

Comparison of Lyme Disease in the United States and Europe

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Adriana Marques. She's chief of Lyme Disease Studies at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. We'll be discussing Lyme disease and how it differs between the U.S. and in Europe.

Welcome, Dr. Marques.

[Adriana Marques] Well, hi Sarah. Thanks for having me on the program.

[Sarah Gregory] I think most people have heard about Lyme disease by now. Why does it seem to get so much more media coverage than other tickborne diseases?

[Adriana Marques] Well, it is well deserved. Lyme disease is the most common tickborne disease in the United States, accounting for over 80% of the reported cases.

[Sarah Gregory] In your study, you compared Lyme disease in the United States and in Europe. How common is Lyme disease in both of these places?

[Adriana Marques] Well, very common. There are estimates of nearly 476,000 cases of Lyme disease diagnosed and treated per year in the U.S. and over 200,000 cases per year in western Europe.

[Sarah Gregory] Are there certain regions where it occurs more often? I recently did a podcast about Lyme disease in treeless Scotland. That was amazing and disturbing.

[Adriana Marques] Most cases of Lyme disease in the U.S. occur in the mid-Atlantic, Northeast, and Upper Midwest regions. And in Europe, the incidence of Lyme disease is highest in the Scandinavian and Baltic states in the north. And in central Europe, Austria, Czech Republic, Germany, and Slovenia have high incidence of Lyme disease. But in all areas, Lyme disease is spreading and increasing both in the geographic area as well as the density of cases in the areas affected.

[Sarah Gregory] Is Lyme transmitted only during certain times of the year?

[Adriana Marques] Well most cases of Lyme disease occur during the summer because that is when the immature stage of the tick (which are called a nymph) are the most active. Nymphs are very, very tiny. They are size of a poppy seed and of course is very difficult for people to see and most people will not feel a tick bite. Therefore the incidence of Lyme disease is greatest during the months where the nymphs are most active, and these are June and July. Adult ticks are a little bigger. They are size of a sesame seed and so they are a little bit easier to see, and they are encountered most often in the spring and in the fall and they usually will be...deer ticks usually become inactive in cold weather. But if an adult female deer tick...they have not fed until the end of the fall, they can become active when you get a warm-up spell in the winter. So whenever the temperature rises and remains above freezing (to about 40 degrees) for some time, ticks can become active again. So it could be transmitting other times, but most of the cases will occur during the summertime.

[Sarah Gregory] How many different kinds of ticks carry Lyme disease?

[Adriana Marques] Well in the United States, most infections are transmitted by the bite of the black-legged tick or the deer tick (which is *Ixodes scapularis*) that transmits most of the infections. In the west coast, *Ixodes pacificus*—this western black-legged tick—is the most important vector. In Europe, *Ixodes ricinus*—which is also called the castor bean tick—is the primary vector for human transmission, and *Ixodes persulcatus* (the tiger tick) is also the source of infection in some regions in Europe and most of infections in Russia and parts of Asia.

[Sarah Gregory] Does transmission of Lyme happen right away after being bitten?

[Adriana Marques] No. The tick has to attach and start feeding. They have to be attached for about 36–48 hours or more before the Lyme disease spirochete can be transmitted.

[Sarah Gregory] So what are the symptoms of Lyme disease?

[Adriana Marques] Well the early signs and symptoms...the first sign is the erythema migrans rash. That rash, which occurs at site of the tick bite, about 70–80% of the cases may see the rash. It's an average of about seven days from the bite. The rash itself usually has few local symptoms and will gradually expand, and they can get quite big. Now most of the rashes in the United States are all red. Sometimes they will clear and enlarge, and you can see the target of bull's-eye rash appearance. But most of the rashes are just red, and sometimes they will have the site of the bite (which we call the punctum) at the center of the rash.

But in the United States, many patients will also have systemic symptoms of fever, chills, headaches, fatigue, muscle and joint pain. And these symptoms can occur in the absence of the rash or sometimes before the rash. From that site of the bite after some time, the bacteria can disseminate and cause other manifestations including multiple erythema migrans rashes in other areas of the body and it can also affect the nervous system, the heart, and the joints.

