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Boxer Update

A NESTLÉ PURINA PUBLICATION DEDICATED TO BOXER ENTHUSIASTS

VOLUME 17 | SPRING 2019

EFFECT OF BARTONELLOSIS

Boxers Susceptible to Heart Disease Endocarditis

PURINA

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BOXERS WITH BARTONELLOSIS

PRONE TO HEART DISEASE



The first documented case of endocarditis associated with *Bartonella clarridgeiae*, a bacterium causing bartonellosis, was in April 2000 in a Boxer being treated at the University of California-Davis Veterinary Medical Teaching Hospital.

The 2 ½-year-old male had a history of heart disease, having been diagnosed with a heart murmur at 16 months of age related to severe valvular aortic stenosis. Now, the trip to the hospital's emergency clinic was due to endocarditis, an inflammation of the heart's inner lining and valves.

Bruno Chomel, DrSc, DVM, PhD, professor of zoonoses in the Population Health and Reproduction Department, remembers the Boxer's case. "He was lethargic and too weak to walk," he says. "An electrocardiogram showed an acute third-degree atrioventricular block, meaning the heart's conduction between the atria and ventricles was severely impaired. The dog died of cardiopulmonary arrest, while the veterinary team was trying to implant a pacemaker."

A necropsy and blood culture were performed. The necropsy confirmed severe aortic endocarditis, and the blood culture was positive for a gram-negative organism identified as *B. clarridgeiae*, a genus of the *Bartonella* bacteria family that causes a group of vector-borne diseases collectively known as bartonellosis.

The source of the Boxer's *B. clarridgeiae* infection was a mystery, though the owner's cats could have been a factor. "Cat fleas are the main species that infect dogs with this bacteria," Dr. Chomel says. "We realized we needed to investigate this more to better understand how *B. clarridgeiae* is transmitted among cats and dogs, as well as the respective roles of fleas and ticks as vectors for this bacterium and the potential risk for humans to acquire this infection."

A scientific article detailing the Boxer's aortic valve endocarditis caused by *B. clarridgeiae* was published in October 2001 in the *Journal of Clinical Microbiology*. This was the second incidence of *Bartonella* species causing clinical disease in dogs.

AN EMERGING DISEASE

Bartonellosis is one of the most important emerging infectious diseases in dogs and humans, says Edward B. Breitschwerdt, DVM, DACVIM, the Melanie S. Steele professor of medicine and infectious diseases and co-director of the Vector Borne Disease Diagnostic Laboratory at North Carolina State University. Infections can be life-threatening in dogs, thus the importance of early diagnosis for a better prognosis.

Related to the pathogen's effect in Boxers, Dr. Breitschwerdt says, "Exactly why bartonellosis manifests as endocarditis or myocarditis (inflammation of the heart muscle) in this breed has yet to be determined. In our experience, Boxers and Golden Retrievers do not handle *Bartonella* well, though bartonellosis occurs in all breeds, particularly affecting large-breed and mixed-breed dogs."

Meanwhile, researchers in Israel discovered *Bartonella henselae* and *Bartonella koehlerae* in two littermate Boxers that died from endocarditis. Their findings were

published in 2010 in *Veterinary Microbiology*. It was the first time these *Bartonella* species were identified in dogs with endocarditis, suggesting their pathogenic role in the dogs' heart disease. It also was the first time *B. koehlerae* was reported in dogs.



B. henselae DNA was detected in aortic valve tissue from one of the Boxers that had been diagnosed with moderate subaortic stenosis. The other Boxer, diagnosed with severe subaortic stenosis, was found to have *B. koehlerae* DNA in its aortic valve. *B. henselae* also was identified in a spleen aspirate from the dogs' dam and from a cat that lived in the house with the dogs. It was not known exactly how

ONGOING RESEARCH TO UNDERSTAND & DIAGNOSE BARTONELLOSIS IN DOGS

The American Boxer Charitable Foundation is sponsoring two studies funded by the AKC (American Kennel Club) Canine Health Foundation aimed at better understanding and diagnosing *Bartonella* infection in dogs.

