

# Leishmaniasis Control in Dogs

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

[Sarah Gregory] Hi, I'm Sarah Gregory, and today I'm talking with Dr. Domenico Otranto in Italy. Dr. Otranto is a professor of human and animal parasitic diseases in the Department of Veterinary Medicine at the University of Bari.

Welcome, Dr. Otranto.

[Domenico Otranto] Buongiorno Sarah. Hi!

[Sarah Gregory] Hi!

[Domenico Otranto] And thank you for inviting me. It's a pleasure to be here today.

[Sarah Gregory] So, let's begin. Could you explain what leishmaniasis is? Where does it usually occur, and what are its symptoms?

[Domenico Otranto] Yes, Sarah. I would say, leishmaniasis, because almost 21 species of *Leishmania* protozoa have been isolated from humans, and they may cause cutaneous, mucocutaneous, and visceral forms of the disease.

So, they represent a major burden in endemic areas, with at least 350 million people at risk in the world and approximately 1.5 million new cases each year. These infections have been known for centuries overseas, as they have been supposed to be originated in South America, about 47 to 36 millions of years ago. And just consider that cutaneous forms have been represented in potteries, "huacos," in pre-Colombian times. And they were also well known in the Mediterranean Basin, in the Middle East as "bouton de Aleppo."

So, they are typically anthroponotic...they are typically anthroponotic *Leishmania* species, such as *Leishmania donovani*, and other zoonoses, such as *Leishmania tropica*, *major*, and *infantum*. The latter, *Leishmania infantum*, is the main agent of canine leishmaniasis, which is one of the most important vectorborne parasitic diseases of dogs, occurring on all countries except Oceania.

So, their distribution is mostly tropical and subtropical. *Leishmania* is endemic in Eurasia, Africa, and the Americas, although I would say that *Leishmania* causing cutaneous lesions on macropods, like kangaroos or wallabies, has been characterized in the north of Australia.

So, the epidemiology of leishmaniasis is complex, as it involves different vectors, hosts, and parasite species living in a constantly changing environment. Other factors have been relevant in the introduction and spread of the disease to regions where infections were not previously found. For example, the adoption and transportation of dogs from areas of canine leishmaniasis endemicity or the establishment of permanent sand fly vector populations in previously free areas. Which is the result...so, the result is *Leishmania* is expanding to new areas in Europe, northwards from the Mediterranean regions, and in the Americas, southwards, to the triple-border between Argentina, Brazil, and Paraguay, and has also reached Uruguay.

So, the pathogenesis of this disease is rather complicated. Indeed, depending on the parasite tropism, amastigotes invade macrophages in the skin, mucosa, and internal organs, mostly the spleen, the liver, and bone marrow, and they cause their depletion. Accordingly, this pathogenesis I briefly summarize: clinical presentations may vary from localized skin lesions to

generalized disease, with fever, weight loss, enlargement of the spleen and liver, anemia, leukopenia, and thrombocytopenia.

In dogs, the infection by *Leishmania infantum* may be asymptomatic. And this is quite important considering over 80% of the cases in some areas are asymptomatic or may evolve to life-threatening overt disease with a wide range of clinical signs, from localized skin alterations to severe loss of weight and generalized lymphadenomegaly.

Therefore, it's really difficult to say which are the symptoms, because the severity of the infection depends on the host's immune system, nutritional status, but also by protozoon species by themselves and the strain, and also to a lesser extent, sand flies...by the sand fly species involved in the transmission. Yes, just a detail, this infection is transmitted by small, tiny yellowish insects also known as sand flies.

[Sarah Gregory] So, how does it spread?

[Domenico Otranto] So, the *Leishmania* protozoa are transmitted through the bites of sand flies, Phlebotominae. These are the only proven biological vectors of the parasites, although biting midges infected by *Leishmania* have been found in Australia. Secondary modalities of transmission in dogs may be sexual or congenital, as well as transmission by blood transfusion. In a study conducted in Madrid in human patients, the amastigotes of *Leishmania infantum* have also been found in macrophages from 34 to 52 percent of discarded syringes of drug addicts. And this raises the question on possible mechanical transmission among drug users. However, I would say that all these secondary modalities are of minor concern, since I would say that the only relevant transmission way for these protozoa are sand flies.

[Sarah Gregory] So, what animals can get...can get it besides dogs and humans?

