORRELIA PERSISTERS*

- ▶ Spirochetes have developed strategies to sense and survive in these diverse environments.
- ▶ Survival is achieved by altering the level of gene expression in response to multiple host and vector dependent factors.
- ▶ *Parasites & Vectors* **volume 12**,  
Article number: 237 (2019)

# METAMORPHOSES OF LYME DISEASE SPIROCHETES: PHENOMENON OF *BORRELIA* PERSISTERS

NATALIE RUDENKO,  
MARYNA GOLOVCHENKO,  
KATERINA KYBICOVA &  
MARIE VANCOVA

PARASITES & VECTORS VOLUME 12, ARTICLE NUMBER: 237 (2019)

- ▶ A combination of two or three drugs from different classes of antibiotics shows significant improvement in eliminating multiple persisters' forms *in vitro*.
- ▶ Pulse dosing treatment shows great potential for eradicating persisters.

# THREE-ANTIBIOTIC COCKTAIL CLEARS 'PERSISTENT' LYME BACTERIA IN MOUSE STUDY

- ▶ Slow-growing variant form of Lyme bacteria caused severe symptoms in a mouse model.
- ▶ The slow-growing variant form, may account for the persistent symptoms seen in ten to twenty percent.
- ▶ Johns Hopkins University Bloomberg School of Public Health. April 23, 2019

# TREATING LYME DISEASE WITH DISULFIRAM

- ▶ Studying the medication **Disulfiram** to see if it will help to reduce persistent **Lyme** disease symptoms.
  - ▶ **Disulfiram**, has been shown in the laboratory setting to be effective in the killing of the bacteria that cause **Lyme** disease.
  - ▶ Columbia University Lyme and Tick Bourne Center, New York, NY
- 
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## AND THE UGLY

Therapies that I've been asked about but have concerns

# THE UGLY

- ▶ **Lyme Disease Offers a Diagnostic Puzzle; Try Malariotherapy**
  - ▶ For 60 years (1918-75) malariotherapy was used successfully to treat the tens of thousands of neurosyphilis patients who filled mental hospitals.
  - ▶ It was originally believed that malarial fever cured neurosyphilis.
- 

## THE UGLY CONTINUED:

### INFECTIONS CAUSED BY RESISTANT ORGANISMS: COULD ORGANIC ARSENIC COMPOUNDS BE AN EFFECTIVE TREATMENT?

- ▶ The age of targeted chemotherapy in 1910 with the discovery of the anti-syphilitic organic arsenic agent, arsphenamine or Salvarsan (also known as 606).
- ▶ Used in treating syphilis until penicillin and other antibiotics were introduced clinically in the 1940s.
- ▶ To suggest their potential for the treatment of infections caused by resistant organisms..

▶ [Warner VD<sup>1</sup>, Soloway AH<sup>2</sup>.](#)

▶ [Med Hypotheses. 2017 Jul;104:78-79. doi: 10.1016/j.mehy.2017.05.026. Epub 2017 May 26.](#)

# LYME DISEASE AND CIRTS CASE 4



Middle age couple doing yard work in Johns Creek, GA, May 2019.

Wife develops myalgias, arthralgias and EM. The husband is asymptomatic.

Treated with doxycycline symptoms resolve.

Husband admitted to ER late July with chest pain and dizziness. MI ruled out

Over the next several months chest pain continues, develops POTS (tilt table confirmed) and complains of brain fog along with myalgias and arthralgias. Chronic diarrhea, *C. difficile* negative x 3.



## LYME DISEASE AND CRIS

Improvement on first doxycycline then minocycline but the patient is still symptomatic. POTS better but still present. Diarrhea persists.

VCS: Fail

C4a TNP unfortunately

MSH 17.2 0-100 working range 35-81

Started on cholestyramine

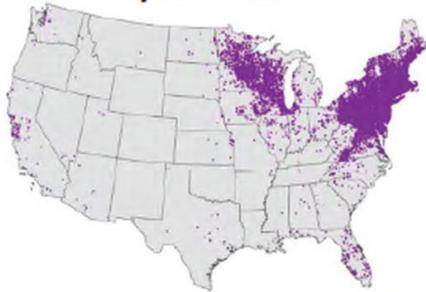
Repeat labs pending COBRA

# OTHER CHRONIC INFECTIONS

And Other Zoonotic Concerns  
Including Viruses, Tourism and  
Biowarfare

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**Lyme disease**



**Anaplasmosis**



**Babesiosis**



**Ehrlichiosis**



**Rocky Mountain Spotted Fever**



**Tularemia**



Each dot represents a reported case in the county of residence

Eisen R. Emerging tickborne diseases. CDC Public Health Grand Rounds, March 21, 2017.  
[www.cdc.gov/cdcgrandrounds/archives/2017/March2017.htm](http://www.cdc.gov/cdcgrandrounds/archives/2017/March2017.htm). Accessed June 7, 2017.

# DISTRIBUTION OF TICK RELATED ILLNESSES IN THE UNITED STATES

# ANAPLASMA PHAGOCYTOPHILUM (ANAPLASMOSIS)

- ▶ Anaplasmosis was formerly named human granulocytic ehrlichiosis (HGE).
- ▶ In 2001, the organism was reassigned to the genus *Anaplasma*.
- ▶ Cases of anaplasmosis have been identified worldwide;
- ▶ Nilmarie Guzman; Sary O. Beidas. Last update Nov. 5<sup>th</sup>, 2019

# ANAPLASMA PHAGOCYTOPHILUM (ANAPLASMOSIS)

- ▶ Anaplasmosis generally presents with nonspecific symptoms such as fever, chills, malaise, headache, and myalgias.
- ▶ On rare occasions, a rash may be present.
- ▶ The patient may also report nonspecific symptoms.
- ▶ Nilmarie Guzman; Sary O. Beidas. Last update Nov 5<sup>th</sup>, 2019.

# ANAPLASMA PHAGOCYTOPHILUM (ANAPLASMOSIS)

- ▶ A low number of patients manifest with life-threatening complications.
- ▶ Immunosuppressed patients are more likely to have a higher risk of suffering severe complications.
- ▶ Occasionally, co-infection with other tick-borne organisms *Ixodes* ticks are the common vector.
- ▶ Nilmarie Guzman; Sary O. Beidas. Last update Nov 5<sup>th</sup>, 2019.

