Dr. Richard Ford: Our challenge today is to discuss emerging tick-borne diseases—a progressively important topic in companion animal medicine. I’d like to begin the roundtable by addressing the term “emerging.” Are emerging tick-borne diseases really new or are we now just recognizing them because of emerging technology?

Dr. Rick Alleman: With the advent of molecular tools used in infectious disease diagnosis, the production of better serologic assays, and a better understanding of various disease processes, we can detect disease in places where we could not in the past. So the fact that these diseases are so-called “emerging” is in part due to better diagnostic capability. The use of in-house diagnostics by practicing veterinarians, along with annual screening of animals for certain tick-borne diseases, has resulted in heightened awareness of clinically and subclinically infected animals.

Dr. Edward Breitschwerdt: There are two other important factors. First, there is a convergence of ecological change, and that has been emphasized where we have urban sprawl. Secondly, we have more deer in most parts of the country than we have had in the last 100 years. We have numerous small mammals—opossums, raccoons, and rodents—that move in and out of these suburban environments, as well as deer, carrying ticks.

Second, I believe another factor affecting the prevalence of tick-borne diseases and disease expression is global warming. Some ticks, such as *Amblyomma americanum*, now have a more northward range than two decades ago. Many of these ecological factors that impact ticks have been stable for hundreds, if not thousands or millions, of years. It is possible that the human race is contributing to dramatic changes in the dynamics of tick-borne diseases.

Dr. Matt Eberts: I don’t think the disease is emerging; I think people are moving into the disease areas. In
my area in Minnesota, the white tail deer population has increased dramatically in the past 10 years. People are buying huge lots in wooded areas that were previously untouched, so we are gaining exposure to the vectors that were already there. Now we have tiny lap dogs living on a five-acre parcel in woods that are tick-infested.

**Alleman:** Also consider that geographic distribution can change significantly because owners and rescue groups transport pets around the country. We rarely saw Lyme disease in dogs when I first arrived in Florida. Now it is well-seeded in the state, particularly in the coastal areas where people from the Northeast come in and out. So that has had an impact on disease progression. You might think the disease is emerging, but it’s been around; it just hasn’t reached a particular area.

**GEOGRAPHIC DISTRIBUTION**

**Ford:** Traditionally, one of the principal variables in the diagnostic equation has been risk assessment based on geographic distribution of vector ticks. From the early days of heartworm infection, we have said that geographic distribution is important. We looked at the South and the Southeast for heartworm disease. Today, canine heartworm disease is well established in Canada. Obviously vector-borne infections are not static. Consider the geographic distribution of Lyme disease. Human and canine cases of Lyme disease are clustered in the northeastern United States and the upper Midwest. Are we seeing it in other locations around the country?

**Breitschwerdt:** The northeastern and north central United States and California to Oregon are the areas in which *Borrelia burgdorferi* is particularly endemic in either *Ixodes scapularis* or *Ixodes pacificus* ticks.

In North Carolina, we have looked at the prevalence of *B. burgdorferi* infection in dogs initially using IFA (indirect fluorescent antibody) testing, whole antigen ELISAs (enzyme-linked immunosorbent assays), and, more recently, the C6 antibody test in the IDEXX 3Dx or 4Dx assay.

Our most recent study suggests that despite the dynamics of dog movement, deer expansion, animal population movement, and other factors, North Carolina has not seen an increase in *B. burgdorferi* infection in dogs over the past 20 years. According to the study, which included nearly 1,000 samples sent to the North Carolina State University Vector-borne Disease Diagnostic Laboratory, the four C6-positive dogs had all been in New England. The dogs either had originated from New England or hunted there on multiple occasions. This information is important to clinicians because it suggests that the C6 peptide affords us a very specific test with few to no false-positive results. It also suggests that veterinarians in areas not endemic for *B. burgdorferi* should, if they get a positive Lyme result using the 4Dx test, follow up with a Western blot test, particularly if there is no travel history. That would reflect the actual movement of *B. burgdorferi*-infected ticks into their practice area.

**Ford:** Dr. Alleman, what is your perspective from Florida?

**Alleman:** We assume that Lyme disease in Florida results from animals moving back and forth between the Northeast and our coastal areas. There are certain areas of the country where the potential for Lyme disease is low, but to my knowledge it has been reported in all states.

**Breitschwerdt:** There is no doubt that the movement of individuals with their pets from high disease-prevalence states to low disease-prevalence states has impacted the distribution of canine infections. When IDEXX first introduced the 3Dx test in North Carolina, I would get phone calls from veterinarians in the Raleigh area saying their families moved here from the Northeast four years ago, and all three dogs in the household are C6 antibody-positive on the 3Dx test. They wanted to know what to do. I was fairly convinced that the dogs had not been infected in North Carolina. Instead, it was assumed they had become infected previously and had maintained that infection for three or four years. Based on the experimental literature, it appears that once a dog is infected, it may be infected for life. Whether we can influence that infection therapeutically is debatable.

**Ford:** Dr. Eberts, in the years you’ve practiced in Minnesota, have you seen significant change as far as risk in individual dogs?

**Eberts:** Yes. During the past six years, I’ve seen an increase in the *Ixodes* tick population. When I started practicing in central Minnesota, a dog would come in loaded with ticks. We would pluck ticks, and half of them would be *Ixodes* and half of them would be *Dermacentor*. It was an even distribution, but that has changed. The *Ixodes* ticks are now more prevalent. It is a surprise now to see *Dermacentor*, and it used to be one of the primary tick populations.
Also, I live in a resort area, and every day people drive up in their motor homes with their dogs. Pet travel is big business. So when the dogs leave my area and head home to the South, their practitioners are not aware of the dogs’ tick exposure. In my residential population, at least 40% of dogs are C6-positive for Lyme infection. I know the seasonal visitors are taking that infection with them when they leave, and that has always been a concern. If they get sick in an area that is not used to Lyme disease, we may have some misdiagnoses.