[Domenico Otranto] In most cases, leishmaniasis are zoonoses, affecting the poor in rural and natural areas where a plethora of domestic and wild reservoir hosts and sand fly vectors maintain the infection. While there is an increasing number of other mammalian hosts, like cats, rats, foxes, dogs really have...they play a major role in maintaining and transmitting the infection to other receptive hosts through the sand fly vectors.

So, just consider that in disease-endemic areas, 13 out of the 21 human-infective *Leishmania* have also been reported in domestic dogs. However, many species of rodents, marsupials in the wild are considered hosts as alternative reservoirs of zoonotic *Leishmania*. For example, the reservoir of *Leishmania major* in the Middle East are gerbils.

[Sarah Gregory] Some countries are trying to control this disease by culling dogs. Tell us about this culling.

[Domenico Otranto] Yes, indeed. Dogs are regarded as the principal reservoirs of *Leishmania infantum*, which is so far considered the most important and spread zoonotic *Leishmania* species. Therefore, as far as canine leishmaniosis, the culling of seropositive dogs has long been the recommended for a control strategy in several countries, as a means to decrease the prevalence of infection in dogs, and ultimately reducing the incidence of human leishmaniasis.

So, we know that the culling of animal reservoirs has been a common practice since ancient times for controlling the propagation of many diseases of zoonotic concern, not only leishmaniasis, including rabies, for example. However, the impact of this measure on disease transmission depends on the biology and virulence of the etiological agents which are...that are

involved, or on the transmission modality, direct versus vector transmission, the number...on the number of animals infected and of those that are culled, the epidemiological scenario, epidemiology versus endemic situation, and also the existence of alternative wildlife reservoirs. So, the rationale is that dogs serologically positive to *Leishmania infantum* are culled in order to reduce the number of infected dogs and ultimately the risk of zoonotic visceral leishmaniasis in humans, for example, in Brazil, where about 3,500 human cases of visceral leishmaniasis are reported each year. But this strategy is absolutely not successful.

[Sarah Gregory] What are the ethical implications of culling? And I want to say here for listeners in case there are a few that don't...aren't clear that culling is euthanizing, right? Killing the dogs?

[Domenico Otranto] Yes. I will say that, as a scientist, veterinarian, and as the representative of the most evolved biped animal living on our earth, I just say that we should not be killing other animals. This was the teaching of many great persons, such as San Francesco from Assisi, who left a mark in the way of thinking of the Western culture, also for non-Catholics.

However, coming back to canine leishmaniosis, as veterinarians, we swear to use scientific knowledge and skills for the benefits of society through the protection of animal health and welfare, the prevention and relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge. So, specifically, an important weakness of this strategy for canine leishmaniosis could be represented by culling seropositive, but healthy, dogs which have a minimal, if not null, impact in the spreading of the infection to animals and humans. This is just unethical. Again, scientific data clearly suggest that dog culling is not a useful strategy for the control of visceral leishmaniasis by *Leishmania infantum*. For example, in Brazil, where it is a common practice, there has not been any reduction in the overall year number of human cases and, therefore, would be unethical to kill animals.

[Sarah Gregory] Where is dog culling most commonly practiced?

[Domenico Otranto] This practice is recommended officially in South America: Argentina, Brazil, Colombia, Uruguay and Venezuela; in the Mediterranean region: Morocco, Tunisia; Middle East and Central Asia: like Armenia, Azerbaijan, Iran, Iraq, Syria, Uzbekistan. But in many parts of the world where there is not an official recommendation, but it is eventually unofficially done in practice, there...dog culling is a common practice as well, like in South America: Paraguay, in Albania and Algeria in the Mediterranean area, also in Middle East and Central Asia.

However, we should mention that, for a long time, dog culling strategy was applied indiscriminately to all seropositive dogs. For example, in Brazil, regardless if they were sick or subclinically infected, regardless if they were not only exposed or truly infected. Nowadays, something is changing. Owners have the right to treat their dogs, if infected and sick. So, the dog culling strategy is becoming selective... this is really important... and it has been for a long time in other countries where canine leishmaniasis is endemic. For instance, in the United States, seropositive dogs may be eliminated, but only if the owners agree. Whereas this strategy is not accepted in the European Union, where euthanasia is generally reserved to severely sick dogs, as a means to avoid prolonged suffering. So, you see, the situation is quite different all over the world.

[Sarah Gregory] Is it mostly pets or strays that are culled?