# EVOLUTION OF ANTIGEN VARIATION IN THE TICK-BORNE PATHOGEN ANAPLASMA PHAGOCYTOPHILUM.

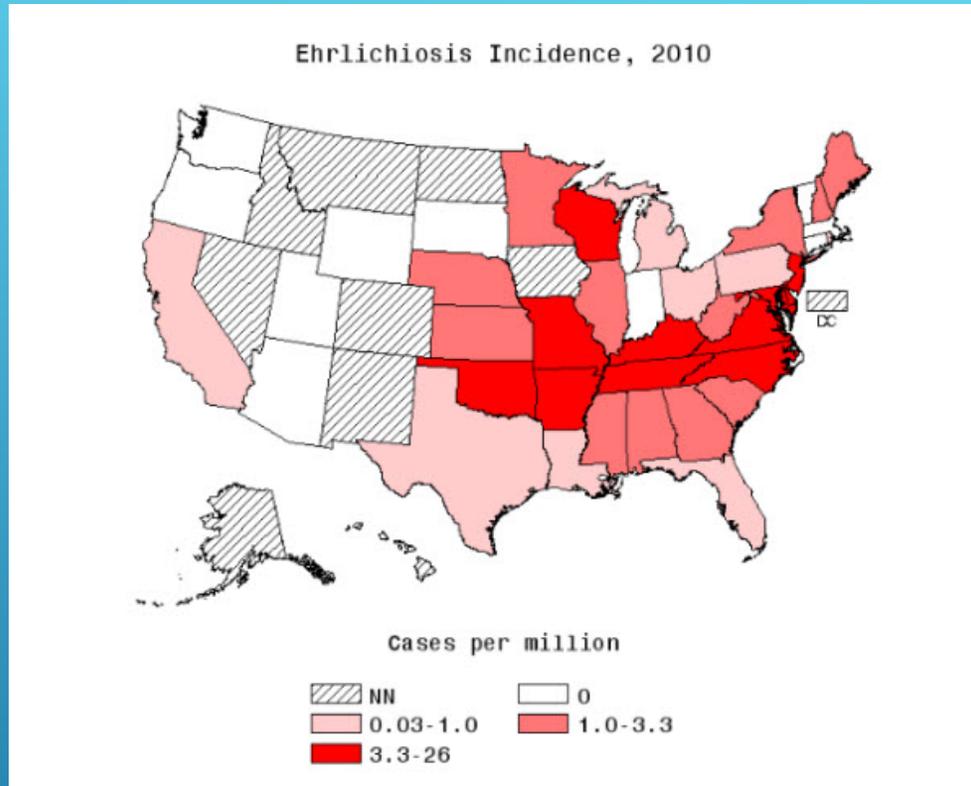
- ▶ A. phagocytophilum may comprise random genetic drift
- ▶ After hosts develop strong adaptive immunity.
- ▶ Mol Biol Evol. 2012 Jan;29(1):391-400.

# EVOLUTION OF ANTIGEN VARIATION IN THE TICK-BORNE PATHOGEN ANAPLASMA PHAGOCYTOPHILUM.

- ▶ Anaplasma phagocytophilum is an obligately intracellular tick-transmitted bacterial pathogen of humans and other animals.
- ▶ A. phagocytophilum utilizes gene conversion, which codes for the major surface antigen and major surface protein 2 (MSP2).
- ▶ Mol Biol Evol. 2012 Jan;29(1):391-400.

# EHRlichia

- ▶ Ehrlichia is a genus of Rickettsiales bacteria that are transmitted to vertebrates by ticks. These bacteria cause the disease ehrlichiosis, which is considered zoonotic, because the main reservoirs for the disease are animals.



# ERLICHIOSIS INCIDENCE CHART 2010

# PHASES OF EHRLICIA

- ▶ Acute Phase
  - ▶ Fever, chills
  - ▶ Severe headache
  - ▶ Muscle aches
  - ▶ Nausea, vomiting, diarrhea, loss of appetite
  - ▶ Confusion
  - ▶ Rash (more common in children)
- 
- A decorative graphic consisting of several parallel white lines of varying lengths, slanted upwards from left to right, located in the bottom right corner of the slide.

# PHASES OF EHRLICIA

- ▶ Chronic or Late
  - ▶ Damage to the brain or nervous system (e.g. inflammation of the brain and surrounding tissue (called meningoencephalitis))
  - ▶ Respiratory failure
  - ▶ Uncontrolled bleeding
  - ▶ Organ failure
  - ▶ Death
- 



## CASE 5

38 year old female presents with low grade fever, myalgias, arthralgias and sinus congestion.

Dx Viral Syndrome

Labs WBC 2.8, Plt 100k



## CASE 5

Symptoms worsened

Returns with husband

Admitted, started on IV  
doxycycline

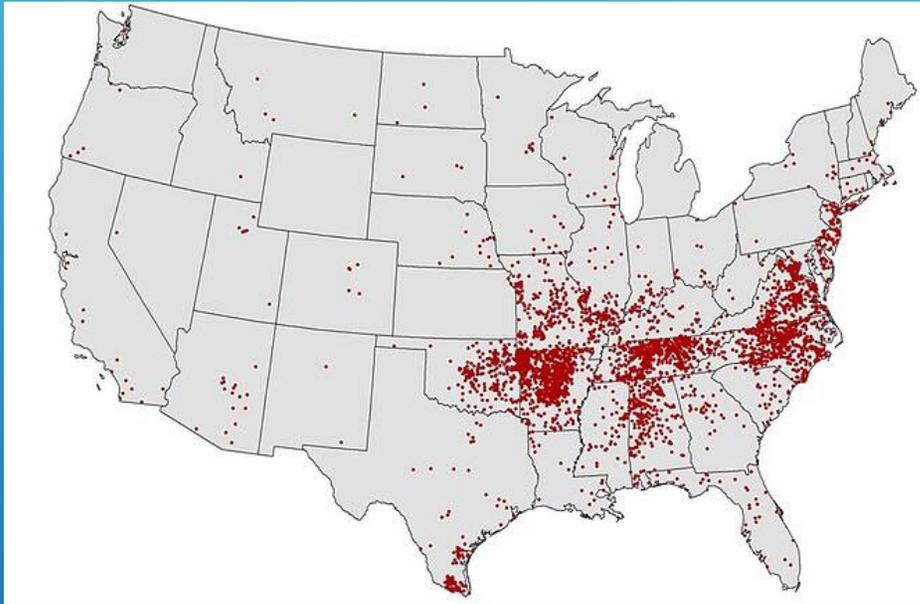
LP WBC 25 predominant  
Lymphs, N glucose, elevated  
protein

