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Opinion Article/Artigo de Opinião

How effective is dog culling in controlling zoonotic visceral leishmaniasis? A critical evaluation of the science, politics and ethics behind this public health policy

Quanto é efetivo o abate de cães para o controle do calazar zoonótico? Uma avaliação crítica da ciência, política e ética por trás desta política de saúde pública

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ABSTRACT

Introduction: Zoonotic kala-azar, a lethal disease caused by protozoa of the genus *Leishmania* is considered out of control in parts of the world, particularly in Brazil, where transmission has spread to cities throughout most of the territory and mortality presents an increasing trend. Although a highly debatable measure, the Brazilian government regularly culls seropositive dogs to control the disease. Since control is failing, critical analysis concerning the actions focused on the canine reservoir was conducted. **Methods:** In a review of the literature, a historical perspective focusing mainly on comparisons between the successful Chinese and Soviet strategies and the Brazilian approach is presented. In addition, analyses of the principal studies regarding the role of dogs as risk factors to humans and of the main intervention studies regarding the efficacy of the dog killing strategy were undertaken. Brazilian political reaction to a recently published systematic review that concluded that the dog culling program lacked efficiency and its effect on public policy were also reviewed. **Results:** No firm evidence of the risk conferred by the presence of dogs to humans was verified; on the contrary, a lack of scientific support for the policy of killing dogs was confirmed. A bias for distorting scientific data towards maintaining the policy of culling animals was observed. **Conclusions:** Since there is no evidence that dog culling diminishes visceral leishmaniasis transmission, it should be abandoned as a control measure. Ethical considerations have been raised regarding distorting scientific results and the killing of animals despite minimal or absent scientific evidence

Keywords: Kala-azar. Visceral leishmaniasis. Control. Dogs. China. Brazil.

RESUMO

Introdução: O calazar zoonótico, uma doença fatal causada por protozoários do gênero *Leishmania*, é considerada fora de controle, particularmente no Brasil, onde se urbaniza e a letalidade aumenta. Apesar de ser uma medida muito controversa, o governo brasileiro abate cães soropositivos regularmente para controlar a doença. Assim, diante da falha do controle, foi efetuada uma análise crítica das ações para o controle do reservatório canino. **Métodos:** Em uma revisão da literatura, foi feita uma abordagem histórica focalizada principalmente na comparação das bem sucedidas tentativas chinesas e soviéticas de controlar a doença. Também foi efetuada uma análise dos principais estudos acerca do papel de cães como fatores de risco para humanos e dos principais ensaios de intervenção acerca da eliminação destes animais. A reação política do Brasil a uma revisão sistemática recentemente publicada que concluiu pela ineficácia do programa de eliminação de cães e os seus efeitos nas políticas públicas são revisadas. **Resultados:** Não foram encontradas evidências firmes do risco conferido por cães para os seres humanos. Além disto, foi confirmada a falta de apoio científico à política de eliminação de cães. Foi notada uma tendência para distorção dos dados científicos para o suporte da política de eliminação dos animais. **Conclusões:** Uma vez que não existem evidências de que o abate de cães diminui a transmissão de leishmaniose visceral, este programa deve ser abandonado como estratégia de controle. São levantadas as implicações éticas acerca da distorção da ciência e sobre a eliminação de animais na ausência de mínima ou nenhuma evidência científica.

Palavras-chaves: Calazar. Leishmaniose visceral. Controle. Cães. China. Brasil.