[Domenico Otranto] The procedures of the dog culling strategy may vary from region to region, as mentioned, but typically reservoir control programs target privately owned dogs that are seropositive and stray dogs, regardless if seropositive or not. In endemic areas, so where fatal cases have been reported, some dogs owners may voluntarily give their seronegative dogs due to their fear of the disease. This is a problem.

The real problem for the governments is represented, in my opinion, by the unowned infected dogs. For example, in Italy, under the EU no-kill regulation, unowned dogs are usually serologically screened before entering into a municipal kennel and, if positive and sick, their treatment is covered by the municipality. So, you clearly understand that the adoption of such policy is very expensive in the era of the global economic crisis and this is completely unrealistic in developing countries. In addition, I would say that putting several infected dogs in a kennel could represent a public health risk if sand flies are not controlled and if noninfected dogs living within and nearby the kennel are not permanently protected against sand flies with topical insecticides.

[Sarah Gregory] You're part of the Companion Vector-Borne Diseases World Forum. What is this group?

[Domenico Otranto] So, the Companion Vector-Borne Diseases World Forum is a group of key opinion leaders working on canine, feline vectorborne diseases. And it was created by Norbert Mencke, Bayer Animal Health, a specialist in the field of parasite prevention, more than 15 years ago. He was extremely brave in understanding the significance of companion vectorborne diseases and their impact on our lives.

We share our planet with pets but also with many blood-feeding ectoparasites like ticks, fleas, mosquitoes, and sand flies, which transmit a plethora of viral, bacterial, protozoan, and helminthic pathogens which may cause diseases such as Lyme...Lyme borreliosis, babesiosis, and leishmaniasis. Many of these diseases are also zoonotic. And this group contributes to an ongoing discussion and update on vectorborne diseases from around the world, and their effect on dogs, cats, and also humans.

[Sarah Gregory] How did this group get involved in the discussion about canine leishmaniasis and dog culling?

[Domenico Otranto] Yes...as scientists, as you know, we try to translate results coming from our researches in advices for policymakers. For example, over the last 20 years, I have been involved in many projects on the control of canine leishmaniasis in Europe as well as in other regions of the world, such as in Brazil, with my colleague and friend Filipe Dantas-Torres from Fiocruz in Recife, Brazil. Hence, since canine leishmaniasis is one of global importance, we discussed about the control of the disease. And we tried just to be more proactive. And at the 13th Symposium of CVBD World Forum, held in UK on March 2018, we discussed about the control of canine leishmaniasis caused by *Leishmania infantum* in the context of One Health, and consolidated a consensus statement regarding the usefulness of dog culling as a means of controlling visceral leishmaniasis.

[Sarah Gregory] Okay. So, the Companion Vector-Borne Diseases World Forum put together a statement about whether or not culling is effective. Can you summarize that statement?

[Domenico Otranto] It is important to clarify that this statement was based on the systematic reviews of studies evaluating the effectiveness of dog culling as a means of control strategy. This is really important. Based on that, we have concluded that available scientific information is insufficient to support its use. For example, in spite of thousands of dogs culled every year in Brazil, the prevalence of canine *Leishmania infantum* infection is still high in several foci. Finally, dog culling is ineffective.

Therefore, for the control of canine leishmaniasis and for reducing the risk of human infection, companion animals should be protected from sand fly bites in order to prevent, firstly, the leishmania infection, then the spread from already infected dogs. Additional control measures, including environmental vector control, vaccination, and prophylactic medication, may also be used when...when available. And finally, the dog culling strategy, in areas where visceral leishmaniasis is endemic, should be replaced with alternative “nonterminal” measures that can prevent infection in dogs. And this was our final recommendation.

[Sarah Gregory] Could you go into a little more detail about why culling, as horrible as it is, doesn't actually work?

[Domenico Otranto] Yes. The reasons for the failure of this strategy—of dog culling strategy—used, for example, in Brazil, have been extensively discussed in recent years and they include, for example, the fact any other animal, such as marsupials, rodents, and humans themselves, may act as the reservoir of *Leishmania infantum*. In addition, dog population screenings for *Leishmania infantum* may be inaccurate when based on serological tests, and the rapid...and also the rapid replacement of culled dogs with young animals increase the proportion of susceptible animals in the population. So, the ineffectiveness of such a strategy is indicated by the rising trend in the number of human cases of zoonotic visceral leishmaniasis observed between the 90s and 2010, in spite of the incalculable number of dogs which have been killed during the last decades in Brazil.

[Sarah Gregory] Okay. Talk to us now a little bit about leishmaniasis control in the context of One Health.