- [A three-year, \\$219,026 study at North Carolina State University led by Dr. Edward B. Breitschwerdt and Dr. Matthew Breen](#) is looking at a possible association between *Bartonella* infection and cardiac and splenic hemangiosarcoma in dogs in certain geographical areas of the U.S.
 - [A three-year, \\$120,983 study at Western University of Health Sciences led by Dr. Pedro Diniz](#) involves the development of a next-generation sequencing diagnostic platform for studying tickborne diseases in dogs and determining the bacteria responsible for disease.
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CLINICAL SIGNS OF BARTONELLOSIS IN DOGS

- Fever
- Lameness
- Swollen or inflamed lymph nodes
- Vomiting
- Diarrhea
- Cough
- Seizures
- Arthritis

the *Bartonella* was transmitted to the Boxers, but a possibility was cat fleas, a common vector for both species, given that the cat and the dogs shared the same household.

Although the *Bartonella* pathogen has existed and evolved for millions of years, only two species, *Bartonella bacilliformis* and *Bartonella quintana*, were identified worldwide before 1990. *B. bacilliformis* was recognized because the bacteria are visible on a blood smear, whereas other *Bartonella* species are not seen on blood smears under the microscope using standard testing at clinical pathology laboratories. Today, more than 44 *Bartonella* species and subspecies have been named.

“Understanding this disease is complicated by the fact that bartonellosis is transmitted in myriad ways,” Dr. Breitschwerdt says. “*Bartonella* species are probably transmitted by more vectors than any other pathogenic organisms that exist on the planet. Primarily arthropod vectors such as fleas, ticks, sand flies, and lice carry the pathogen, though spiders, bed bugs, and deer keds can carry these bacteria as well.”

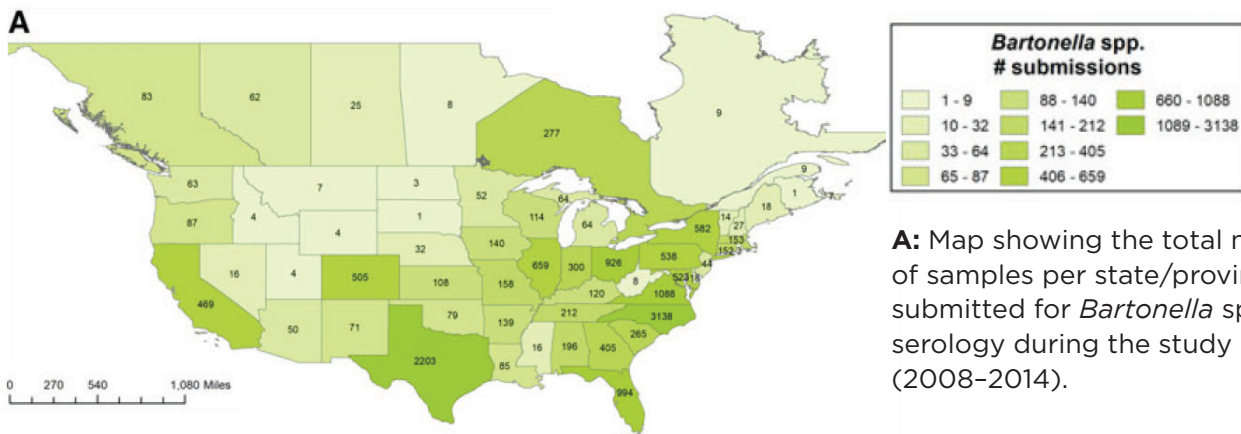
A zoonotic infectious disease, bartonellosis can be spread to people from infected animals. Dr. Breitschwerdt worries that owners

of infected dogs, veterinarians and veterinary technicians are particularly at risk of getting sick. “I receive six to eight emails a week from affected people or veterinarians seeking advice and help,” he says. “I estimate that up to 25 percent of sick veterinarians have *Bartonella* DNA in their blood due to exposure to infected animals. Direct contact with body fluids, a needle stick, scratch or bite from an infected animal puts a person at risk.”