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INTRODUCTION

Kala-azar, or visceral leishmaniasis, is a curious disease with peculiar geographical distribution. In the Indian subcontinent, where most of the cases in the world have occurred, the disease occupies a very limited area to the northeast, affecting certain districts of Bihar State, India, Bangladesh and Nepal[1]. In these places, the disease is exclusively anthroponotic; i.e., is only transmitted between people. The predominant transmission among humans is also observed in East Africa, mainly in Kenya, Sudan, Uganda and Ethiopia. It was also anthroponotic in the plains of eastern China, but was extinguished from the lowlands in the 1950s[2]. In the rest of the world, particularly in the highlands of China, Central Asia, the Middle East, Transcaucasia, the Mediterranean, South and Central America, it is a zoonosis; i.e., it is transmitted between animals and, secondarily, to people. The main known reservoirs are domestic dogs, coyotes and foxes, although other mammals may be involved in transmission[3]. The agents of the anthroponotic and zoonotic diseases are different but very similar. They are protozoa of the species *Leishmania donovani* and *L. infantum*, respectively, which appear to have genetically diverged a million years ago in Central Asia[4]. American parasites are often referred to as *L. chagasi*, but they are genetically identical to *L. infantum*, and have probably been introduced on many different occasions by European settlers[5,6]; however, it is possible that indigenous populations may also exist. They are transmitted by species of sand flies that breed in decomposing solid organic matter and belong to several species of the genus *Phlebotomus* (in the Old World) and *Lutzomyia* (in the Americas). The geographical distribution of the vector species determines the geographical distribution of the disease, so that the factors that limit it should be the same as those that guide the distribution of the disease[3]. Despite the ecological differences, the disease is very similar in different regions: fatal if untreated, characterized by prolonged fever, weight loss, anemia, bleeding, enlarged liver and spleen and accompanied by bacterial infections that are often severe[7]. It has been estimated that at least 59,000 people die annually of the disease around the world, particularly in India and Sudan[8].

Much has been opined on the elimination of domestic dogs to control zoonotic visceral leishmaniasis, but few studies have actually assessed the efficiency of such a measure. A recently published systematic review of strategies for controlling the disease summarizes these studies and indicates directions that this cruel policy should take[9]. Since there are some indications that despite this systematic review, actions involving dog killing will continue, I decided to specifically review this strategy. The literature review was restricted to research and programs whose effects are related only to people. The author conducted a PubMed search with combinations of the following keywords: visceral leishmaniasis, kala-azar, control, dogs, history, and the name of countries and continents where the disease is endemic. Except for a historic description, only studies with control groups and with a statistical analysis were used to evaluate the role of dogs and the effect of control measures. This work also quotes previously identified theses and conference abstracts and several references that were identified in the texts examined. I only consulted references that were in English, French, Spanish or Portuguese.

HISTORICAL BACKGROUND

Old World

The first proposal concerning a program to eliminate dogs in order to control leishmaniasis appears to have come from Adler & Tchernomoretz[10]. Since the authors were unable to cure dogs in Palestine when using pentavalent antimony or aromatic diamidine, they suggested that the removal of dogs to other places or their elimination would be viable alternatives for control. It was probably these remarks that triggered control operations through the elimination of dogs. This concept was later emphasized by Hoare in his prestigious review of 1962[11]. In the 1950s, two extensive programs of disease control began in China and in the Central Asian republics of the then Soviet Union, given the broad distribution of the disease and its high incidence. These programs were implemented under the aegis of socialist policies and under the mantle of revolutionary and centralized states.

Although no precise figures exist, the situation in China was the worst and really desolating. It is assumed that there were a staggering 500 to 600 thousand people with the disease in 1951[12], with the very high prevalence of 3 to 5 individuals per thousand inhabitants, including the capital Beijing[13]. Moreover, access to treatment was very difficult for the majority of patients[14], which suggests that kala-azar killed Chinese patients by the thousands. The disease was distributed in 16 of the 33 administrative areas, all north of the Yangzi River, with three distinct ecological patterns: a) the main type, responsible for the vast majority of cases, was anthroponotic, located mainly in the crowded eastern plains in river valleys, the transmission of which was soon interrupted; b) zoonotic, associated with the presence of infected dogs, located in mountainous areas of the northeast, north and northwest; c) presumably zoonotic, but with no known animal reservoir, in the extreme northwest desert region (**Figure 1**)[2,12,13,15,16]. The main vector of the disease, both in the plains and the mountains, has always been *Ph. chinensis*, which is more endophilic, but in the desert, *Ph. longiductus* and *Ph. alexandri* still prevail, which are exophilic and more difficult to control[17].