[Domenico Otranto] Yes. To reduce the burden of visceral leishmaniasis and other tropical diseases in developing countries, a better quality of life—better nutrition and housing conditions, access to basic sanitization, and so on—and increase access to basic healthcare should be promoted. And we believe that the synergism between medical physicians, veterinary practitioners, researchers, public health authorities, and politicians is central to found a new base platform for planning sustainable control strategies against canine leishmaniasis. So, these synergies amongst all these expertise is the best example of One Health perspective.

[Sarah Gregory] What are better public health strategies that would help to prevent leishmaniasis?

[Domenico Otranto] So, the better public health strategies that would help to prevent canine leishmaniasis, based on the epidemiology and the biology of this disease, and therefore, to reduce the risk of human infection, is to improve the general health and nutritional status and the housing of dogs: improve the environmental and the housing conditions, so as to enhance sand fly control and reduce the exposure of people to the vectors; to promote sand fly bite prevention to reduce the risk of *Leishmania infantum* infection in noninfected dogs and its spread from already infected dogs; and to implement latest concepts regarding the clinical management of

canine leishmaniasis, including approaches to diagnosis and treatment. You see, all these measures are both focused on improving human and animal health and welfare in their environment. This is the best example of One Health approach.

[Sarah Gregory] I believe you touched on this some earlier, but is there an actual preventative for dogs for getting leishmaniasis?

[Domenico Otranto] Yes, the use of repellents such as synthetic pyrethroids on dogs has become the most effective tool for preventing *Leishmania infantum* infection in these animals. Their mode of action, a toxin...a toxic and irritating effect on sand flies, causes insect disorientation and sudden abandonment of the host, followed by death soon after the landing of an insect on the coat of a treated animal. And...the blood feeding usually does not occur, the infection is usually prevented.

The efficacy of these repellents against sand flies has been evaluated under laboratory and field conditions with encouraging results. For example, the insecticidal effect of some of pyrethroids was experimentally tested against different sand fly vectors with generally positive results and high rates of anti-feeding effects. Therefore the use of pyrethroids with repellent properties in different formulations and preparations was demonstrated to be a suitable approach to reduce the risk of *Leishmania infantum* infection in dogs under natural conditions. So, based on current knowledge, topical insecticides used on dogs present a promising tool for reducing the transmission of infection to dogs. For sure, more large-scale studies would be needed to assess whether the massive use of collars in dogs living in a given community, would also significantly impact on the incidence of the disease in humans.

[Sarah Gregory] And along those same lines, how do you balance the use of insecticides to prevent diseases spread by sand flies and mosquitoes against potential risk...against the potential risk of being exposed to these chemicals?

[Domenico Otranto] So, we should clarify that control measures aimed at reducing vector populations in the environment have been employed with a transitory effect since it is typically unsustainable in the long term, as you mentioned, due to complex ecology of vectors as well as to the severe technical and economic reasons. For example, a variety of sand fly species may be potentially involved in the transmission of *Leishmania infantum*, and the ecology and behavior of each species may vary widely. Similarly, the size of the area to be treated in countries where leishmaniasis is endemic may be vast and make environmental control economically unaffordable.

However, the application of insecticides on the walls and roofs of human habitations and in animal shelters was shown to be effective in reducing the population of sand flies in outbreaks of human leishmaniasis, when a high density of sand flies is found near or in human habitations. Synthetic pyrethroids are currently used by public health authorities in several countries. But I would say that the treatment with pyrethroids of dogs is not really effective. It's not really...a major concern—even because synthetic pyrethroids are important to prevent not only sand flies, the sand fly bites, but also ticks, fleas, and other ectoparasites which may feed on dogs, so we need to treat our animals against arthropods.

[Sarah Gregory] Once a dog or a person gets leishmaniasis, is there a treatment for it?

[Domenico Otranto] Yes, sure, there are many. The treatment of canine leishmaniasis has evolved considerably in the past decades, and available protocols may promote clinical cure of

infected dogs, reduce parasitic load, and decrease the risk of *Leishmania infantum* transmission. Therefore, we have to clarify that the treatment of dogs with canine leishmaniasis is not only aimed at increasing their life expectancy and improving quality of life of diseased animals, but also to diminish the parasite load, and thereby reducing their infectiousness to sand flies.