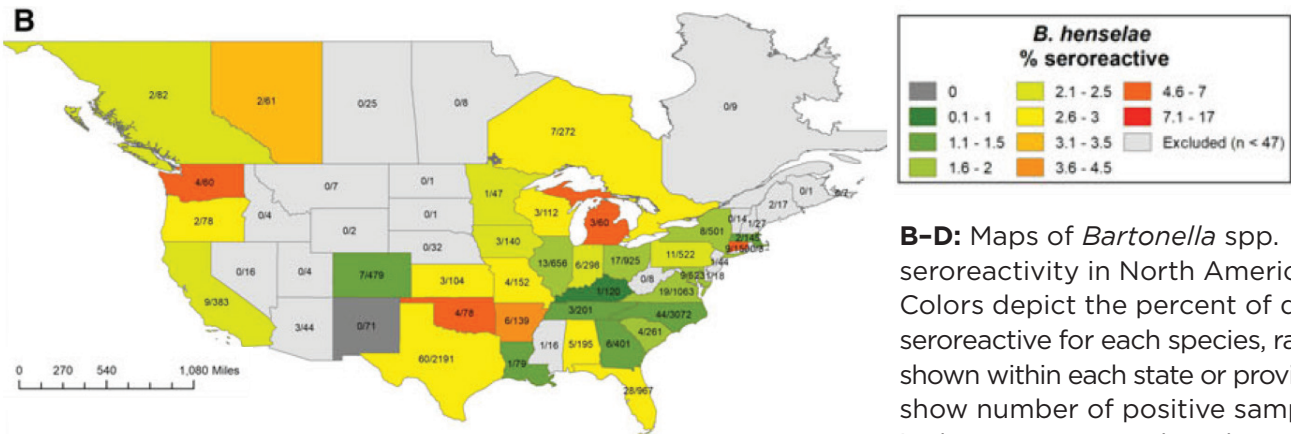
THE STORY OF ‘TUMBLEWEED’

In 1993, the first incidence of *Bartonella* infection in a dog with endocarditis was recognized in Dr. Breitschwerdt’s laboratory. “Tumbleweed,” a 3-year-old yellow female Labrador Retriever, had been unsuccessfully treated for nine months when she arrived at the North Carolina State Veterinary Hospital extremely ill with endocarditis.

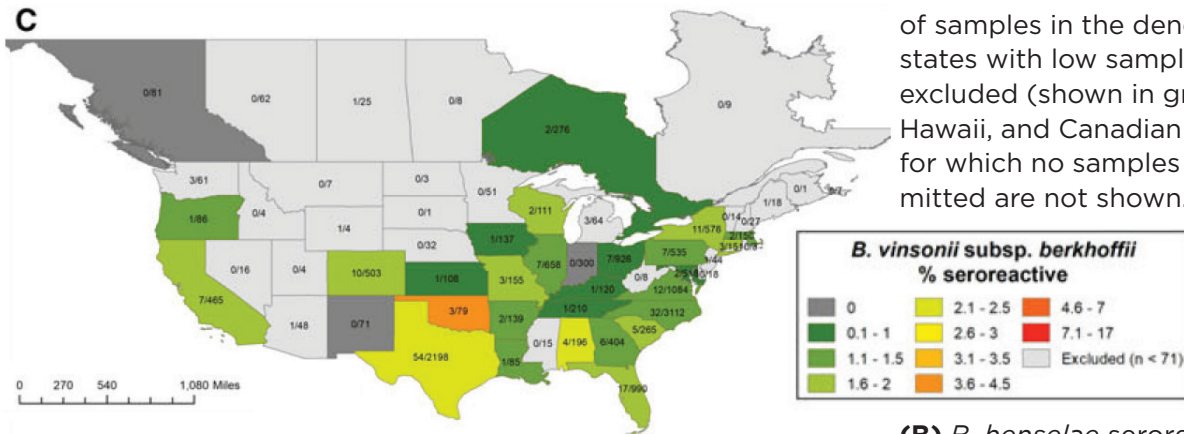
“Initially, the primary veterinarian said she was lethargic and had intermittent loss of appetite,” says Dr. Breitschwerdt. “She had a shifting-leg lameness that suggested polyarthritis and was also mildly anemic and hyperproteinemic (abnormally high blood protein level). Two weeks later, she had a grand mal seizure and spontaneous urination. For the next month, her