**Ford**: In New England, anecdotal reports from practicing veterinarians indicate a seroprevalence of C6 antibody in up to 70% of dogs. Dr. Eberts has seen 40%. If you find a positive test in a healthy dog, do you treat the dog?

**Eberts**: Signs compatible with Lyme polyarthritis. Of that same group of 20, three or four became C6-negative without treatment. So some of the dogs were clearing it on their own. But one in four got us thinking. Based on our experiences, the doctors in my practice are sold on treating positive animals at least once. We go over the options with clients, but we all recommend treatment.

**Ford**: When you did that study in-house, did you know the *Anaplasma* status of those dogs?

**Eberts**: We didn’t do serologic tests for *Anaplasma* on those patients, but I think most of those dogs were getting sick from Lyme disease. There were no signs of coinfection on in-house diagnostics when these dogs presented with clinical disease.

**Ford**: Define “sick.”

**Eberts**: I would treat it. When we first started using the 3Dx test in my practice, this was a big question. So we decided to follow 20 *B. burgdorferi*-positive dogs. We found that within 16 months, 25% of those dogs became sick with what we diagnosed as Lyme disease and responded to doxycycline.

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**Ford**: So it’s fair to say that a blue spot for C6 antibodies denotes infection, but infection doesn’t necessarily correlate with clinical illness. My impression is that veterinarians in high-prevalence areas tend to treat healthy animals with positive C6 results more than those in low-prevalence areas like North Carolina.

I’d like to go back to geographic distribution and risk assessment. If you review the vector vs. the agent, there is a lot more overlap than people appreciate. Lyme disease, for example, is not just transmitted by *Ixodes* ticks, and the multiple species of *Ehrlichia* expand the geographic distribution and the risk. So should we be looking outside of *Ixodes* ticks for Lyme disease rather than being so tick-specific?
Alleman: Yes. There are multiple tick species that can actively transmit a particular organism. There are other situations—and I am not a tick expert—where we might find the organism in a tick species that is not the typical vector, but we can demonstrate transmission. In other cases, the tick might carry the organism but be unable to transmit it.

Breitschwerdt: Keep in mind that many of the maps showing distribution are 30 or 40 years old.

Ford: We can pick up any infectious disease textbook in veterinary or human medicine and find a map showing the vector distribution. There is an opinion that if you’re outside of that area, the risk is not present. I’m trying to argue that distribution is dynamic. Twenty-year-old maps don’t apply today, and there are other ticks transmitting these infections. Dr. Eberts, have you experienced this?

Eberts: Yes. Ticks and diseases don’t read maps.

Ford: We can’t overemphasize this point: The movement of pets throughout the world, particularly the dog population, can literally move a tick population. Dr. Eberts, you’ve referred to the outbreak of tick-borne diseases in major cities. The ticks didn’t get dropped into those cities by an airplane.

Eberts: That’s right. One factor is the Internet. You wouldn’t believe how many of my clients acquire their dogs online. So I’m getting patients that have been bred in different parts of the country. This is a new phenomenon in my practice, but it’s only going to increase.

Ford: Let’s discuss *Ehrlichia*, the spotted fever group, and the *Anaplasma* group. Dr. Alleman, do you recognize a specific geographic distribution associated with those pathogen groups?

Alleman: Overall, yes. It appears that some generalities still exist regarding high prevalence in specific diseases and specific tick vectors in defined geographic locations.

Breitschwerdt: I think there are two issues. First, some tick-borne organisms induce chronic infection in dogs vs. other organisms that induce only acute infection that becomes self-limiting. Chronic infections lead to the clinically apparent problems we’ve alluded to: A dog can become infected today, remain infected for months to years, and then be transported to a nonendemic area and break with the disease. Therefore, any veterinarian in any part of the country or any part of the world could see tick-borne diseases that develop in chronically infected dogs.

Ford: Dr. Eberts, considering the three pathogen groups we’ve mentioned (*Ehrlichia*, spotted-fever group, *Anaplasma*), do you perceive there is a reasonable risk of infection in the upper Midwest?

Eberts: With *Anaplasma*, definitely. Now that we are screening for it with the 4Dx, we are seeing more *Anaplasma*-positive dogs than *B. burgdorferi*-positive dogs. Our percentage is over 50%—this may seem high, but it’s true. We are also seeing more *Ehrlichia canis*-positive dogs. This brings us back to the map issue. When I looked at the maps, they showed few *E. canis*-infected dogs in our part of the country. The vector, the *Rhipicephalus* tick, is not up there, and so we have never really considered it. When we first started seeing *E. canis*-positive dogs using the 3Dx, there was a travel history—they came from Missouri or somewhere south. This year we are getting quite a few dogs that are testing positive without travel histories. I don’t know if we are getting cross-reaction or we are truly seeing *E. canis*-infected dogs now. There are always changes, and it’s frustrating because it makes my job harder.

CLINICAL SIGNS

Ford: There is a convention in our profession that when a dog is sick, you decide what disease to test for based on the spectrum of clinical signs. My hypothesis is that this isn’t practical with regard to tick-borne diseases. Dr. Alleman, I would like you to start this discussion by talking about the clinical spectrum of signs that you see in dogs with tick-borne infection.