For instance, a reduction in the *Phlebotomus perniciosus* infection rate—*Phlebotomus perniciosus* is one of the main vectors of *Leishmania infantum* in the Mediterranean basin—after the treatment with the meglumine antimoniate, alone or in association with allopurinol, was recorded in *Leishmania infantum*-infected dogs. So, the use of allopurinol in association with the meglumine antimoniate treatment could contribute to keeping dogs noninfectious, especially during the disease transmission season, which is from late May to early October in southern Europe. Altogether, these studies clearly indicate the benefits of treating infected dogs in areas where *Leishmania infantum* infection is endemic.

[Sarah Gregory] So, summarizing, overall, what steps do you think communities should take to prevent leishmaniasis and what do you foresee is the biggest challenge in this?

[Domenico Otranto] It's not easy...that's not an easy question. Leishmaniasis is a multifaceted disease and for this reason its control is not easy to achieve. In fact, the control of such a complex disease requires a well-rounded approach, based on current knowledge of the biology of the parasite and its vector, while also considering interaction with the host at individual and population levels.

At present, different strategies are available for the prevention and control of canine leishmaniasis, including vaccination, use of repellents, and the treatment of infected dogs, but not dog culling. Governmental authorities should set up affordable surveillance systems to optimize economic resources and to achieve the best outputs possible. Importantly, the effectiveness of the combined use of repellents plus vaccination in the prevention of canine leishmaniasis should be assessed in large-scale randomized controlled field trials.

So, the biggest challenge is probably represented by the high percentage of asymptomatic infections may occur in dogs and humans. Both may potentially serve as a source of infection to sand fly vectors. The definitive diagnosis also of *Leishmania infantum* infection in asymptomatic dogs is troublesome due to the inherent limitations of serological and parasitological methods. The immunogenic as well as immunosuppressive molecules released by sand flies while taking a blood meal greatly may interfere with the individual host immune response.

So, further studies on the interactions between immunomodulatory molecules, which represent...which are present in a population of sand flies, by sand flies, and the host immune response would contribute to the development of vaccines, for example, for sand fly-concealed antigens. Again, another concern is the cost...is the cost of control campaigns at the population level, which are often not affordable for the local governmental authorities in developing, as well as in developed, countries, in industrialized countries. So, in a time of global economic crisis, stray and sheltered dogs maintain...which are maintained in municipal kennels, may represent a risk factor for zoonotic visceral leishmaniasis transmission in areas with a high rate of infection and high vector densities. These are the biggest challenges, in my opinion.

[Sarah Gregory] Do you have dogs of your own?

[Domenico Otranto] Yes, two. They are Aragon, I have Aragon, who is a clever and energetic German Shepherd, and Zena, who is a lazy Labrador. Both complement each other—very similar

to the characters of my two daughters, Sofia and Agata, but I will not tell them this—and they have a great relationship with my family. Yep.

[Sarah Gregory] Yes, dogs are wonderful! Tell us about your job and what brings you the most joy from it.

[Domenico Otranto] Ah, okay. I feel as a researcher I have been privileged in becoming very early in my age, full professor at 33 years of age. Since then I have been working on vectorborne diseases, I was lucky enough in doing some amazing researches, such as elucidating the biological life cycle of the human eyeworm, *Thelazia callipaeda*, in Europe, and working on many basic and applied aspects of vectorborne disease-causing pathogens. And I have always been working with colleagues, ah, who become friends.

But the most thrilling thing of my job, in my opinion, is working with young researchers coming from all over the world. For example, sharing with them our research experience through the ParSCo, which is a residential parasitology summer course I organize with Filipe Dantas-Torres since seven years. It means sharing our lives and research experience with junior colleagues and it brings me the most joy. This...let me think... as my life would last even a little bit more than what actually shall be.

And definitely, I believe in the social commitment of all scientists. I believe that science should not only be free and available to all people and researchers in the world but it should also make people free.

And an important concept inspiring my daily life is the equality of all human beings must not be undermined by any form of discrimination—racial, political, economic, religious, gender, or based on one's sexual orientation, or poverty. We all deserve the same opportunities in our pursuit of scientific knowledge toward a better world for all. This is my main driver. And it is also clearly reported in the program of the 8th parasitology summer course we will run in Iran next summer.

[Sarah Gregory] Well thank you so much for speaking with us today, Dr. Otranto.

[Domenico Otranto] E' stato un piacere. It was really amazing. Grazie! Thank you. Ciao, Sarah.

[Sarah Gregory] Ciao!

And thank you listeners out there for joining us. You can read the December 2019 article, Canine Leishmaniasis Control in the Context of One Health, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for Emerging Infectious Diseases.

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