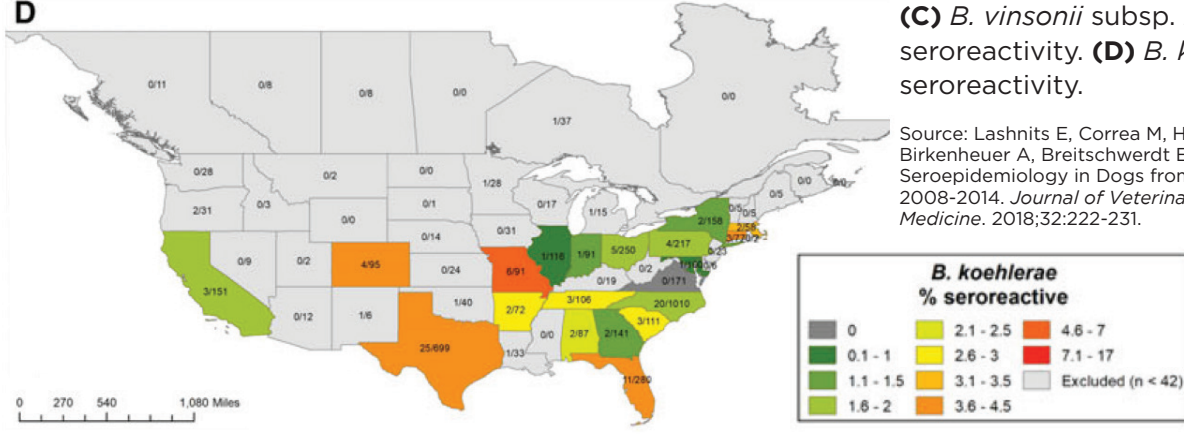
A: Map showing the total number of samples per state/province submitted for *Bartonella* spp. serology during the study period (2008-2014).



B-D: Maps of *Bartonella* spp. seroreactivity in North America. Colors depict the percent of dogs seroreactive for each species, ratios shown within each state or province show number of positive samples in the numerator and total number of samples in the denominator; states with low sample sizes are excluded (shown in gray). Alaska, Hawaii, and Canadian provinces for which no samples were submitted are not shown.



(B) *B. henselae* seroreactivity. **(C)** *B. vinsonii* subsp. *berkhoffii* seroreactivity. **(D)** *B. koehlerae* seroreactivity.



Source: Lashnits E, Correa M, Hegarty BC, Birkenheuer A, Breitschwerdt EB. *Bartonella* Seroepidemiology in Dogs from North America, 2008-2014. *Journal of Veterinary Internal Medicine*. 2018;32:222-231.



lethargy continued along with weight loss, epistaxis (nose bleeds) and ultimately endocarditis.”

The referring veterinarian was treating Tumbleweed for systemic lupus erythematosus with immunosuppressant drugs based on a positive autoantibody test. Coincidentally, the medications most likely increased the amount of *Bartonella* in her blood, making it more detectable by isolation and polymerase chain reaction (PCR) testing.

