VISCERAL LEISHMANIASIS IN BRAZIL

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Abstract. Brazil is the only country endemic for zoonotic visceral leishmaniasis (ZVL) that regularly conducts epidemiologic and prophylactic control programs that involve the treatment of human cases, insect vector control, and the removal of seropositive infected dogs. This report reviews 60 studies reporting data on the efficacy of these recommended control tools and concludes that in Brazil 1) eradication of the disease in Minas Gerais was achieved by the concomitant use of the three control methods, 2) although seropositivity by an immunofluorescent assay is not completely related to infectiousness, the removal of seropositive dogs leads to a significant reduction of canine and human incidence, 3) improvement of the sensitivity of the diagnostic tool used for canine control should optimize the efficacy of control, and 4) although difficult and expensive, the public health dog control campaigns performed in Brazil reduced the incidence of ZVL and should be maintained since treatment of dogs is an unrealistic intervention, both because of its prohibitive cost and relatively poor effectiveness.

INTRODUCTION

Visceral leishmaniasis (VL) or kala-azar is a chronic and frequently lethal disease caused by protozoan parasites of the Leishmania donovani complex (Order Kinetoplastida). The etiologic agents are L. donovani and L. infantum in the Old World and L. chagasi in the Americas. The disease is lethal if not treated early after the onset of the symptoms. Clinical signs include malaise, anemia, cachexia, hypergammaglobulinemia, hepatosplenomegaly, and progressive suppression of the cellular immune response. Leishmania donovani complex species are intracellular parasites of monocytes and macrophages of lymphoid organs such as the spleen, lymph nodes, bone marrow, and liver. Their biological cycle alternates between the amastigote form in vertebrate host and the promastigote form in the gut of the insect sand fly vector.

Approximately 500,000 new human cases of VL are reported annually. More than 90% of them occur in Brazil, Bangladesh, India, and Sudan. During the last 16 years, (1984–1999), 37,294 new cases of human VL were reported by the Brazilian Ministry of Health (annual mean number = 2,330). Approximately 90% of these cases correspond to the northeastern region of the country, a semi-arid, and poorly forested area with xerophilic vegetation. Visceral leishmaniasis is mostly a rural disease, with a domestic or peridomestic epidemiology. Recently, however, the disease has been found in towns or in the outskirts of large cities such as Belo Horizonte, Montes Claros, Rio de Janeiro, Salvador, and Fortaleza.

Epidemiology of Visceral Leishmaniasis

Several species of vertebrate mammals have been found naturally infected with Leishmania. Canids are the most commonly described reservoirs for the visceralotropic species in the Mediterranean region, Asia, North Africa, and South America. Depending on the presence or absence of reservoirs for Leishmania, two basic types of epidemiologic cycles are noted: zoonosis or anthroponosis.

Anthroponotic human VL was first described in India. This form is usually associated with L. donovani. Assuming that transmission of infection was related to a hematophagous arthropod, how could humans become the source of infection if parasites were mainly located in target viscera: spleen, liver, and bone marrow? In Indian VL, Leishmania are readily found in blood. Short observed that they could be found in 98% of blood smears. However, at this time, the existence of an animal reservoir of L. donovani did not seem to be of major relevance. During outbreaks, human cases of this disease represented an evident and abundant source of infection, but no citations of finding wild domestic reservoirs existed. Conversely, in North African VL, Adler isolated Leishmania from the blood of human patients, only with great difficulty, by cultural methods. In East Africa, subsequent examination of numerous smears of human peripheral blood failed to detect any parasites. With regard to the description of a reservoir of infant VL in Asia and the Mediterranean region, dogs and canids were incriminated since the first report of Leishmania-infected dogs in Tunisia. Visceral leishmaniasis with dogs as reservoir hosts is usually associated with L. infantum in the Old World, which has been shown to be identical with L. chagasi in the New World. Adler and Theodor reported that this was one of the principal differences between Indian and Mediterranean VL. Indian VL involves a heavy blood and skin parasitism and an anthropophilic vector, making humans the reservoir of the disease, a true anthroponosis. In contrast, in Africa and the Mediterranean region, blood parasitism in humans was not detected. Thus, humans were considered to be the final host of the parasite and sand flies become infected by feeding on the skin of canids (dogs and foxes), making the Mediterranean VL a canid zoonosis.