[Sarah Gregory] Why did you want to examine this comparison between the U.S. and Europe?

[Adriana Marques] I always thought it was a very interesting topic because they reflect difference into the pathogenesis of Lyme disease. And understanding the various mechanisms underlying the infection and how these different factors play a role in the disease, including the ability of the bacteria to disseminate and persist in the host, are key pieces that can lead to new avenues of research and possibly care for patients with Lyme disease.

[Sarah Gregory] Go ahead and tell us a little bit about your study and how you went about collecting all this data.

[Adriana Marques] This paper was a review paper, and we reviewed the literature focusing on the different aspects of Lyme disease, comparing the studies from the United States and Europe.

[Sarah Gregory] How is Lyme disease treated?

[Adriana Marques] Lyme disease is treated with antibiotics, usually doxycycline, amoxicillin, or cefuroxime. Some manifestations may need to be treated with intravenous antibiotics, usually ceftriaxone.

[Sarah Gregory] Is the infection different in any way in the United States and Europe?

[Adriana Marques] Yes. Well, the main one is that Lyme disease in the U.S. is mostly caused by *Borrelia burgdorferi sensu stricto*, and there are a few cases caused by the

recently recognized *Borrelia mayonii* in the Upper Midwest, but most of the cases in the U.S. will be *sensu stricto*. In Europe, there is many different *Borrelia* that can cause Lyme disease. There's *B. burgdorferi sensu stricto* as well, but most of the infections in Europe are caused by *Borrelia afzelii* and *Borrelia garinii*. There is also *Borrelia bavariensis*, which is associated with neurological disease and is closely related to *Borrelia garinii*. There's a few others that can cause human disease. These ones are not found in the United States.

In terms of the clinical manifestations, there are both small and large differences between the geographical areas. For example, there are two skin manifestations of Lyme disease that occur exclusively in infections acquired in Europe. One is called borrelial lymphocytoma and the other one is acrodermatitis chronica atrophicans, and these are principally caused by *Borrelia afzelii*. Lyme neuroborreliosis is also more frequent in Europe, most often caused by *Borrelia garinii* and *Borrelia bavariensis*. And when we compare the erythema migrans rash, which is the most common manifestation in both places, the patients who acquired infection in the United States—they appeared to have more systemic symptoms than patients who acquired the infection in Europe. Also, the untreated infection in the United States is particularly linked with development of arthritis.

[Sarah Gregory] How does this happen that the same disease can be different in two different continents?

[Adriana Marques] Oh that's a very interesting question that we don't know. It will be very important to understand the factors that drive these differences.

[Sarah Gregory] Can you have Lyme without having the rash?

[Adriana Marques] Yes. But one thing is that the rash may not have been recognized or could have been missed altogether. And as we spoke, the rash of Lyme disease in the United States is usually not a bull's-eye rash, it's a red patch that expands. And there is a group of patients who presented with only known specific symptoms of fever, joint and muscle pain, headache, and fatigue in the summer or early fall. Now did they ever have the rash or they missed it is one of the questions. And some patients may present with only the later manifestations like arthritis, and they do not remember having had the rash or febrile illness. So it's possible that Lyme disease can present without having the initial rash, either because it was not recognized or was not there.

[Sarah Gregory] In the U.S., the bite of the lone star tick can cause a rash similar to Lyme. How can you tell the difference between the two or how can a clinician?

[Adriana Marques] That is very difficult. It can be really, really difficult in the areas where both ticks are common unless the patient actually saw the tick bite and removed the tick and kept the tick, and you can then identify to see if it is one or the other tick. The lone star tick is the most abundant human biting tick in the southeastern and south-central U.S., but its range has spread northwards along the eastern seaboard. And now it has many areas where you have both ticks coexisting. And then you really can't really tell clinically, it's very difficult. We do not know the cause of STARI and there is no test for it.

[Sarah Gregory] So how do people get treatment? The right treatment?

[Adriana Marques] If it's possible to be Lyme disease, you treat as you would treat Lyme disease.

[Sarah Gregory] So because Lyme is most prevalent, we start with Lyme disease for treatment?