Alleman: It’s a tough topic because they can vary even with a specific organism. For example, let’s take the dog with granulocytic anaplasmosis. Classically, we think of the animal presenting with

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—Dr. Edward Breitschwerdt
A dog can become infected today, remain infected, and then be transported to a nonendemic area and break with the disease. Therefore, any veterinarian in any part of the country or world could likely see tick-borne diseases.

Dr. Edward Breitschwerdt

polyarthritis. However, sometimes these dogs will present with such nonspecific signs as depression, chronic fever, or anorexia.

Then consider the myriad findings when a dog has chronic monocytic ehrlichiosis. These animals might have ocular lesions, joint disease, lymphadenopathy, or splenomegaly—the presentation is varied. But to generalize, one thing we look for, whether the animal presents with nonspecific illness or more specific clinical signs, is thrombocytopenia on the complete blood count (CBC). With the exception of Lyme disease, thrombocytopenia is the most common hematologic abnormality seen with a number of tick-borne diseases, including ehrlichiosis, anaplasmosis, and babesiosis, to name a few. Animals with Lyme disease do not develop thrombocytopenia.

Ford: So you are alluding to two aspects: One is the physical presentation and the other is the laboratory presentation. What physical signs would be indications to test?

Alleman: An animal would exhibit fever, mild lymphadenopathy, splenomegaly, and polyarthritis. These are signs that could indicate systemic infection as seen with tick-borne diseases.

Ford: What might the owner perceive?

Alleman: The owner would observe lethargy, anorexia, and limping in pets with polyarthritis. These signs could be suggestive of tick-borne infection. We know that many of these animals are thrombocytopenic, but many of them don’t show clinical evidence such as petechiae or epistaxis.

Breitschwerdt: One of the concepts that I have come to grips with as a clinician is that these tick-transmitted organisms have been around for a very long time. That fact equates to tremendous immunologic and evolutionary adaptation between the organism, the tick, and the dog.

One of the most important concepts for veterinarians to understand is that these organisms are highly adapted to persist in dogs’ blood or other tissues for a long time without causing disease; when clinical disease occurs, something went wrong. The dog’s immune system started recognizing the organism, or the organism, perhaps because of coinfection, created an immunologic imbalance within the host. So instead of dealing with just B. burgdorferi, there is a superimposition of Anaplasma phagocytophilum, and the animal becomes sick.

When should we test? There is no right or wrong answer to this question. For example, polyarthritis, which was historically associated with B. burgdorferi infection, can also be caused by Ehrlichia ewingii, Rickettsia rickettsii, and Bartonella infection—that is both Bartonella henselae and Bartonella vinsonii berkholfii. Our list of organisms causing idiopathic immune-mediated polyarthritis has gotten a lot longer and may continue to expand.

Ford: Dr. Eberts, as a practicing veterinarian, what are your indications for testing?

Eberts: The classic signs I see in dogs with a tick-borne disease are fever, lymphadenopathy, and any type of joint pain or swelling. One of the more interesting things I see with anaplasmosis is acute vomiting without any of the other classic signs. The dogs often have a fever, but their joints feel normal. In my experience, most of the dogs diagnosed with anaplasmosis have a decreased platelet count, but there are no signs of bleeding. A few dogs present with petechiae, but they usually have a very low platelet count. I can think of one German shepherd that came in for epistaxis. It had a moderately low platelet count (130,000/µl), but it wasn’t low enough to expect spontaneous hemorrhage. The epistaxis resolved quickly with doxycycline. We saw neutrophil inclusions in this dog that were consistent with ehrlichiosis.

Alleman: The German shepherd is a good example. We are talking about spontaneous bleeding, and while many of these animals are thrombocytopenic, they don’t often show clinical evidence of that. It would be interesting to look at the animals that actually are bleeding.
The work on coinfections indicates that it is not just the *Anaplasma* infection or the *E. canis* infection that causes animals to bleed. It could be a coinfection with *Bartonella* or some other organism.

**SURVEILLANCE TESTING**

**Ford:** Essentially, there is so much variability in the way an individual dog might manifest clinical signs that the clinician cannot afford to wait for the appearance of classic signs to test for the disease. It raises the issue of surveillance testing. Is it appropriate to test a healthy animal?

**Breitschwerdt:** I believe that veterinarians who are informed and understand the limitations of surveillance testing are providing a service to their clients by performing surveillance testing. I also believe this is valuable from the standpoint of animal health and human health. I am a proponent of surveillance testing with the caveat that we have to understand how to use the data.

**Alleman:** Even though I am a clinical pathologist, I do teach infectious disease and molecular biology courses. After years of evaluating this approach, I agree with Dr. Breitschwerdt. I am a proponent of surveillance testing in specific instances where diseases with subclinical components can become clinical and, possibly, fatal. I think heartworm disease, Lyme disease, anaplasmosis, and ehrlichiosis are good examples.

I also agree that you need to understand these disease processes when you are testing so you know what to do with the data you have collected. What does a positive test result mean, and what can we do as veterinarians to prevent disease in the animals tested as well as to reduce disease incidence by preventing transmission and reducing the reservoir?

I tell students and practitioners that I would rather know if an animal has antibodies to a specific disease agent and is potentially a subclinical carrier than not know. Whether you want to treat the positives is debatable. I like to treat them. Another important scenario in surveillance testing is the animal that, for some reason, is immuno-compromised. Examples may include cancer patients that require chemotherapy, patients with immune-mediated disorders that require immunosuppressive therapy, animals scheduled for elective surgery, or animals that have experienced accidental trauma, such as hit-by-car cases. I would want to know if that animal is a potential carrier of a tick-borne disease.