American VL was initially considered to be similar to the Mediterranean, Chinese, and Central Asian forms of VL. One of its important similarities with Mediterranean VL was the presence of an extra-human reservoir of infection: dogs and other canids. Among the latter, Dusicyon vetulus and
Cerdocyon thous (both foxes) were considered to be wild reservoirs in northeastern\textsuperscript{26–28} and northern Brazil,\textsuperscript{29} respectively. However, recent studies have questioned these findings, concluding that C. thous is the unique wild canid neotropical reservoir of L. chagasi.\textsuperscript{30} Opossums (Didelphis albiventris and D. marsupialis) naturally infected with L. chagasi were also described;\textsuperscript{31,32} however their epidemiologic relevance remains to be determined. Thus, American and Mediterranean VL are considered to be canid zoonoses.

Zoonotic visceral leishmaniasis (ZVL) is one of the most important emerging diseases.\textsuperscript{31} Its etiologic agent (L. chagasi) is introduced into the domestic cycle when infected foxes visit houses to scavenge poultry. Peridomestic sand flies acquire the parasite by feeding on the skin of the foxes and transmit it to dogs. The subsequent transmission to humans by sand flies causes human VL.\textsuperscript{14,15} All European studies on ZVL correspond to L. infantum infections while the American data describe infections due to L. chagasi. The American and European forms of ZVL show several similarities, with both being canid zoonosis that affect mainly children and young human adults.

**Risk factors for canine VL.** Studies of the risk factors associated with the breed, sex, age, occupational use, and most desired characteristics of dogs are few and their results are not always in agreement. There appears to be an increased prevalence rate for L. chagasi infection associated with age.\textsuperscript{20–24} In Portugal, Abranches and others observed leishmaniasis only in old and young adult dogs while infection was detectable in dogs of all ages.\textsuperscript{25} In support of these findings, another study in Montes Claros, Brazil verified that although a greater number of younger animals composed the dog population, the prevalence of infection was higher in older dogs (França-Silva JC and others, unpublished data). Age and prevalence followed two inverse pyramidal distributions, with 34% of the animals ranging in age from 0 to 6 months, continuously decreasing to 1.5% of dogs more than 10 years old, and a prevalence of L. chagasi infection of 8.1% in 7–12-month-old dogs increasing to 12.8% in 6–7-year-old animals. As a reflection of the high prevalence of infection, all age intervals had seropositive animals.

No specific pattern of sex distribution was found for ZVL in several endemic areas.\textsuperscript{20,21,24,25} However, in France, a greater prevalence of ZVL was found in male dogs.\textsuperscript{22}

With regard to breed of dog, the German shepherd,\textsuperscript{23,25} Boxer,\textsuperscript{21} and Doberman\textsuperscript{24,25} were found to have higher prevalence rates in France, Portugal, and Greece. In contrast, the Collie was the least infected breed in Greece.\textsuperscript{24} These findings could be related to the animal’s fur length, with the short-furred animals being more easily bitten by the sand flies.\textsuperscript{22} However, in Brazil, the most affected breeds were both, the long-furred Cocker Spaniel (26.9%) and the short-haired Boxer (24.6%) (França-Silva JC and others, unpublished data), while in Italy, no breed-related specific prevalence rates were found.\textsuperscript{21} Other factors such as habits and immunologic status could be associated with susceptibility to infection by visceral Leishmania.\textsuperscript{24} With regard to occupational use, in contrast to that reported by Abranches and others,\textsuperscript{22} the infection rate in working breeds was reported by Hasibeder and others to be three times higher than that of companion dogs.\textsuperscript{26} In Brazil, prevalence ranged from 26.9% in retrievers and water retrievers to 6.6% in companion dogs (França-Silva JC and others, unpublished data).

**Treatment of canine VL.** Cumulative evidence indicates that chemotherapy for infected dogs using pentavalent antimonial, which is commonly used for human treatment, was mostly unsuccessful, even causing exacerbation of disease.\textsuperscript{27–30} However, reports about an increase in survival rate\textsuperscript{31} and a possible cure potential\textsuperscript{32} stimulated dog therapy for ZVL. In Italy, Gradoni and others\textsuperscript{33} and Mancianti and others\textsuperscript{34} showed that antimonial therapy might be an additional tool in control of ZVL. Elimination of symptomatic dogs and treatment of asymptomatic and oligosymptomatic dogs led to a 67% reduction of the frequency of canine disease in a two-year study.\textsuperscript{35} Subsequently, infected dogs were then treated in Europe and, recently, in Brazil. However, this is not recommended by the World Health Organization since both the human and canine treatment are performed with the same drugs and this can give rise to drug-resistant parasites.\textsuperscript{36} Furthermore, many relapses were described after treatment. Clinically, major signs of disease disappear, but this may not indicate the complete absence of parasites. Indeed, dogs were shown to be infective to sand flies several months post-treatment.\textsuperscript{36,37} The presence of latent infections in dogs is typical and important in maintaining the long-term presence of the parasite in endemic regions.