Ehrlichia titers in CSF 1:1056

# ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

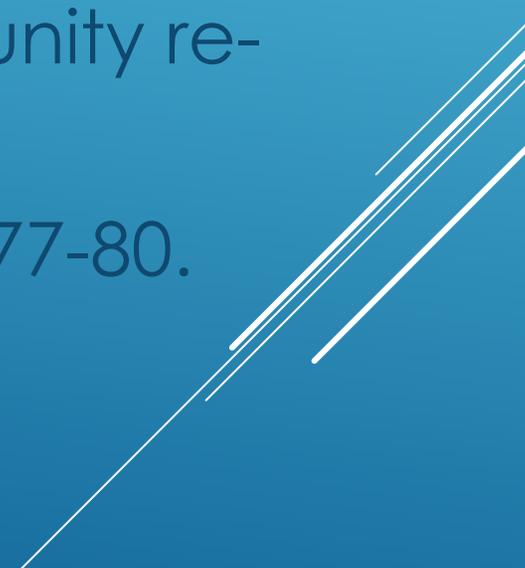
- ▶ RMSF is a bacterial disease spread by ticks. It typically begins with a **fever** and headache,
  - ▶ The rash is generally made up of small spots of bleeding and starts on the wrists and ankles.
- 
- A decorative graphic consisting of several parallel white lines of varying lengths, slanted upwards from left to right, located in the bottom right corner of the slide.

# RMSF DISTRIBUTION



There's more  
RMSF east of the  
Mississippi than in  
the Rocky  
Mountains

# PERSISTING IMPAIRMENT FOLLOWING ROCKY MOUNTAIN SPOTTED FEVER: A CASE REPORT

- ▶ Long term impairments associated with, RMSF
  - ▶ Developing rehabilitation care plans and in assisting such patients with community re-entry.
  - ▶ Arch Phys Med Rehabil 1997;78:1277-80.
- 
- A decorative graphic consisting of several parallel white lines of varying lengths, slanted diagonally from the bottom right towards the top right, set against the blue background.

# CASE 6



35 year old electrician rewiring an older house in Gwinnett County Friday and Saturday.

Saturday night wife finds an engorged tick between the scapula and is removed.

Sunday night in the ER with fever to 102, headache and joint pain. Unable to detect rash patient is African-American

Labs WBC 1.8K 50% neutrophils 50% lymphocytes

Plt 25K

Lyme serology negative

DDx Ehrlichia, RMSF, Anaplasma

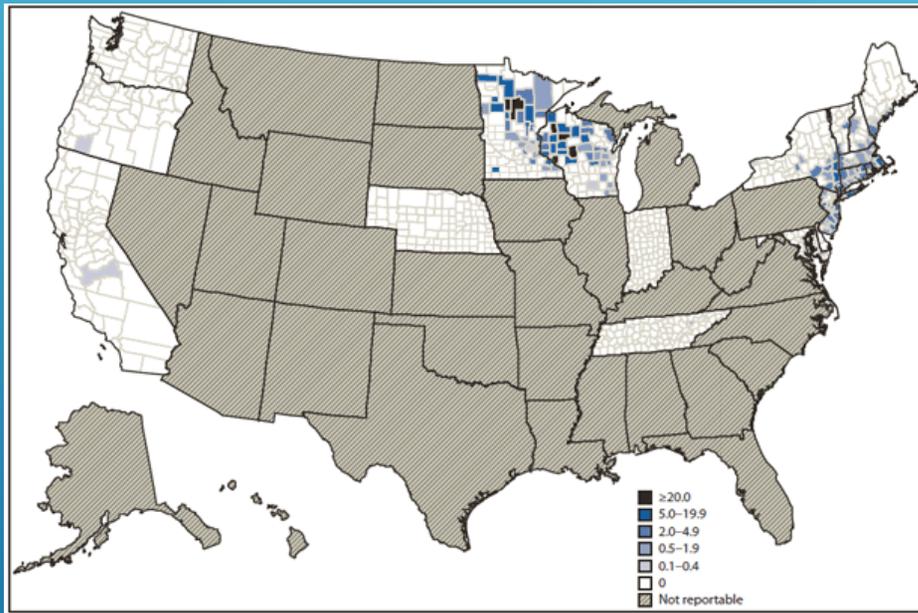
Admitted responded well to IV doxycycline

All serologies subsequently negative

**Babesiosis** is a rare, sometimes severe, disease caused by the bite of a tick infected with **Babesia microti**, a microscopic (tiny, not seen without a microscope) parasite that infects red blood cells.



# BABESIOSIS OCCURRENCES

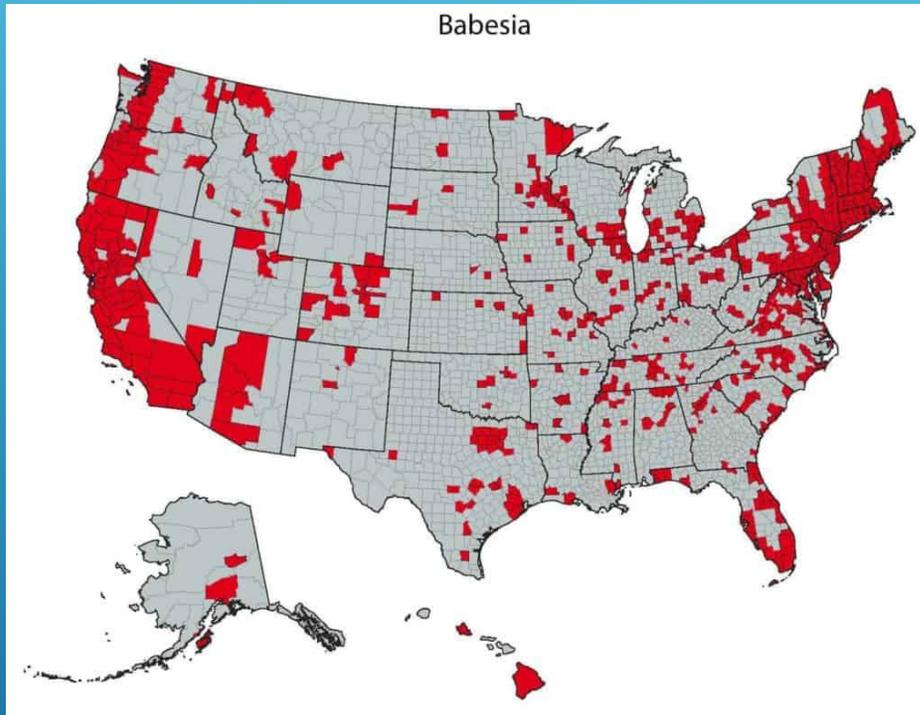


Human babesiosis is infrequent and occurs in limited geographic locations.

It is usually an asymptomatic infection in healthy individuals.

Several groups of patients become symptomatic.

The disease most severely affects patients who are elderly, immunocompromised, or asplenic.



Babesiosis is difficult to diagnose.