**Ford:** You all seem to be saying that surveillance testing is OK and one should not feel guilty about testing a healthy seropositive dog. That has led to avoidance, resistance, or reluctance to use testing. So what would you say to the practicing veterinarian who says, “I don’t test because I don’t know what to do if the test is positive and the dog looks healthy?”

**Alleman:** Again, I think knowing that a dog tests positive is better than not knowing, regardless of whether you take immediate action on that positive result. But in terms of protocols, there are some things you can do. You can run a CBC on this patient and take a closer look during the physical examination to see if you have a mild lymphadenopathy or a splenomegaly. You might notice that the animal has a mild nonregenerative anemia or thrombocytopenia. This would indicate that the infection is having a clinical impact on the animal, even though it is not visible to the owner. I think those are two easy steps.

**Ford:** What about biochemical changes?

**Breitschwerdt:** With *B. burgdorferi*, there are no useful hematologic...
abnormalities or biochemical abnormalities. Based on the ACVIM Lyme consensus statement, it’s worthwhile to screen urine for microalbuminuria in a dog that is *B. burgdorferi* C6 antibody-positive to determine if there is active protein loss associated with a protein-losing nephropathy. Then you have a baseline for future comparison.

We know that *Ehrlichia* and *Anaplasma* can induce hematologic abnormalities, including anemia, thrombocytopenia, and lymphopenia, and that *Ehrlichia* can typically induce biochemical abnormalities such as hyperglobulinemia and hypoalbuminemia. With *Anaplasma*, the only potential biochemical change would be an increase in alkaline phosphatase (ALP) activity and, occasionally, an increase in alanine transaminase activity. *Ehrlichia* can also induce ALP and leakage enzyme elevation from hepatocellular damage in some dogs, perhaps those dogs that become coinfected with *Babesia* or *Bartonella* species.

**Ford**: Dr. Eberts, is that how you practice? Do you take the positive healthy dog and investigate further?

**Eberts**: Absolutely. The biology of the organism we are testing for dictates what I recommend. Because of how *B. burgdorferi* infections act in a dog, my first inclination is to treat and begin a monitoring program where we look at the quantitative C6 or urine protein to gauge the level of infection.

With *Ehrlichia* and *Anaplasma* infections, my first inclination is to increase our database. I have found that the CBC is the best test to determine whether a patient with subclinical infection (i.e., a healthy seropositive dog) is developing a clinical infection. So that is the first thing I recommend if I’ve done the physical examination and I don’t see signs of disease.

Then if a low platelet count or anemia is present, that moves the animal from a subclinical status to a clinical status. In those cases, I’m inclined to treat the animal. If I don’t see abnormalities, then there’s no benefit to treating those diseases based on the presence of antibodies. This protocol gives me vital information and allows me to present reasonable options for monitoring these dogs.

**COINFECTION**

**Ford**: Today, we know that both dogs and people can become coinfected, meaning one individual may be infected with two or more pathogens following tick exposure. What is the likelihood of an individual tick transmitting multiple infections simultaneously?

**Alleman**: A single tick can carry multiple species of pathogens. We see it with *Babesia, Ehrlichia,* and *Anaplasma* species.

**Ford**: Dr. Breitschwerdt, do you think coinfection with tick-borne pathogens is a significant issue in the clinical setting?

**Breitschwerdt**: In my lectures to veterinarians, I usually suggest that coinfection is far more important to us than physicians because pets are simply more likely to become infected with ticks. Unfortunately, it is also more likely that a pet will become coinfected either simultaneously or sequentially with organisms that persist chronically.

The most impressive result that we ever achieved in the Vector-borne Disease Diagnostic Laboratory was the identification of six different tick-borne organisms from four different genera in a blood sample from a dog in North Carolina. We identified the DNA fingerprint, not antibodies. So this dog was walking around with six organisms that we could detect, and there are likely other organisms in the blood for which we do not specifically test.

A lot of our work relative to coinfections evolved from trying to help veterinarians understand why some of their *Ehrlichia* patients were not getting well. Ten years later, I can tell you some dogs were not getting well because they were coinfected with *Babesia* or *Bartonella* species, which may or may not be visualized on a blood smear or respond to doxycycline administration for six months.

**Eberts**: We are just starting to scratch the surface on this topic. I see a lot of dogs come in for something completely unrelated—for example, hot spots. I treat them for the skin infection, but they don’t get better. I then discover that they had subclinical Lyme disease or anaplasmosis or both,
which became clinical due to the unrelated skin infection. So it shows you that these agents are held in check by the immune system, but if the immune system is compromised, you may see disease. I definitely see a lot of coinfections, and they often present as treatment failures. I treat a dog for a disease and the dog does not get better, and that prompts me to look closer.

**DIAGNOSTICS**

**Ford:** Let’s discuss the interpretation of the positive result. All diagnostic tests are not the same. Dr. Alleman, would you address the differences between ELISA, IFA, and Western blot?

**Alleman:** Sure. I’ll start with the IFA test. If the organism can be cultured, an IFA assay is easy to establish. One of the problems is that this test has been around a long time. Many of us who work in the diagnostic area have to compare any new diagnostics with the results of the IFA test, but I don’t think it is a gold standard for comparison. What we discovered when we used whole organisms in a diagnostic assay, such as the IFA, is that we have a lot of shared antigens on these organisms. They are shared by closely related and even not-so-closely related pathogens.