Dr. Breitschwerdt and his team luckily isolated the bacterium and realized it was a new *Bartonella* subspecies, which they named in collaboration with researchers at the Centers for Disease Control and Prevention as *Bartonella vinsonii* subsp. *berkhoffii*. More than half of dogs infected with this pathogen lack an antibody response, thus making serology (blood testing) an insen-

sitive diagnostic testing modality.

The risk factors fit Tumbleweed’s lifestyle: heavy flea and tick exposure and rural home environment. Additionally, endocarditis associated with *B. vinsonii* subsp. (*berkhoffii*) occurs in large-breed dogs with a potential predisposition for aortic valve involvement, such as retrievers.

“Tumbleweed was the first dog in the world found to have a *Bartonella* bacterium, and she ended up with one never previously isolated,” says Dr. Breitschwerdt. “Subsequently, I wanted to know how often we had missed the diagnosis of bartonellosis in the past. In short order, we realized that it was virtually impossible to prove a dog was infected with *Bartonella* using cultures. This resulted in ongoing efforts to confirm the diagnosis of bartonellosis in dogs and humans.”

Dr. Breitschwerdt was the lead

investigator of a [two-year, \\$103,013 study funded by the AKC \(American Kennel Club\) Canine Health Foundation](#) that focused on developing a more sensitive diagnostic assay to identify bartonellosis in dogs. Completed in 2018, the study explored using improved blood diagnostic tests to detect the disease and to aid prevalence studies. Importantly, an improved blood test would help to establish an early and accurate diagnosis.

“This proved not as easy as we were hoping it would be,” he says. “Our objective was to evaluate the sensitivity and specificity of *Bartonella* immunofluorescent antibody assays (IFA) using eight cell culture-grown *Bartonella* isolates. IFA testing is the historical ‘gold standard’ for *Bartonella* blood diagnosis in animals and humans, though most diagnostic laboratories test against only one or two *Bartonella* species. We thought testing against a broader panel of *Bartonella* antigens would enhance diagnostic abilities.”

An article of the research [was published in 2018 in the *Journal of Veterinary Internal Medicine*](#). Importantly, the research team concluded that IFA sensitivity remained poor, and the need to develop a reliable blood test to facilitate the diagnosis of *Bartonella* infection in dogs remains an ongoing objective for them.

THE ROLE OF GENETICS

Part of the challenge in studying *Bartonella* is due to the bacteria’s ability to invade and live within many different cells in the body. “If you are trying to understand the pathogenesis of a disease process, particularly in individual patients, it helps if the organism only affects one organ system,” Dr. Breitschwerdt says. “In this case, the disease pattern can vary among dogs of a particular breed and also among breeds.”

Genetics are likely to play a role

in the disease progression. A dog’s nutritional status and environmental factors also are important.

Bartonellosis in dogs has been shown to affect three organ systems:

- Cardiovascular, causing endocarditis or myocarditis
- Neurologic, including seizures or paralysis
- Rheumatologic, affecting the joints

“Treatment is complicated, and a dog can be sick for months prior to diagnosis,” says Dr. Breitschwerdt. “Most dogs require more than one antibiotic to recover, usually given over six weeks. Treatment also often involves managing hormonal changes affecting the thyroid and adrenal glands, decreasing stress affecting the dog, and getting the immune system reconstituted so that antibiotic elimination of the infection can be achieved. Dogs caught early and treated with antibiotics typically fully recover.”

Research to better understand dogs’ immune response to bartonellosis potentially would help researchers improve diagnostics. Ultimately, this information could be used to develop a protective vaccine to prevent the disease.

“It is absolutely critically important to develop a vaccine for bartonellosis,” Dr. Breitschwerdt says. “Dogs are our best sentinels to understand the epidemiology of this disease and its transmission. It is necessary to determine how we protect dogs from getting this and how we keep dogs from potentially giving bartonellosis to their owners.” ■

Purina thanks Dr. Joyce Campbell, chair of the American Boxer Club Health and Research Committee and a trustee of the American Boxer Charitable Foundation, for helping us to identify this topic for the *Boxer Update*.

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