**Zoonotic visceral leishmaniasis in Brazil.**

The initial descriptions of VL in Brazil\textsuperscript{37–39} resulted in three prophylactic strategies that were recommended and used in some areas where the disease was endemic: 1) systematic treatment of human cases, 2) elimination of seropositive infected dogs, and 3) residual insecticide treatment within domestic and peridomestic human and dog habitats, storerooms, hen houses, and animal shelters as a form of vector control.\textsuperscript{19,40,41} The reduction of either or both vector and dog reservoir populations in endemic areas should have an obvious impact on the reduction of human cases of VL. Brazil is the only country endemic for VL that has conducted systematic control programs since 1980,\textsuperscript{42} although both vector and reservoir control programs have been reported since 1961.\textsuperscript{40} However, these programs are very expensive and labor intensive; therefore, their efficiencies and feasibilities have been reviewed.\textsuperscript{19,43}

All three vertebrate reservoirs have been identified in Brazil: humans, domestic dogs, and foxes. Skin parasitism was more frequent and abundant in dogs and foxes. The possible contribution of each reservoir of L. chagasi during outbreaks was investigated by determining their infectious potential to the sand fly vector.\textsuperscript{12} Fourteen human patients (children), 16 infected dogs, and one fox were subjected to xenodiagnosis with females of Lu. longipalpis. The presence of Leishmania promastigotes was assayed in sand fly guts 3–15 days after feeding. Four (28.5%) of the 14 human patients, 12 (75%) of the 16 domestic dogs, and the fox were infective for sand flies.\textsuperscript{13} All Latin American sand flies are described as primarily sylvatic and no other species has adapted to the domestic and peridomestic habitat as well as Lu. longipalpis. It is an extremely catholic feeder and its natural food sources range from wild mammals to birds. In domiciliary situations, it is commonly associated with ani-
mals such as donkeys, horses, cows, and chickens. Studies on *Lu. longipalpis* host preferences in a focus of VL showed that the number of flies attracted to a host depend on the size of the host. In endemic areas in Minas Gerais, the highest densities of *Lu. longipalpis* are frequently found inside dog houses, with most sand flies engorged with blood from the resident dog.

**DOG CONTROL VERSUS VECTOR CONTROL IN BRAZIL**

A series of regular government programs were implemented in endemic areas for monitoring domestic and stray dogs. Human leishmaniasis currently shows its highest incidence in Brazil, Bangladesh, India, and Sudan, but was highly prevalent in China in the past. Before 1949, the exact incidence of kala-azar in China was unclear. After 1949, mass surveys and free medical treatment were carried out in these areas and since 1958 kala-azar has been kept under control after a national wide campaign that involved mass treatment of patients, elimination of reservoir hosts (dogs), and widespread spraying of insecticides. Six hundred thousand human cases of kala-azar were reported between 1949 and 1958 in the northern, northeastern, and northwestern regions of China and were successfully treated with a penta-valent antimonial made in China. Only 48 cases were reported in 1979, and sporadic cases (1,241 between 1980 and 1988) were subsequently reported. The mass elimination of dogs, shown to be the main reservoir of *L. infantum* in endemic regions in China, was fruitful in the control of kala-azar. The widespread spraying of insecticides such as DDT or γ hexachlorobenzene (γ-BHC) annually during the sand fly season was useful in the reduction of sand fly density. For these reasons, disease surveillance by checking vector density and infected dogs was recommended for endemic areas.