One of the drawbacks with IFA is the high occurrence of false-positive test results. I think we need to be leery of IFA titers, particularly those on the low side, less than 1:64. I am always leery when practitioners call to tell me they have a dog with *E. canis* and it has a titer of 1:40. Make sure a reputable lab runs it, and be aware that false positives can occur.

With regard to ELISAs, many of them are not based on whole organisms. They are based on recombinant proteins or synthetic peptides representing the target pathogen. The ELISAs, therefore, are particularly useful because of their immunogenic specificity. You get much better specificity when you can design an assay that is based on a specific peptide or protein.

**Breitschwerdt:** To follow up, the C₆ peptide, a highly conserved protein associated with *B. burgdorferi*, is not an immunodominant protein shared by other *Borrelia* species. So the beauty of the C₆ antibody is its specificity for *B. burgdorferi sensu lato*. It is very different from the two synthetic peptides used in the 4Dx test for detection of *Ehrlichia* and *Anaplasma* antibody. That is important because the target for *Ehrlichia* 10 years ago was *E. canis*, whereas now we know that infection with *Ehrlichia chaffeensis* and *Ehrlichia ewingii* also induces ehrlichiosis in dogs. And there is *Ehrlichia noonantium* infection in dogs in South Africa. The immunodominant *Ehrlichia* genus peptides will be positive to varying degrees with every one of these species. The same is true for *Anaplasma* peptides in the 4DX platform.

**Ford:** Dr. Eberts, are you concerned about the type of test method when you are submitting blood or purchasing a test for in-hospital use?

**Eberts:** With the increase in new technology, there is a big burden placed on the practitioner. We have to go beyond the package insert and understand what these products are testing for, how they are testing for it, and the limitations of those tests. We need to understand the biology of the organism and where that test fits into our philosophy of testing and screening. This is why some practitioners may find interpreting test results difficult or confusing. It’s important for practicing veterinarians to be confident when they interpret diagnostic test results.

**Ford:** Regarding advanced diagnostic technologies, I’d like each of the panelists to address the C₆ antibody test for Lyme disease.

**Alleman:** Antibody to the C₆ peptide is very sensitive and specific for the diagnosis of *B. burgdorferi* infection in animals because the antibodies are produced in the course of the infection, maybe even before clinical signs develop. The other nice thing is that following treatment, the antibodies will decline over the next four to six months.

It’s important to note, however, that the SNAP test for C₆ antibody has a fixed threshold for positivity. While treatment is expected to reduce the antigen load in the patient, with subsequent decline in antibody titer, the SNAP C₆ ELISA may not necessarily become negative following treatment. On the other hand, the Quantitative C₆ Antibody Assay does provide information regarding the decline of antibody following treatment. Also, vaccinating animals for Lyme disease will not cause them to become positive for C₆ antibody. Uniquely, the C₆ antibody test for canine Lyme disease will allow the clinician to distinguish between an infected dog and a vaccinated dog.

“A Roundtable Discussion”

“**I see a lot of coinfections, and they often present as treatment failures.**”

—Dr. Matt Eberts
A single tick can carry multiple species of pathogens. We see it with Babesia, Ehrlichia, and Anaplasma.

Dr. Rick Alleman

Ford: You’ve mentioned the Quantitative C₆ Antibody Assay. This test does require that serum or plasma be sent to IDEXX Laboratories. By virtue of its ability to measure actual units of C₆ antibody, the test has two applications in clinical practice. If a healthy dog has a positive SNAP test, a high quantitative test result indicates that this seemingly healthy patient may be at high risk for developing clinical signs. In addition, the Quantitative C₆ Assay allows the practitioner to monitor the actual amount of antibody decline over time following treatment. What is your experience with the Quantitative C₆ Antibody Assay?

Alleman: I can’t comment on the first aspect of the testing or on the level of antibodies that would predict disease. But I will say that a decline in antibody titer may, indeed, be a good indicator of treatment effectiveness. If it returns to a negative status and remains that way, then you may have actually cleared the organism. What can also happen with any kind of titer is that it can fluctuate with treatment. So if an animal is cleared and stays clear, that is one thing. If you just see a drop in antibody titer during or shortly after therapy, I don’t know that you can equate that with clearing infection.

Eberts: We are using the Quantitative C₆ Antibody test extensively now because it appears that B. burgdorferi infections may not be completely cleared following treatment. The results tell me if we are managing the infection appropriately or if there are host factors that are preventing this infection from responding. When we see a blue dot for Lyme disease, our first inclination is to treat it. Then we use the Quantitative C₆ Antibody Assay as our baseline for monitoring the dog. My experience is that most dogs that undergo treatment will have stable values. When the units of antibody start increasing again, it usually indicates re-exposure—we have had a lapse in tick control. Then when I have quantitative evidence that the body is responding aggressively to that infection, I can start another course of treatment. It is an important tool in my practice for monitoring these patients long-term. But most dogs don’t require additional therapy.

Ford: Dr. Alleman, what about some of the other tests that might not routinely be used in private practice? What can we say about the future of diagnostic testing?

Alleman: The most significant addition to serology is PCR (polymerase chain reaction) analysis. There is currently a lot of PCR work in the area of infectious disease diagnostics. PCR testing has highly defined diagnostic applications. It also has significant limitations, such as availability (turnaround time to practitioners can be prolonged), and sensitivity may be reduced in subclinical or chronically infested animals.