[Adriana Marques] Yes, as we do not know the cause of STARI and we don't know if this caused this infection or another cause, but there is the possibility of Lyme disease that we know what cause is and how to treat, then the best approach would be (if there is the question of being possible Lyme disease) to treat as would we for Lyme disease.

[Sarah Gregory] So let's go back to this rash again. So you said in the United States it doesn't always manifest as a target (a rash). What about in Europe?

[Adriana Marques] In Europe it's more common for patients to have the central clearing and present with like what you call the bull's-eye rash.

[Sarah Gregory] That's so interesting that even the rash would be different.

[Adriana Marques] Well there is overlapping, but just know as a group there is more common to manifest as with the central clearing than the patients that acquired the infection in the United States.

[Sarah Gregory] I see, okay. And you mention that Lyme disease could affect the nervous system, especially in the United States. What are some of these neurologic symptoms that people should be aware of?

[Adriana Marques] Well in the United States, the most common presentation of early Lyme neuroborreliosis is facial nerve palsy. That's when you have either weakness on one side or both sides of the face. Patients who can present, like, with headaches and...usually they will present with fever, headache, and then they might develop the facial nerve palsy. Patients also can have together lymphocytic meningitis and in the United States (not that common) but you also can have the painful radiculitis which is inflammation of the nerves. Painful radiculitis is more common in Europe, and Lyme neuroborreliosis seems to be more common in Europe than the United States.

[Sarah Gregory] And is this...these neurologic manifestations, are they treated differently than if you don't have them?

[Adriana Marques] The neurologic manifestations of Lyme are treated with antibiotics. And depending of the type of manifestation, it can be either doxycycline or ceftriaxone depending on which manifestation we see.

[Sarah Gregory] And if it's left untreated, can this neuroborreliosis cause permanent damage?

[Adriana Marques] Yes, it can. It's important to recognize and treat it. Recognition and early treatment gives the best outcome.

[Sarah Gregory] Okay, so treatment right away. Okay.

In your article, you mention that there are no studies on neuroborreliosis in the United States that are comparable to studies done in Europe. Is there a reason for this?

[Adriana Marques] Well, one reason was that the number of cases in the United States seem to be less than what they have in Europe. Another big advantage that Europeans have is that because of their centralized health system in many countries, that makes much easier to acquire information in large number of cases and regarding many aspects of the disease.

[Sarah Gregory] I see, okay.

So Lyme can also cause arthritis, right? So why does it cause different kinds of symptoms in different people?

[Adriana Marques] Well, that is the question, right? And remember talking before, we do not know why it cause different symptoms in different people. To me, it's likely to be due to combination of factors from, now, factors from the bacteria itself, the host immune response, as well as time to diagnosis and treatment of the infection.

[Sarah Gregory] And how common is Lyme arthritis?

[Adriana Marques] In the United States from the old studies we know that about 60% of the patients who had erythema migrans that goes untreated will develop Lyme arthritis over a two-year period. Now for the cases reported to the CDC that also had information regarding manifestation, 28% of the cases were Lyme arthritis. Lyme arthritis appears to be less frequent in Europe.

[Sarah Gregory] And there are a lot of studies that show men being more affected by Lyme neuroborreliosis and Lyme arthritis. Do you know why men are more susceptible to these than women?

[Adriana Marques] No, we don't know the reason.

[Sarah Gregory] What types of tests are used to detect Lyme? And is testing for Lyme disease the same in Europe as it is in the U.S.?

[Adriana Marques] Well most of the tests that are used to help the diagnosis of Lyme disease in clinics are tests that are based on the detection of antibodies against the *Borrelia burgdorferi*. And the testing is similar for both (the Europe and the U.S.)—as they are based on the detection of these antibodies against the pathogen. Because there are different species in Europe, the criteria is different in the interpretation of the tests, but overall the formulation is similar.

[Sarah Gregory] And after a person is bitten by a tick, should they go get tested for Lyme or any kind of tickborne disease, just in case?

[Adriana Marques] No. That is not recommended. The current tests that we just talked about, they are based on the detection of antibodies against the bacteria and that would take time—there would be no time to develop an immune response soon after the bite. What people should do is that they should watch carefully the site of the bite and promptly seek medical care if there are any signs or symptoms of the disease. They also can consult their care provider regarding the possibility of getting antibiotic prophylaxis after a known deer tick bite in an endemic area.