In the northeastern states of Brazil, permanent campaigns of removal and elimination of seropositive dogs infected with *L. chagasi* are conducted. For example, the control of canine VL in Ceará initially involved the clinical and parasitologic survey of suspect dogs in the areas concerned. A hundred dogs found around houses with one human or canine case of VL were investigated. At this time, canine control procedures and prevalence evaluation by immunofluorescent (IF) assay were sporadic and non-systematic. Later, the complement fixation reaction (CFR) was used instead of the IF assay, enhancing the sensitivity of VL diagnosis. From 1953 to 1960, 78,929 of 279,423 monitored dogs were killed. Among them, 3,712 showed a positive CFR, giving a prevalence of 1.3%. In recent years, an average of 23,000 IF-seropositive dogs are eliminated annually. In the study reported by Alencar, DDT (1.5 grams/m²) was used on the internal and external walls of the residences, up to 3 meters in height, and in associated animal shelters. Sprinkling of residual insecticides inside and around residences is the indicated tool for control of *Lu. longipalpis* in the specific case of Brazil. Usually, the insecticide treatment is extended to 200 meters around the residence where one case of human or canine VL was reported. Treatment of areas endemic for VL with DDT was adopted in several cities of Ceará state. An 11.9% increase in human cases was observed in untreated areas, while a reduction of 58.2% was reported in cities that had regular treatment with DDT. No statistical analysis of the significance of these differences was included in this report, nor data for evaluation. Alencar proposed that the increase in the number of human cases was a consequence of the improved campaign that allowed a more efficient detection and diagnosis. Also, the periodic serologic survey of domestic and hunting dogs was recommended. It remained unclear if treatment with DDT was performed before this study. If it was, interruption of the use of DDT in a specific area could lead to an increase in the sand fly population and therefore of infective pressure. This area would not be a suitable control in a specific study. Furthermore, there are no data available to confirm that the incidence of human and canine VL in the two areas prior to this study was similar. Nevertheless, several mathematical models were elaborated based on the interpretation of these data and they attributed a higher impact of insecticide vector control as a tool for eradication of VL.

Dye, in his model of leishmaniasis control, concluded that in endemic areas, dog removal has a smaller effect on the prevalence and incidence of human and canine cases of VL than sand fly control by insecticide, human or canine vaccination, and nutritional support. This model was designed considering the results of Alencar; however, the control strategies used in Brazilian endemic areas since 1961 were already different, with systematic serologic (IF) canine control surveys of all domestic dogs. Alencar had previously referred to the parasitologic examination of liver puncture or lymph samples of dogs clinically suspected to have VL. The CFR began to be used only in 1960, and Alencar reviewed data obtained from 1953 to 1960. The canine control strategies in Brazil showed much improvement up to 1996 (35 years) when the model of Dye was reported. The changing pattern of surveillance certainly increased the sensitivity of detection of *L. chagasi*-infected dogs, recognizing not only the symptomatic and parasitologically positive dogs, but also the seropositive but asymptomatic dogs already infectious for sand flies. The number of seropositive dogs increased with the development of more sensitive methods, thus increasing the probability of targeting and removing infectious dogs. These facts, if taken into account in the model of Dye, would have led to an increased impact of dog removal in the success of the leishmaniasis control campaign.

The models of Dye and Burattini and others infer that the dog population in endemic areas is composed of four mutually exclusive groups: those susceptible, those resistant, those susceptible that become latent after a sand fly bite (asymptomatic), and those infectious to sand flies that emerge from latent dogs at a constant rate. Dogs born resistant would not become infectious for sand flies or develop the disease, but they would become seropositive after a sand fly bite. They would include seropositive, non-infectious, asymptomatic dogs from endemic areas, and would be able to maintain an effective cellular immune response against the parasite. However, the constant rate of transformation from latent to infectious is hypothetical, with no basis on any result or observation raised from experimental or natural
infection. Differences between individuals with resistant infections and those with latent infections are unknown. These are the more difficult cases for control of transmission of the disease in the field. These potentially infectious dogs are recognized only by sensitive serologic assays. Alvar and others demonstrated that naturally infected asymptomatic seropositive dogs (resistant or latent) are infectious for sand flies. Dye also refers to a previous unpublished (Quinell RJ, Courtenay O, and Dye C) cohort study that showed, by xenodiagnosis, that infected dogs became infectious for sand flies after a median period of approximately 200 days, and that although several dogs died of clinical VL, the data indicate that infectiousness was unrelated to the severity of symptoms. Conversely, the infectiousness to sand flies has been shown to be positively associated with antibody titers detected by an enzyme-linked immunosorbent assay (ELISA) and to the intensity of skin disease (dermatitis, alopecia, and chancres) (Courtenay O, unpublished data). This model demonstrated that the targeting control at infectious dogs has a greater potential impact in reducing transmission that a strategy of mass elimination of seropositive animals.