In our experience with in-vitro culture and isolation, many of these organisms can be propagated in vitro, but they are difficult to introduce into a culture system from an infected animal. When you also consider the limitations of working with these organisms in vitro, it would be challenging at best.

Breitschwerdt: We are seeing a dramatic increase in the number of veterinarians who request PCR testing. For varying reasons, practitioners are trying to generate DNA evidence to use in conjunction with serologic evidence of exposure or hematologic abnormalities consistent with tick-borne infections in their patient population. As testing demand has increased, we are detecting more E. ewingii, E. chaffeensis, Babesia gibsoni, and Babesia canis DNA-positive samples.

Veterinarians should know that despite the advances in PCR testing, there are still problems that can occur in a laboratory on a day-to-day basis. Using a laboratory with a good track record for PCR testing is critical until the validation and technology are more standardized among laboratories worldwide.

Eberts: There is no such thing as one test for one problem. You have to put together a picture using various puzzle pieces. As a practitioner, I am biased toward products and processes that I can do immediately to help manage a clinical case. So I am biased toward using quality in-house diagnostics that offer some immediate answers. We use DNA tests when cases don’t fit the mold. But these advanced diagnostics are
not designed to replace my in-house diagnostics. They complement our standard testing and diagnostic plans.

**Zoonotic Potential**

**Ford:** In current textbooks, I find it intriguing that diseases like spotted fever, ehrlichiosis, borreliosis, and even bartonellosis are occasionally listed under the topic of urban zoonoses. There is some debate over whether these diseases are zoonotic. Dr. Alleman, do you consider anaplasmosis, ehrlichiosis, Rocky Mountain spotted fever, and Lyme disease to be zoonotic diseases?

**Alleman:** There are two questions to address: Can I catch it directly from my pet and do the organisms infect both species? If you are talking about catching the infection from your pet, I would say the likelihood is very low. I don’t know that it has ever been documented with the diseases you mentioned. Are the pets good sentinels for disease in their area? Absolutely. So there should be more concern that people could be exposed to it from tick transmission than from the pet.

**Breitschwerdt:** Bartonellosis is truly zoonotic. Cat scratch disease is a zoonotic infection that is transmitted on a daily basis in this country by a cat bite or scratch. The research we have done in the last year suggests that dogs also pose an increased risk for transmitting *Bartonella henselae* or *Bartonella vinsonii berkhoftii* directly to humans via a scratch or bite.

**Ford:** Dr. Eberts, do you warn clients about their risk if a dog tests positive for Lyme disease in Minnesota?

**Eberts:** Absolutely. Education is my most important job. We get these questions every day. Am I at risk? Is my son or daughter at risk? We are not physicians, but we can educate them by saying, “Just because Fluffy has Lyme disease does not mean that Timmy is going to get it. But because Timmy is chasing Fluffy through the weeds and they are playing together outside, there is a potential for exposure. We know these diseases are out there because your dog has been infected.”

**Breitschwerdt:** Dr. Ford, if we use rabies, toxoplasmosis, and the vector-borne diseases that we have discussed today as examples, veterinarians play a tremendous role in public health on a daily basis. The last issue of *Emerging Infectious Diseases* published by the Centers for Disease Control and Prevention, states that rabies is absolutely endemic in the human population in India, Africa, Pakistan, and China because it is transmitted by dog bites. Veterinarians have totally interrupted dog transmission of rabies in the United States through effective vaccination. I’m so happy to hear that, as a practitioner, Dr. Eberts has accepted the responsibility of educating his clients on public health.

**TREATMENT**

**Ford:** Earlier in our discussion, I asked whether we would treat subclinical infections. Dr. Breitschwerdt and I, both from North Carolina, would say “no.” In Minnesota, Dr. Eberts would say “yes,” knowing that as many as 25% of his positive dogs develop significant clinical signs. Dr. Alleman, you would have a qualified “yes” to the question. The point is, there is no defined standard of care. You don’t just treat a dog because it is seropositive. On the other hand, I would like to address the expected outcome of treatment if a seropositive dog is, in fact, sick. Let’s start with Rocky Mountain spotted fever. What is the expected response to treatment?

**Breitschwerdt:** In regard to Rocky Mountain spotted fever, people are infected with the same *Rickettsia* species as dogs. If placed on doxycycline or tetracycline, the individual (dog or person) should improve within 24 hours, and there should be signs of resolution in 48 hours unless there was a delay in diagnosis or the patient has neurologic abnormalities, which can take months to resolve. The rickettsiae should be eliminated either by immunologic clearance or by therapeutic clearance within two to three weeks.

**Ford:** Would a clinically ill dog treated with doxycycline for 28 days respond the same with Lyme disease as it would with Rocky Mountain spotted fever?