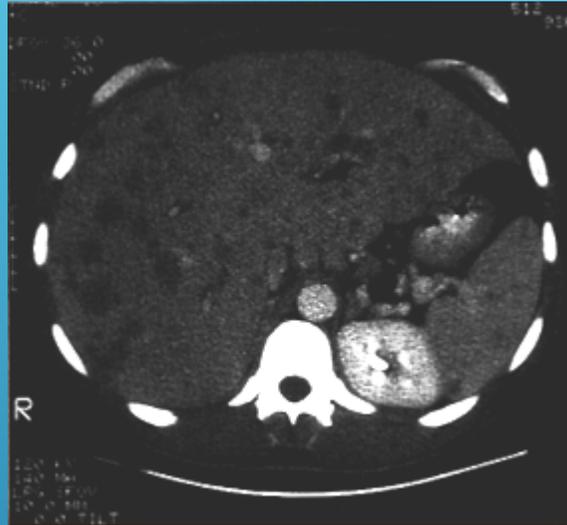
Patients with babesiosis have few, if any, localizing signs to suggest the disease.

Confirmation of the diagnosis depends on the degree of parasitemia and the expertise and experience of the laboratory personnel.

Courtesy of Ignex.



BACILLARY ANGIOMATOSIS  
DUE TO BARTONELLA HENSELEA



*BARTONELLA HENSELAE*/BACILLARY  
ANGIOMATOSIS:  
HEPATOSPLENOMEGALY IN PELIOSIS  
HEPATICIS

# RECOMMENDATIONS FOR TREATMENT OF HUMAN INFECTIONS CAUSED BY *BARTONELLA* SPECIES

- ▶ *Bartonella* infections present a unique treatment challenge.
- ▶ Intraerythrocytic phase that apparently provides a protective niche for the bartonellae.
- ▶ Antimicrobial Agents and Chemotherapy  
48.6.1921-1933.2004

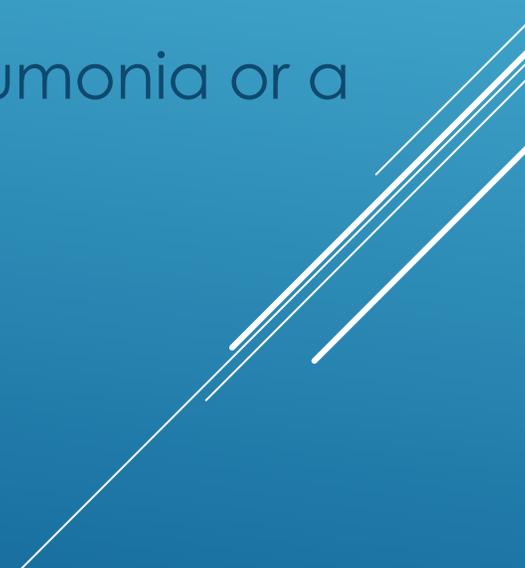
# RECOMMENDATIONS FOR TREATMENT OF HUMAN INFECTIONS CAUSED BY *BARTONELLA* SPECIES

- ▶ The extreme diversity of disease manifestations is dependent on the infecting species of Bartonella and on the immune status of the patient.
  - ▶ Antimicrobial Agents and Chemotherapy  
48.6.1921-1933.2004
- 
- A decorative graphic consisting of several parallel white lines of varying lengths, slanted upwards from left to right, located in the bottom right corner of the slide.

# RECOMMENDATIONS FOR TREATMENT OF HUMAN INFECTIONS CAUSED BY *BARTONELLA* SPECIES

- ▶ Treatment of Bartonella infections should be adapted to each clinical situation.
- ▶ Whether the disease is in the acute or the chronic form
- ▶ Antimicrobial Agents and Chemotherapy  
48.6.1921-1933.2004.

# TULAREMIA

- ▶ **Tularemia**, also known as rabbit fever, is an infectious disease caused by the bacterium *Francisella tularensis*.
  - ▶ Symptoms may include fever, skin ulcers, and enlarged lymph nodes.
  - ▶ Occasionally, a form that results in pneumonia or a throat infection may occur.
- 

Typical presentation of Tularemia is usually a hunter or trapper of small animals such as rabbits, squirrels that present with fever lymphadenopathy and skin ulcers.



shutterstock.com • 636931879

# TULAREMIA



Groundskeepers with big powerful lawn mowers presenting with a sore throat or atypical pneumonia.

## CASE 7



Breaking up a fight between the patient's kitty and a feral cat in the backyard. Was scratched by both cats. Presents to the ER with fever, tender lymph adenopathy and skin ulcer.

Responded well to IV then oral doxycycline

Tularemia diagnosis confirmed by positive blood culture.

The patient was also treated for rabies and her cat was cleared after observation.

# BRUCELLOSIS AND INTERNATIONAL TRAVEL.

- ▶ The clinical presentation can vary from asymptomatic infection with seroconversion to a full-blown clinical picture of fever, night sweats and joint manifestations
- ▶ Since travelers may be affected, travel health physicians need to know the clinical presentation.
- ▶ J Travel Med. 2004 Jan-Feb;11(1):49-55.

# CHRONIC BRUCELLOSIS AND PERSISTENCE OF *BRUCELLA MELITENSIS* DNA

- ▶ After acute brucellosis infection, symptoms persist in a minority of patients for more than 1 year.
- ▶ Patients may suffer delays in both diagnosis and treatment.
- ▶ Journal of Clinical Microbiology May 6<sup>th</sup>, 2009

# SYMPTOMS OF CHRONIC BRUCELLOSIS

- ▶ With the **chronic** form of **brucellosis**, in which the illness has lasted longer than 1 year
  - ▶ An afebrile pattern is typical, with a history of myalgia, fatigue, depression, and arthralgias.
  - ▶ **Chronic** fatigue syndrome is the most important disease in the differential diagnosis.
- 

## CASE 8 CUTANEOUS ANTHRAX



College professor of history with an expertise in Westward Expansion, American Frontiersman.