Dye also states that in endemic areas, removal or elimination of infected dogs would be followed by immediate substitution with susceptible puppies. However, in northeastern Brazil, most residences covered by the control program correspond to a low socioeconomic level and more than one dog is found in each. Therefore, substitution with a new dog is neither obvious nor mandatory. Conversely, there is no reason to suppose that a susceptible dog will have enhanced probabilities of being the candidate for substitution. Since the factors affecting susceptibility to VL are poorly known, one must assume at least equal probabilities of substitution for a resistant or a susceptible dog. In addition, in northeastern Brazil, which has been endemic for VL for at least 70 years (54 generations of dogs), strong selective pressure may favor the survival of resistant dogs, thus enhancing their probabilities of being infected. A detailed study of the change in relative proportions of dog populations (susceptible or resistant) with time is not yet available. Such a study is needed to evaluate this hypothesis.

Dietze and others conducted an experimental study in three valleys in Pancas, Espírito Santo, Brazil, an area endemic for human and canine VL, with the aim of determining the relevance of dog elimination in control of the disease. The three valleys were subjected to serologic screening (dot-ELISA), while the elimination of seropositive animals was performed only in two of them, with the third remaining as a control. No vector control was done in these areas during the assay period. Twelve months after the beginning of the assay, an increase in the seroprevalence of human VL was detected, both in the intervention (from 15% to 54%) and control (from 14% to 54%) valleys, while the canine seroconversion index decreased in all three valleys (from 36% to 14% in the intervention valleys and from 52% to 11% in the control valley; \( P < 0.05 \)). The investigators concluded that the elimination of seropositive canines in the intervention valleys did not result in any statistically significant difference in the incidence of human seroconversion or human disease, suggesting the possible involvement of other reservoirs of infection. The reason why the investigators choose to work in three different valleys is unclear.

The number of dogs participating in the assay in each valley is not revealed, nor is the previous prevalence and incidence of human and canine disease. The homogeneity of these variables in the three valleys is a necessary condition to prove that the risk factors for VL were comparable.

In Jacobina, Bahia, Brazil, Ashford and others analyzed the impact of canine control in two neighborhoods of comparable socioeconomical and population characteristics. In the intervention area, the serologic analysis (Fast-ELISA) and removal of seropositive dogs was performed, while the control area was surveyed only by serologic screening. A significant reduction of canine seroprevalence (from 36% to 6%; \( P < 0.001 \)) and human incidence of disease (from 10 to 2 pediatric annual cases; \( P < 0.01 \)) was observed in the intervention area, while canine seroprevalence oscillated from 24% to 28%, with no change in the mean number of annual human cases (6–7) in the control area.

Furtado Vieira and Coelho using FNS data analyzed the evolution of canine and human VL incidence in Brazil from 1980 to 1997. In most sanitary districts in endemic areas and in cases of epidemics, serologic analysis of canines covers 100% of the animals. In larger towns, due to enhanced difficulties in access to the animals, diagnosis is usually performed by sampling. Blood samples are collected from all dogs, whether symptomatic or not, and only the seropositive dogs considered infected are removed and killed. In some cases, infection is confirmed by the analysis of parasites in bone marrow punctures or skin biopsies. It is known that infected dogs, whether symptomatic or not, might be infectious for sand flies. Furtado Vieira and Coelho also observed a decreasing trend in mean canine seroprevalences (from 12.8% to 1.8%), with an increase in human incidence from 2,000 to 3,000 annual cases. They suggested that other variables, such as vector density, rate of parasitic infection, and individual susceptibility to VL, rather than canine control, would be responsible for the reduction of canine cases of VL. However, this interpretation is a paradox because seroprevalence values express variations in proportion of dog seropositivity. The observed decrease in canine seroprevalence is related to an increase in the total number of dogs analyzed in the period due to unrelated reasons such as improvement in the control campaign, extension to new areas, and a rabies epidemic. The number of collected samples increased from 526 to 1,353,812 between 1980 and 1996. This increase in the number of non-related canine cases would dilute the real incidence of canine VL. If instead of analyzing canine seroprevalence versus human incidence, absolute numbers are taken into account, i.e., canine incidence versus human incidence, a higher ratio of increase of canine cases with time is observed (\( F = 32.09, P = 0.00001 \)), with a lower rate of increase in human cases (\( F = 7.35, P = 0.0169 \)) (Figure 1). Indeed, no correlation was found between these two curves (Pearson correlation coefficient: \( P = 0.256 \)). Regression analysis showed that the increasing trends of these two curves were significantly different. Since the canine values correspond to seropositive dogs that were removed by the control program, in our opinion, these results indicate that dog removal, e.g., the intensification of the control program, led to the maintenance of the annual human cases at basal levels (Figure 1). For example, in 1990, the ratio of canine to human cases was 13:
Figure 1. Evolution of canine and human leishmaniasis in Brazil (1980–1996). The canine curve represents the evolution of canine cases (immunofluorescent, seropositive dogs killed from 1980 to 1996). The human curve represents the cases officially reported to the Ministry of Health from 1980 to 1998. These are official data from Fundação Nacional de Saúde-FNS (1983–1997) and Cadernos de Epidemiologia do CENEPI-FNS (1998) (canine data versus time: correlation coefficient 0.816, $R^2$ 0.66731, regression type trend, alpha coefficient 1430.130719, beta coefficient 1055.4716; human data versus time: correlation coefficient 0.58676, $R^2$ 0.344, regression type trend, alpha coefficient 769.5102941, beta coefficient = 110.36323).