**Breitschwerdt:** My understanding is that treating *B. burgdorferi* infection would be analogous to treating toxoplasmosis in a cat. We do not eliminate the organism, which may be protected from the immune system by hiding in connective tissue, but we eliminate the clinical signs and put the dog into a state of remission. If stressed or treated with immunosuppressive drugs, the dog could experience a recurrent bout of borreliosis after treatment. So my impression from the literature is that we don’t actually cure a dog infected with *B. burgdorferi*. We do, however, cure *Rickettsia rickettsii* infection—it can be eliminated therapeutically or immunologically.
As for *Ehrlichia*, I think that most dogs treated for four weeks with doxycycline eliminate their infection. However, there is no long-lasting protective immunity, so dogs can be reinfected if re-exposed to *E. canis*-infected ticks. It is also clear that more dogs than we would have predicted eliminate the infection immunologically without the need for antimicrobial therapy. In highly endemic areas like El Paso, Texas, veterinarians can get 30% to 40% *E. canis* SNAP positives in healthy dogs that are hematologically normal. By PCR testing, most of these healthy dogs are negative for *E. canis* DNA, suggesting that they have cleared the infection immunologically. In contrast, Dr. Eberts would only rarely detect *Ehrlichia* SNAP-positive dogs in his geographic area. Now, if you go to São Paulo, Brazil, and you do a somewhat different clinical experiment, 75% of the dogs will have *E. canis* antibodies and about 80% of the sick dogs will be *E. canis* PCR-positive in our laboratory. So one story does not fit all dogs or all geographic locations. The more I look at patterns of tick-transmitted pathogens, the more I am amazed and confused.

**Alleman:** I also have a hard time understanding these diseases. You think you know what you are doing and then you realize that the diseases are much more difficult to manage than you thought. A lot has to do with the organisms’ adaptability. They are experts at adapting to their environment, and I question whether we really have optimal antimicrobial therapy for some of these infectious agents.

**Ford:** Dr. Breitschwerdt, let me ask you about *Anaplasma* in the same context. What are the results of four weeks of doxycycline?

**Breitschwerdt:** Following Dr. Alleman’s theme, I am confused about *Anaplasma*. I used to believe that most dogs or people infected with *A. phagocytophilum* would behave in a similar manner to *R. rickettsii* infection: acute infection, rapid response to doxycycline, and then immunologic protection with elimination of the organism. The work that Dr. Alleman is doing, as well as a publication out of Sweden, argue against that conclusion. After antimicrobial treatment with doxycycline, some dogs appear to remain chronically infected with *A. phagocytophilum*. For this organism, we need to determine how many dogs are immunologically or therapeutically cured after infection. There must be some immunologic cure in people and in dogs because in Dr. Eberts’ area, 30% of people have *A. phagocytophilum* antibodies, and in many instances they have never been treated. Dr. Eberts, what was the *A. phagocytophilum* seroprevalence in dogs in your practice?

**Eberts:** It’s about 52%.

**Breitschwerdt:** So more than half the dogs coming into Dr. Eberts’ practice have been infected with this organism at some point in time. The burning question is what portion of these dogs are acutely infected, previously infected, or chronically infected? We do not know at this time.

**Ford:** Are we curing these dogs?

**Breitschwerdt:** Perhaps not. I have changed my opinion based on Dr. Alleman’s findings.

**Eberts:** There’s one thing I want to clarify from our earlier discussion. When we were talking about treating a healthy seropositive dog, we discussed my practice tracking dogs that were treated with doxycycline and those that weren’t. And none of the dogs we treated ever became ill with signs of Lyme disease. Although I expect 25% of untreated dogs to become ill within the next 12 months, preemptive treatment seems to lower that percentage dramatically. I have been able to decrease the number of clinical Lyme cases by utilizing aggressive screening and aggressive intervention. Treatment appears to be an enormous benefit to the dogs in my practice.

Regarding Lyme disease and anaplasmosis, if the dog is clinically ill, there are three indications that tell me I am pursuing the right treatment. The first is fever. When I initiate doxycycline therapy with both Lyme disease and anaplasmosis, I expect that fever to break within 12 hours. If it doesn’t, I need to reevaluate the case. The second indication is the clinical illness: vomiting or joint pain in dogs with polyarthritis. I expect that to resolve significantly within 24 hours. The third indication is...
overall wellness. When is that dog going to be up and moving around normally? Sometimes that can take 48 to 72 hours.

These are the indications I expect to see when I initiate treatment in the sick dog. If I am not seeing these results, I know that I need to revisit my diagnosis quickly. In terms of long-term cure, I know that I’m not curing my patients with Lyme disease; I’m managing them.

I’m not sure about anaplasmosis. Although treatment results in resolution of clinical signs, I worry about them getting sick two or three years later. And if they do become clinically ill, is that because of re-exposure or recrudescence of a chronic infection? I don’t know.

**Ford:** IDEXX is supporting research efforts in Dr. Alleman’s laboratory, as well as other specific research projects to clarify this. I’m impressed that, besides developing a test that has documented sensitivity and specificity, IDEXX is also trying to fill in the scientific gaps to help us understand these diseases.

**Alleman:** I agree. The work that IDEXX has allowed me to do has resulted in some good scientific knowledge, but one of the issues that Dr. Breitschwerdt addressed is the question of whether it’s possible for laboratory conditions to mirror what happens in nature. Under experimental conditions, we have seen dogs infected with *Anaplasma* actually carry the organism for almost a year.

“**Under experimental conditions, we have seen dogs infected with Anaplasma actually carry the organism for almost a year.”**

—Dr. Rick Alleman

and we might not be able to eliminate *Anaplasma* infection either.

There has been some indication of that in human medicine. One report describes a post-infection syndrome in people who were treated for anaplasmosis. Up to 24 months after treatment, some participants complained of continued poor health and some had elevated liver enzyme activity. Some had a persistent *Anaplasma* antibody titer.

**PREVENTION**

**Ford:** Obviously, we would rather prevent these diseases than treat them. Today, it’s fair to say that we have better formulations available for tick prevention than we’ve ever had. Dr. Eberts, could you talk about how you select and use tick preventives?