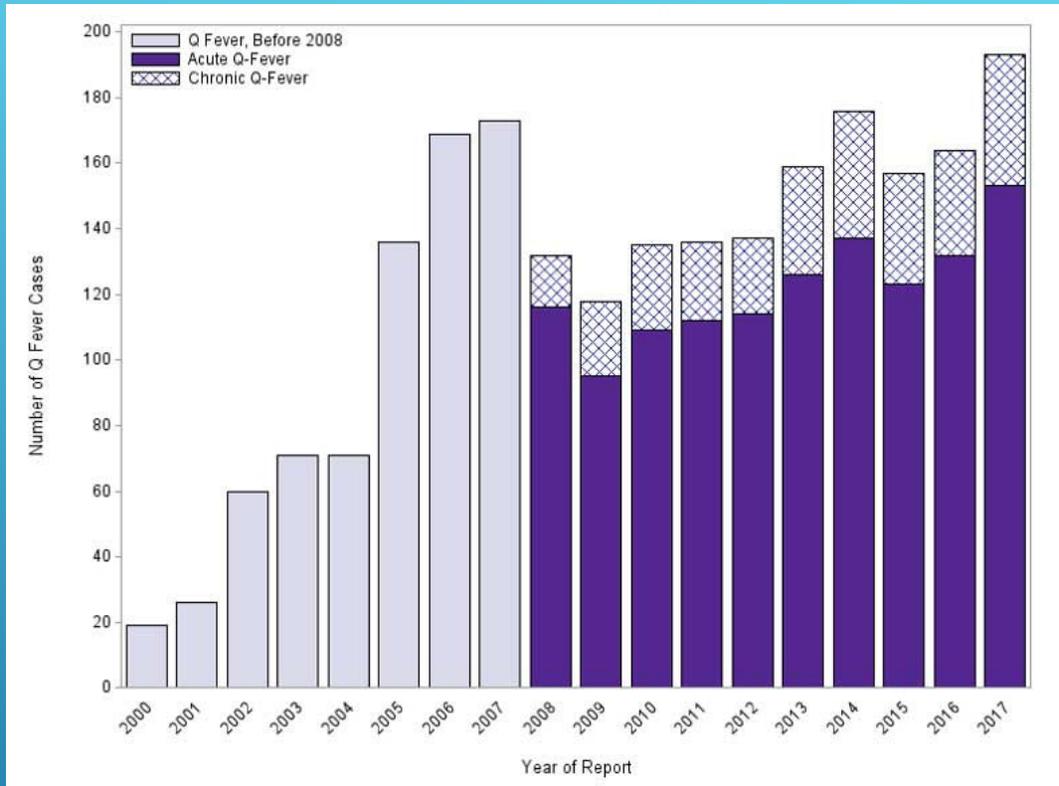
Hunting deer with flintlock rifle and harvesting the animal was part of the college course.

## RISK FACTORS ASSOCIATED WITH THE OCCURRENCE OF ANTHRAX OUTBREAKS IN LIVESTOCK IN THE COUNTRY OF GEORGIA: A CASE-CONTROL INVESTIGATION 2013-2015

- ▶ Anthrax is considered endemic in livestock in Georgia.
  - ▶ Due to increase in human outbreaks associated with livestock handling, there is a need to find out the risk factors of livestock anthrax in Georgia.
  - ▶ RESEARCH ARTICLE PUBLISHED MAY 2<sup>ND</sup>, 2019.
- 

# AIRBORNE GEOGRAPHICAL DISPERSAL OF Q FEVER FROM LIVESTOCK HOLDINGS TO HUMAN COMMUNITIES: A SYSTEMATIC REVIEW AND CRITICAL APPRAISAL OF EVIDENCE

- ▶ Q fever is a zoonotic disease caused by *Coxiella burnetii*. This bacterium survives harsh conditions.
- ▶ Attaches to dust, suggesting environmental dispersal is a risk factor for outbreaks.
- ▶ Human cases without occupational exposure are increasing worldwide.
- ▶ *BMC Infectious Diseases* **volume 18**, Article number: 218 (2018)