Figure 2. Evolution of human leishmaniasis in two Brazilian states: Minas Gerais (southeastern region) and Ceará (northeastern region) during the period 1980–1998. These are official data from Fundação Nacional de Saúde-FNS (1983–1997) and Cadernos de Epidemiologia do CENEPI-FNS (1998).

Figure 3. Evolution of human and canine visceral leishmaniasis and vector insecticide control during the period 1980–1997. A, the human incidence of kala-azar in Ceará (c), Bahia (b), Piauí (p), and Maranhão (m). These four states account for 70.4% of the cases of human leishmaniasis in Brazil. A peak started in 1993–1994. B, evolution of canine seropositivity and dog removal in Brazil. The decrease in dog removal in 1991–1992 was prior to the increase in the incidence of human disease (A). C, intensification of vector control by insecticide use in Brazil, as seen by the increase in number of treated residences in 1992–1993.

1 (20,605:1,600). Magalhães and others also reported a higher frequency of canine infection. The ratio of canine to human cases in that investigation was 22:1.41

Furthermore, Furtado Vieira and Coelho did not analyze the incidence and prevalence separately for each region of the country.42 The dissemination of canine and human VL as epidemics occurred in new areas was not considered. Analysis of the data of the entire country would give rise to misleading information. It is known that the canine control program does not show regularity or homogeneity in different areas. This kind of analysis does not separate the new human cases of recent epidemic areas from those in established endemic areas with lower socioeconomic levels, where the removal of seropositive dogs is regular and better accepted by the owners. In Figure 2, for instance, we show the different dynamics of human incidence variation in Ceará state (northeastern Brazil), where canine control has been regularly conducted since 1960, and in Minas Gerais, where the disease shows characteristics of recent epidemicity.42 Also, the incidence and prevalence of each area prior to dog removal are highly heterogeneous and should be taken into account in order to properly analyze the impact of the control tool.

Ninety percent of the incidence of human VL in Brazil is concentrated in the northeastern part of the country. Bahia, Maranhão, Piauí, and Ceará are the most affected states (70.4% of the incidence).42 The evolution of human cases in these states is shown in Figure 3A. A pronounced increase is detected in the four regions starting in 1992. This increase starts after the decrease of canine removal by killing (Figure
Figure 4. Impact of the prophylactic control against human and canine visceral leishmaniasis in the Rio Doce Valley in Minas Gerais, Brazil (1965–1979) (reproduced, with permission, from Magalhães and others 41). Three hundred and six human cases in 15 different cities were described between 1965 and 1979. Three prophylactic tools were applied. Human cases were diagnosed and treated, a large canine screening was performed with positive dogs removed and killed, and application of DDT was done in the affected residences. The human and canine cases were reduced until the complete eradication of the disease in 1979.

3B) and in spite of the intensification of vector insecticide control (Figure 3C) during the same period. These results support the relevance of canine control in the epidemiology of human VL. However, a different lag phase is noted for the state of Bahia.