**Eberts:** Tick control is an important part of what I do on a day-to-day basis—both for maintaining patient health and generating practice revenue. To select the right product, you need to understand your patient’s lifestyle. That will affect client compliance and also help you anticipate the product’s efficacy. I live in the state of 10,000 lakes, so the frequency of swimming and product application will affect my decision making when I choose a product.

Next is follow-up because not all products work equally well in every individual. So you need a systematic plan. I start off with a topical, and if I still observe ticks—which I often do, especially toward the end of the month—I will change my protocol. Sometimes we will try more frequent applications or I may combine the topical with an amitraz collar.

Client communication is also key to avoiding adverse reactions. The one that comes to mind is misuse on cats. Many times clients will apply these products on cats, and the pets die or become very ill. And I’ve seen dogs get sick from the wrong dose, too. It is important to maintain good communication, especially if you are using products in an extra-label manner.

**Ford:** What is your response to clients who are concerned because they are still seeing ticks even with a topical preventive?

**Eberts:** You have to understand the product’s limitations. Fipronil, for example, doesn’t have a product claim as a tick repellent. Although it’s very effective in killing ticks, they don’t die immediately following application of the product. Ticks may still crawl on the animal for a short period following application, and the client needs to know that. I try to find out if the ticks are just crawling on the pet and then dying or if they’re engorged, which tells me they’ve had a blood meal and my product is not working. That dictates
whether I need to change my strategy. The approach is different for each pet.

**Ford:** Although vaccination plays a key role in prevention, the only vaccine for tick-borne disease is, of course, the Lyme disease vaccine. Dr. Eberts, are you vaccinating dogs against Lyme disease in Minnesota?

**Eberts:** Yes, we vaccinate aggressively for the disease with the understanding that the vaccine may not prevent infection in all dogs following exposure. We still have had many clinical cases of Lyme disease even though we started vaccinating dogs 15 years ago. It was not until we incorporated the screening diagnostics with good tick control that we dramatically reduced the cases of Lyme disease. So I believe in vaccinating when you see a significant number of patients infected with these organisms.

**Ford:** Is Lyme disease a core vaccine in your practice?

**Eberts:** Yes. In my area with a 40% incidence of Lyme infection, I recommend it for all dogs, even small lap dogs.

**Ford:** I’d like your recommendations for traveling pets. What would you advise veterinarians to do when they know a patient will visit a tick-endemic area—vaccination, topical products, or prophylactic doxycycline?

**Eberts:** The bottom line is if you can prevent tick infestation, you can prevent all of the problems that we’ve talked about. So the first and most important step is client education. Pets need tick control, and they need to be on it preemptively.

The second step is vaccination. You would be surprised by the large number of seasonal clients who come from Arizona or Florida to spend time at their summer homes. I tell them to come see me right after they arrive so I can booster the dog for Lyme disease as a secondary step in protecting against infection.

In terms of doxycycline, I do not believe in blind preemptive therapy. It’s not practical, and it is not a good strategy for long-term disease control. We need to use antibiotics when pets have infections.

**Ford:** If you are advising a seasonal client who will be returning to Minnesota next year, when do you recommend they get the vaccine?

**Eberts:** Within two to four weeks of departure is ideal, but sometimes that is not practical. Practices in nonendemic areas are not going to stock Lyme disease vaccine. In those cases, my advice is to unpack their bags when they arrive and come see me later that first day because it just takes a minute to get that shot on board.

**Ford:** I would like to close with a general question to the panelists. In the context of emerging vector-borne diseases, what is of emerging importance? Is it diagnostics? Is it therapeutics? Where should the emphasis be in the future?

**Alleman:** The work that has been done with *A. phagocytophilum* in recent years has highlighted the fact that canine infection is much more significant than we thought five to 10 years ago. Also, the work that Dr. Breitschwerdt is doing with *Bartonella* has been eye-opening. Bartonellosis will continue to be problematic for those of us working in vector-borne diseases.

**Breitschwerdt:** *Cytauxzoon felis* is an important emerging tick-transmitted disease of cats. The geographic distribution has expanded, and the incidence has increased dramatically in the last several years.

Adam Birkenheuer’s group at North Carolina State University has developed a PCR test that can rapidly detect DNA in the blood of an acutely infected cat. This diagnostic test has greatly facilitated early diagnosis and more rapid treatment interventions rather than waiting until the organism can be visualized on a blood smear. They are also conducting a treatment modality study that is generating useful information for veterinarians attempting to treat this serious and often fatal tick-borne illness. The last three infected cats that we treated at NC State have all lived, and, historically, most cats have died.
As Dr. Alleman alluded to, bartonellosis has become an extremely important zoonotic disease for which there is increasing evidence to support tick-transmission of *Bartonella* species. Currently, investigators throughout the world are trying to determine the extent to which various tick species are vector-competent for *Bartonella* transmission.

**Ford:** Dr. Eberts, from your standpoint in clinical practice, what is a pressing issue or a future need?

**Eberts:** The most dangerous thing a clinician can do is be complacent. It is easy to disregard the lesser-known tick-borne diseases because we don’t fully understand them, but it doesn’t mean they’re not affecting our patients. I think we need to expand testing for some of these infectious diseases we know are out there—babesiosis, anaplasmosis, bartonellosis—as a routine protocol for some sick animals, and we are developing the technology that will help us do that. This is especially important in cases that are not responding the way we expect them to. We shouldn’t treat first and then do the diagnostics as a last resort. We need to perform the advanced diagnostics up front on these cases and then determine treatment options.

**REFERENCES**


“We need to perform the advanced diagnostics up front in these cases and then determine treatment options.”

–Dr. Richard Ford