# NUMBER OF ANNUAL Q FEVER CASES, 2000-2017.



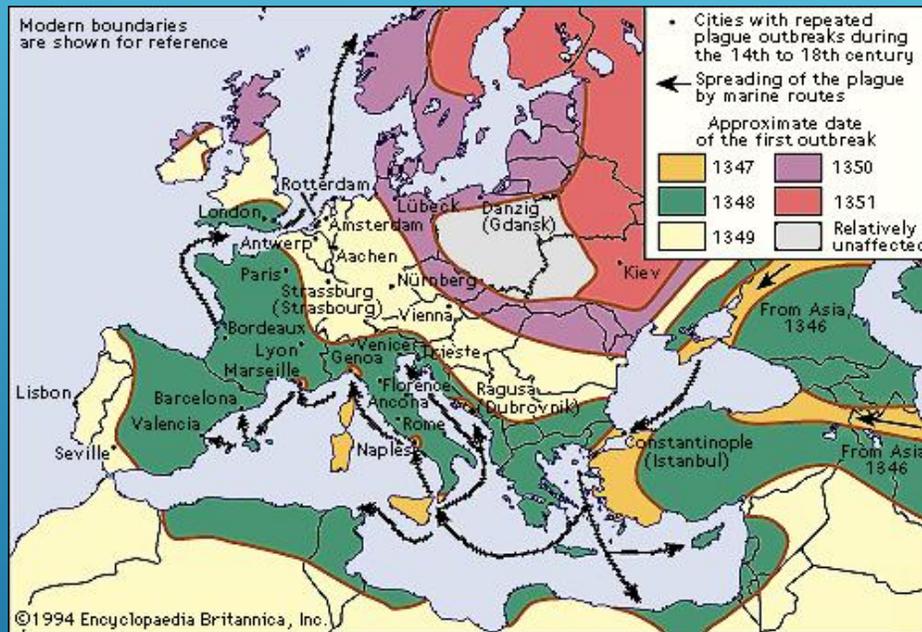
PLAGUE

# PLAGUE IN THE MIDDLE AGES

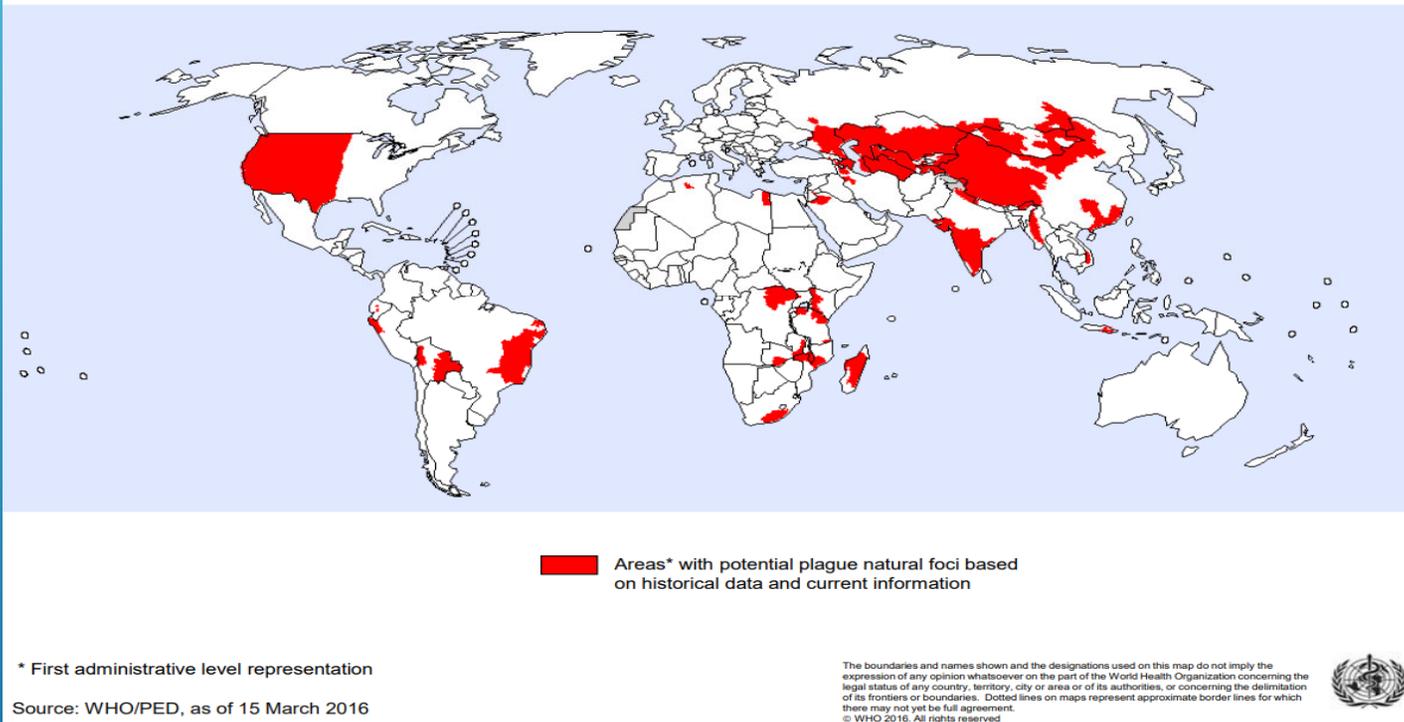
## The Black Death

One of the most devastating pandemics in human history

Estimated 75 to 200 million people in Eurasia, peaking in Europe from 1347 to 1351.



## Global distribution of natural plague foci as of March 2016



# YERSINIA PESTIS

# OUTBREAK OF LEPTOSPIROSIS AMONG ADVENTURE RACE PARTICIPANTS IN FLORIDA, 2005

- ▶ On 21 November 2005, a 32-year-old male resident of New York was hospitalized with suspected leptospirosis.
- ▶ Participated in an endurance-length swamp race on 4-5 November 2005 outside of Tampa, Florida
- ▶ Clinical Infectious Diseases 50(6):843-9 · February 2010.

# LEPTOSPIROSIS IN FLORIDA: RECREATIONAL EXPOSURES HERALD NEW SEROVARS AND HIGHLIGHT ENVIRONMENTAL IMPACT

- ▶ **Synopsis:** Forty-four (23%) of 192 adventure race participants in a 2005 Florida event developed suspected leptospirosis.
- ▶ Serologic testing positive in 45% of the tested individuals.
- ▶ Outbreaks of leptospirosis have become more commonly associated with adventure travel and sports activities.
- ▶ Clin Infect Dis. 2010;50:843-849.

# LEPTOSPIROSIS IN HUMANS

- ▶ Thirty percent of affected people may suffer chronic leptospirosis syndrome.
- ▶ Characterized by weakness, muscle pain, and headaches.

[Curr Top Microbiol Immunol. 2015; 387: 65–97.](#)

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# LEPTOSPIROSIS - CAN IT BE A SEXUALLY TRANSMITTED DISEASE?

- ▶ Summary: Person to person spread of leptospirosis has not been previously reported.
- ▶ Cases occurring in a man and wife which tantalisingly raise this possibility.
- ▶ Postgraduate Medical Journal (1988) 64, 163-164

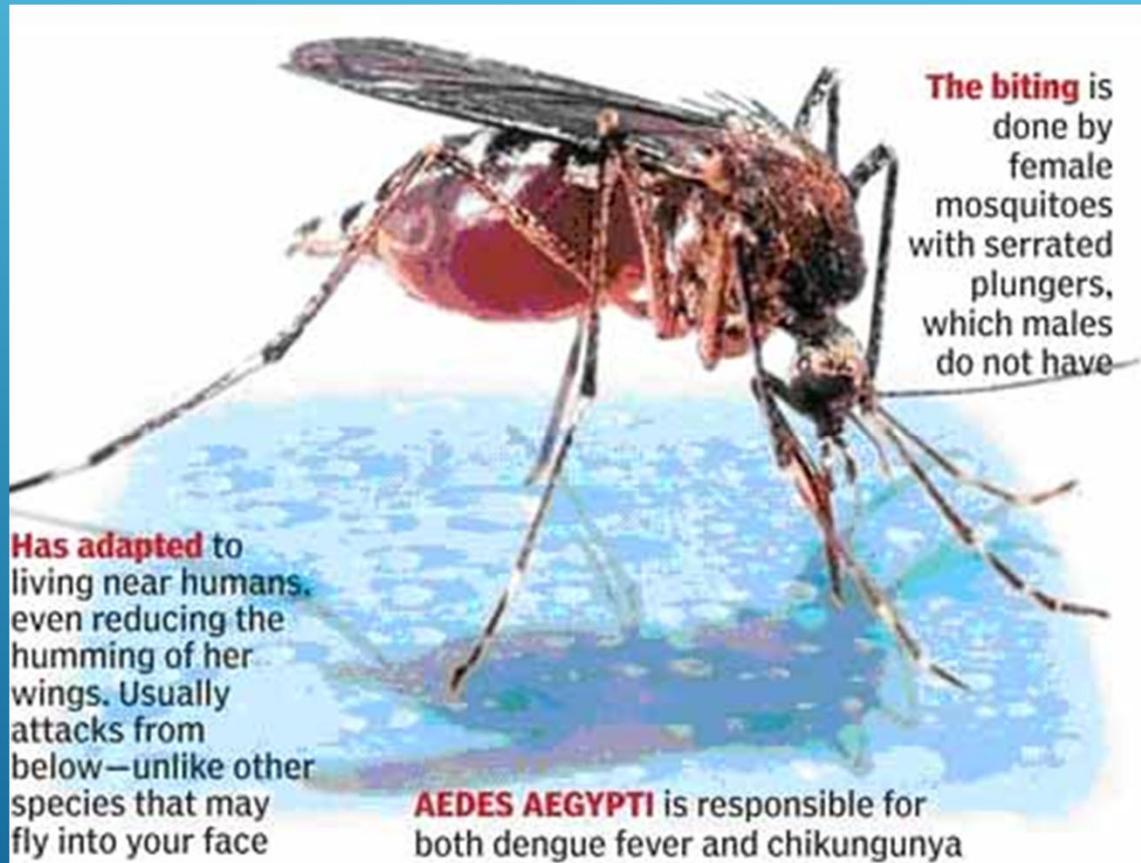
Biologic agent	Disease caused by the agent
Bacillus anthracis	Anthrax
Clostridium botulinum toxin	Botulism
Yersinia pestis	Plague
Variola major	Smallpox
Francisella tularensis	Tularemia
Filoviruses (for example, Ebola, Marburg) and arenaviruses (for example, Lassa, Machupo)	Viral hemorrhagic fevers
Brucella species	Brucellosis
Epsilon toxin of Clostridium perfringens	Food poisoning
Salmonella species, Escherichia coli O157:H7, Shigella	Food poisoning
Burkholderia mallei	Glanders
Burkholderia pseudomallei	Melioidosis
Chlamydia psittaci	Psittacosis
Coxiella burnetii	Q fever
Ricinus communis (castor beans)	Ricin toxin poisoning
Staphylococcal enterotoxin B	Food poisoning