[Sarah Gregory] So if you do get the prophylaxis antibiotic, how long would the regimen be?

[Adriana Marques] Well it's a single dose of doxycycline, and it's recommended to be given within 72 hours of removal of the tick and for what's considered high-risk tick bite, which is a known tick bite from a deer tick in a highly endemic area, and the tick was attached for at least 36 hours.

[Sarah Gregory] I see. So if I call my doctor and say, "Hey, I think I got bitten by a tick. I'm not really sure, it could be a spider, could be something else, but would you give me a dose of doxycycline," that's not really prescribed?

[Adriana Marques] Well, that's not what is recommended.

[Sarah Gregory] And are there different treatment recommendations in the U.S. compared to Europe?

[Adriana Marques] No. The recommendations are very similar for treatment between the United States and the European guidelines. One difference is that some of the guidelines in Europe use penicillin V (or now oral penicillin) as part of their treatment, which is not part of the U.S. guidelines. Another difference is the recommendation of intravenous ceftriaxone for treatment of Lyme disease in pregnant women by some of the European authorities, which is not the recommendation in the United States.

[Sarah Gregory] Can the same tick carry different diseases? Say, so what are the chances of people getting infected with more than one tickborne disease from the same nasty tick?

[Adriana Marques] Yes, ticks can carry more than one pathogen and they can transmit more than one pathogen. The chances will depend of the infection rate of the different pathogens in the area.

[Sarah Gregory] Does having more than one tickborne infection make treatment more complicated?

[Adriana Marques] Yes, it can make it more complicated. For example, babesiosis—which is caused by *Babesia* parasites that infect red blood cells—will require different types of medications. And another infection called anaplasmosis—which is a disease caused by the bacteria *Anaplasma phagocytophilum*—it requires treatment with doxycycline and will not respond to other types of antibiotics used to treat Lyme disease like amoxicillin or cefuroxime.

[Sarah Gregory] How would you like your research to be used going forward?

[Adriana Marques] I hope our manuscript will bring renewed interest to physicians and scientists and increase studies looking into the specific factors that are carried by the different species of *Borrelia burgdorferi* sensu lato and that are responsible and play a role for the variations in the clinical features.

[Sarah Gregory] What are the best ways that people can protect themselves from ticks?

[Adriana Marques] Well, reducing exposure to ticks is the best defense against Lyme disease and other tickborne diseases. The best way to protect themselves and their family from ticks is to learn about all the modes of prevention and how to use them (and to use them). I tell people that they should learn where to expect to encounter ticks and how to prevent tick bites, and also consider how to prevent ticks in their yard. There are many different aspects of tick bite prevention, including recognizing the places where you can get ticks, how to reduce your exposure to ticks—for example, not brush against the vegetation, walk in the middle of the trail, the use of the EPA-approved repellants, consider treating the clothes and gear with products containing permethrin.

As always there are many things to do after coming back indoors from outdoors where you were exposed to ticks, including checking the clothes for ticks, showering within two hours of coming indoors, doing a full body check for ticks, and also checking kids and pets. I recommend the CDC webpage in preventing tick bites and I also like the University of Rhode Island website called tickencounter.org as a resource to learn about tick bite prevention.

[Sarah Gregory] Tell us about your professional background and your job at NIAID.

[Adriana Marques] Well I'm a clinical investigator, as you have already mentioned, I'm the chief of the Lyme Disease Studies Unit at NIAID and I work here at the NIH campus in Bethesda, Maryland. I have been involved in patient-oriented research in Lyme disease for many years.

[Sarah Gregory] These are strange times we're living in, as everyone knows. Is it difficult to be studying ticks when the world is so focused on COVID?

[Adriana Marques] Yeah, well for clinical research due to the restrictions imposed by the COVID-19 pandemic, it has been very difficult.

[Sarah Gregory] Thank you so much for taking the time to talk with me today, Dr. Marques.

[Adriana Marques] Well thank you for having me on the program.

[Sarah Gregory] And thanks for joining me out there. You can read the August 2021 article, Comparison of Lyme Disease in the United States and Europe, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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