Magalhães and others reported the control and eradication of human VL in an endemic area of Minas Gerais in the Rio Doce valley.41 Three hundred six human cases were reported between 1965 and 1979. They corresponded to 15 different cities. In Itanhomi, for instance, the highest number of human cases (81) and canine infection (40.09%) were detected. Three prophylactic tools were applied, as recommended previously.12 Human cases were diagnosed and treated with N-methylglucamine. A large canine screening was performed. Dogs with a positive reaction by the complement fixation reaction (CFR) method (1:10 dilution of blood eluate) or Giemsa-stained smears of the distal edge of the ear, or clinical signs of disease were removed by killing. Application of DDT (1.5 grams/m²) was performed inside and around the affected residences. The success of this procedure is shown in Figure 4. A dramatic decrease in human incidence was detected two years after the start of the control campaign (Itanhomi: from 81 to 3 cases from 1965 to 1967). The human and canine cases were reduced until the complete eradication of the disease in 1979. Canine control was systematic from 1965 and is currently maintained, while insecticide vector control was performed only once a year over a three-year period in 13 cities. Alencar and others also reported that the incidence of VL in endemic areas progressively increased soon after the interruption of the field control campaigns.52

Several investigators reported evidence of the efficacy of canine control. An epidemiologic study performed in São Luiz do Curú, Ceará showed that the area subjected to routine FNS control by IF analysis of blood eluates and elimination of positive dogs showed a decrease of 9% in canine seroprevalence while in another area analyzed by an ELISA of serum samples, a reduction of 27% (P = 0.0015) was detected.51 The investigators concluded that the current FNS program based on IF screening of blood eluates is eliminating only 46% of the infected dogs.51 We recently showed that when analyzed by the FML-ELISA (100% sensitivity and specificity for canine VL),54 the positivity rate was 70.9% in sera, and 43.6% and 47.7% in eluates transported at −10°C or 25°C, respectively (Borja-Cabrera GP and others, unpublished data). Differences between results obtained in sera samples or eluates were highly significant (P < 0.005). Jerónimo and others reported a concomitant decrease in human pediatric cases of VL and of infected dogs in Brotas, Ceará from 1987 to 1997 in an area subjected to FNS canine control.55 In another study in the endemic area of Montes Claros, Minas Gerais, a reduction of 79.3% in canine prevalence was observed after five years of systematic serologic control, dog elimination, and insecticide vector control (Genaro O and others, unpublished data). The human cases were also drastically decreased in the urban area (from 44 to 3), indicating that epi-
demographic surveillance should be systematically applied to obtain effective control in endemic areas.

The fact that the canine control campaign was not able to significantly reduce the number of human cases in some areas of Brazil could be due to 1) the low sensitivity of the IF assay that does not detect seronegative but infectious dogs, thus maintaining the active reservoir of the disease in the endemic area or 2) the potential coexistence of different epidemiologic types of human VL. The first hypothesis has been shown to be correct by the use of more sensitive methods that resulted in more efficient control measures. The second hypothesis was previously reported by Biagi. He reported the coexistence of five different epidemiologic types in Mexico: Mediterranean, Indi-an, Sudanese (sporadic epidemic bursts in young adults, an-throponoses or zoonoses of felines and rodents), Asian (endemic-epidemic, fox and wolf zoonoses), and American. This possibility cannot be ruled out until serious experimental field studies are performed in different areas of Brazil.

Brazilian VL was assumed to be a canine zoonosis, i.e., the Mediterranean type, at the time of the first description of the disease in Ceará; however, no additional studies regarding this assumption have been performed. This may be attributed to high costs of control programs, which require the confirmation of the impact of each control measure. However, new, well-designed field trials are needed to determine the influence of each factor in the control of VL. There is more experimental evidence supporting the usefulness of canine control using serologic analysis and dog elimination than against it. The efficacy of these control measures would be improved by the use of available, more sensitive serologic tests and a more profound knowledge of the time-space distribution and evolution of VL in Brazil. It is important to note that important canine control campaigns have been conducted regularly in Brazil since 1981 with the support of the World Health Organization. On the other hand, no evidence of reduction of canine or human disease is seen in European or Asiatic countries where canine serological control has never been performed, but instead different palliative chemotherapeutic treatments are used with limited or no success against canine visceral leishmaniasis. Acknowledgments: We thank Dr. Jack Woodall (Federal University of Rio de Janeiro) for English language editing. The Federal University of Minas Gerais is gratefully acknowledged for financial support.

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IMPACT OF CANINE CONTROL ON EPIDEMIOLOGY OF VISCERAL LEISHMANIASIS