# BIOTERRORISM AGENTS AND THE DISEASES THEY CAUSE

# BIOTERRORISM AGENTS AND THE DISEASES THEY CAUSE

<i>Rickettsia prowazekii</i>	Epidemic typhus
<i>Vibrio cholerae</i>	Cholera
<i>Cryptosporidium parvum</i>	Cryptosporidiosis
Alphaviruses (for example, Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis) and flaviviruses (for example, West Nile encephalitis, Saint Louis encephalitis, dengue fever)	Viral encephalitis
Influenza virus	Influenza
<i>Mycobacterium tuberculosis</i>	MDR TB and XDR TB

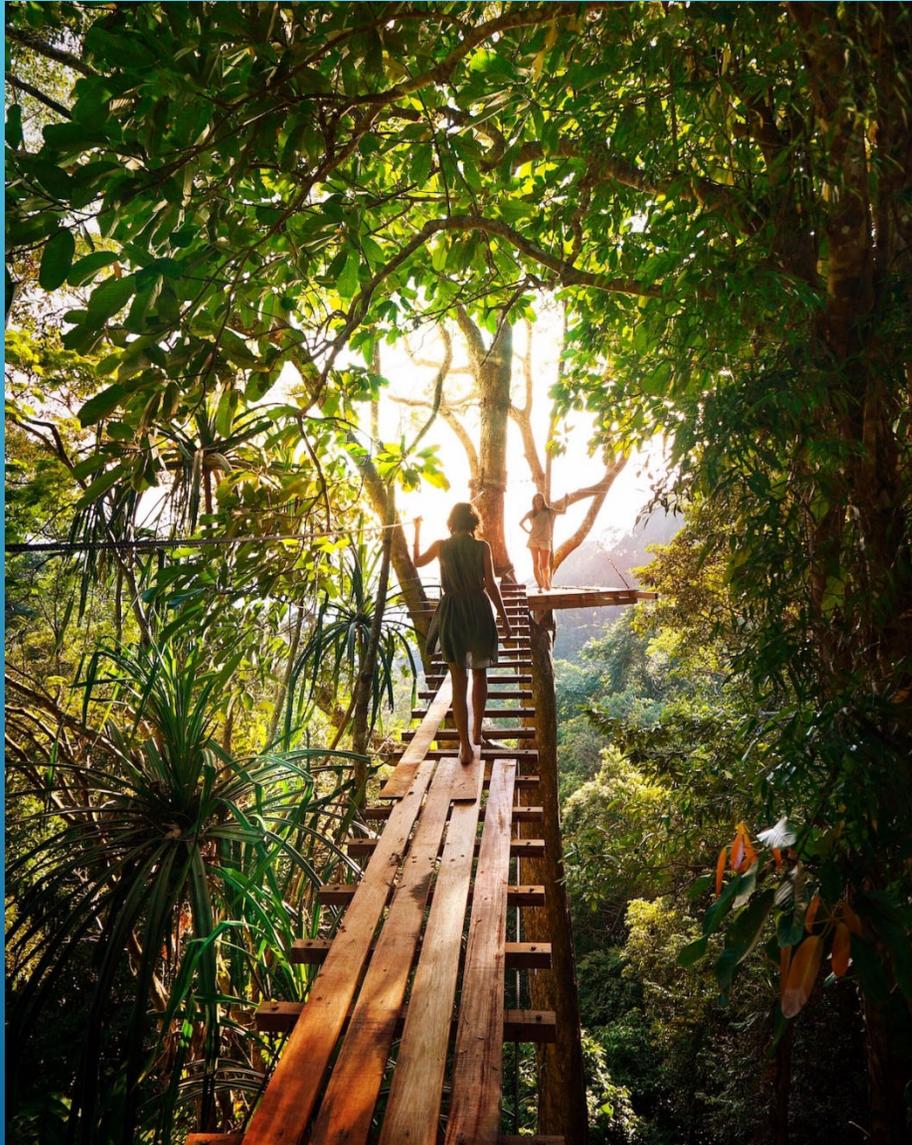
# VIRUSES AND TOURISM



**The biting** is done by female mosquitoes with serrated plungers, which males do not have

**Has adapted** to living near humans, even reducing the humming of her wings. Usually attacks from below—unlike other species that may fly into your face

**AEDES AEGYPTI** is responsible for both dengue fever and chikungunya



## CASE 9

15 year old female on a cruise in the Caribbean visits an eco-park in Honduras. Upon return to the United States, fever to 101, severe arthralgias and nausea.

Working diagnosis:  
Chikungunya

Serologies negative

Still with fluctuating symptoms

Repeat serologies are pending.

## CHRONIC JOINT PAIN 3 YEARS AFTER CHIKUNGUNYA VIRUS INFECTION LARGELY CHARACTERIZED BY RELAPSING-REMITTING SYMPTOMS

- ▶ Of the initial 500 patients enrolled in the study, 482 had serologically confirmed chikungunya infection.
- ▶ 123 patients reported joint pain 20 months after infection, and 54% of those patients reported continued joint pain 40 months after infection.
- ▶ The Journal of Rheumatology July 2019, jrheum.190162;

# ZIKA VIRUS

For anyone who plans to travel to **Zika-affected areas**, avoiding mosquito bites is the best way to avoid exposure to the virus.



Zika virus is primarily spread through the **BITE OF INFECTED MOSQUITOS.**

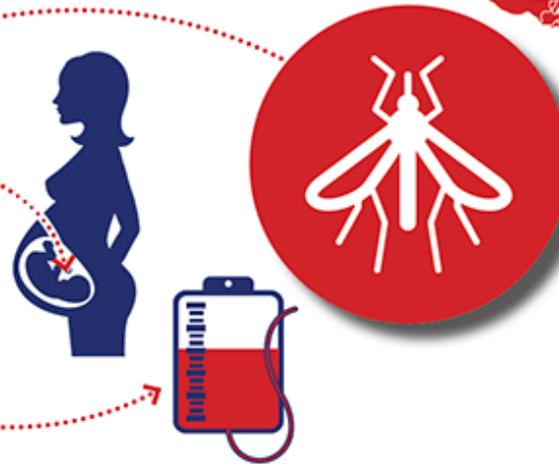
## **MOTHER-TO-BABY & SEXUAL ACTIVITY**

If a pregnant woman is bitten by an infected mosquito, the infection can cross the placenta, infecting the fetus.

The virus can also be transmitted sexually.

## **TRANSFUSION**

The virus can also be transmitted through blood transfusion or laboratory exposure.



# ZIKA VIRUS

# RABIES CASE 10



36 year old scuba enthusiast. Diving trip to Aruba. Several bats seen in the place they were staying. Possible bite. Elected to go through vaccine protocol.

# WOMAN DIES FROM RABIES AFTER RESCUING PUPPY WHILE ON VACATION



A Norwegian **woman** has died after contracting **rabies** from a stray puppy in the Philippines. Birgitte Kallestad, 24, was on holiday with friends when they found the puppy on a street, her family said in a statement. The puppy is thought to have infected her when it bit her after they took it back to their resort.  
May 10, 2019

# BATS IN THE BEDROOM CAN SPREAD RABIES WITHOUT AN OBVIOUS BITE

An elderly woman died and more than two dozen people were treated for possible rabies exposure after her family failed to realize that a nighttime encounter with a bat put her at risk of rabies.

Last August, the woman awoke in her Wyoming home and felt a bat on her neck. She swatted it away and washed her hands. Her husband captured the bat with gloved hands and released it outside.

The woman didn't seem to have any bite wounds, so the couple didn't call a doctor, according to an account of the incident published Thursday in the Centers for Disease Control and Prevention's *Morbidity and Mortality Weekly Report (MMWR)*.



# CURRENT EVENTS TO PONDER

## Fast facts on pandemics

Here are some key points about pandemics.

Pandemics are usually caused by a novel infectious agent, an infectious agent that is newly capable of spreading rapidly, or both.

The death toll in a pandemic is generally higher than that in an epidemic.

The Spanish flu was the worst pandemic in history, killing 100 million people.

Increased travel and mobility have increased the likelihood of new diseases spreading.

Antibiotic resistance increases the risk of future pandemics.



# CHRONIC WASTING DISEASE (CWD)

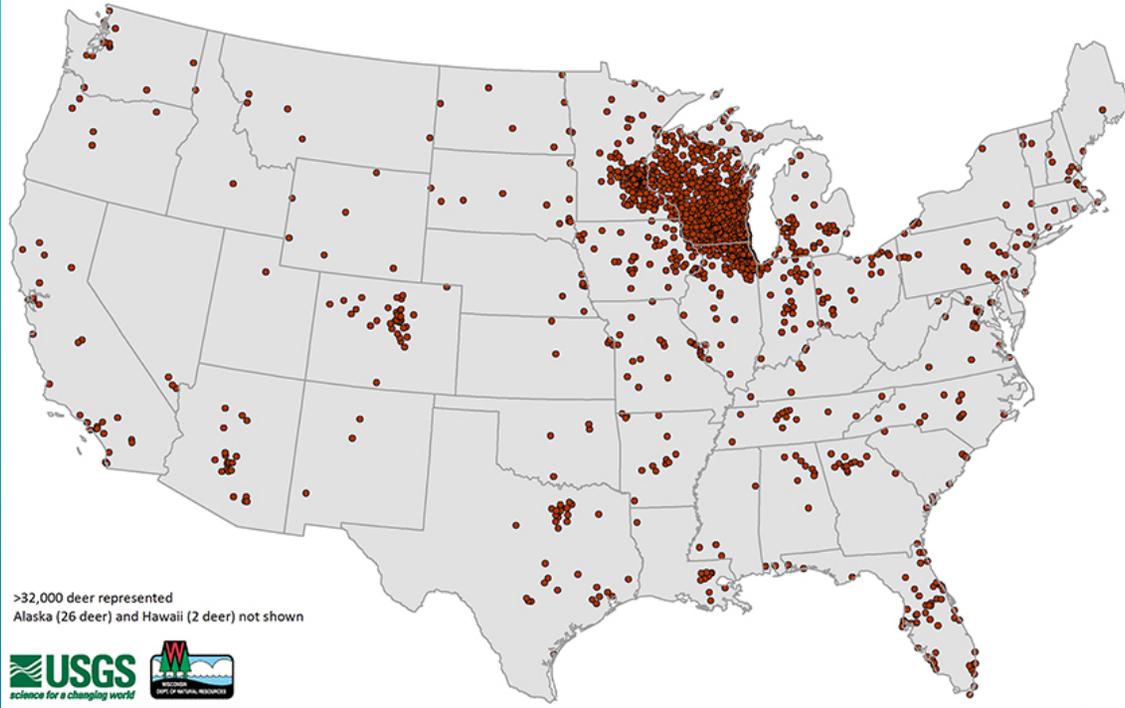


CWD belongs to a family of diseases called transmissible spongiform encephalopathies (TSEs).

Similar diseases include Mad Cow Disease in cattle, CJD in humans, and scrapie in sheep.

### Home Zip Codes of hunters harvesting deer in Dane, Iowa, Richland and Sauk Counties, Wisconsin, 2016-2017

Data: Wisconsin Department of Natural Resources



# CWD DISTRIBUTION

# CORONAVIRUS

- ▶ Coronavirus outbreak: China quarantines 20 million as more cities are contained to stem the spread.

# NOVEL CORONAVIRUS 2019-NCOV: EARLY ESTIMATION OF EPIDEMIOLOGICAL PARAMETERS AND EPIDEMIC PREDICTIONS

- ▶ Our model suggests that travel restrictions from and to Wuhan city are unlikely to be effective in halting transmission across China;
  - ▶ With a 99% effective reduction in travel, the size of the epidemic outside of Wuhan may only be reduced by 24.9% on 4 February.
  - ▶ Unpublished data 1/24/20.
- 

# CLINICAL PEARLS

- ▶ Trust your clinicals
  - ▶ Realize exposure can occur in the backyard or at home
  - ▶ Treatment may be long and labor intensive
  - ▶ Tailor therapy to the individual because presentation and response will probably vary
- 

THANK YOU





QUESTIONS