In these diverse areas, the force of transmission could be estimated by age and delayed type hypersensitivity (DTH). Thus, in the plains, the mean age was greater, similar to Indian kala-azar, while in the mountains and the desert, most of the patients consisted of young children[12,13,18,19], which indicates a lower strength of transmission in the plains. Interestingly, in the desert, no infected dogs were identified, while most of the population presented reactivity to the Montenegro test (unlike in the areas of canine zoonosis in the mountains)[16], which suggests that the greater strength of the infection in zoonotic regions than in the plains is not due to the presence of dogs, but the result of a still poorly understood process, perhaps related to vector feeding preferences[15].

Given the hypothesis that the Chinese anthroponosis would be similar to Indian kala-azar caused by *L. donovani* and that the Chinese zoonotic visceral leishmaniasis would have *L. infantum* as the etiological agent[15], a careful genotypic analysis of isolates of *Leishmania* in different regions was conducted. This analysis highlighted the heterogeneity of the isolates, but showed that *L. donovani* predominated in the eastern plains and that *L. infantum* was concentrated in the mountain areas of Beijing and Gansu, although some *L. infantum* isolates were identified in the plains and

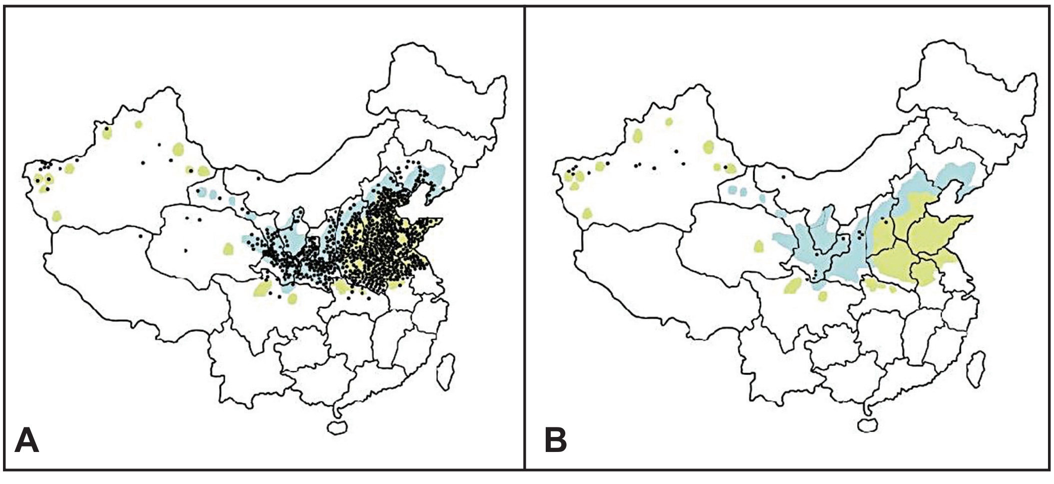

FIGURE 1 - Maps of China before (A) and after (B) actions to control kala-azar in the 1950s. Dots represent the number of cases and colors indicate the areas where only human disease was verified (olive) and areas where dogs were also verified as infected (blue). Based on Leng, 1982, and Xu, 1989.

isolates of *L. donovani* also came from the mountains, including one from a dog. In the northwestern desert, strains of both species were isolated[20]. Thus, although a spatial correspondence between environment and the species of *Leishmania* has been shown, the coexistence of different species in these areas has also been demonstrated. These biological and ecological variations have incurred enormous consequences regarding control efforts[21,22].

Immediately after the communists took power in 1949, two major steps were taken to reduce the impact of the disease in a dramatic way that embodied the revolutionary spirit: mass treatment of the sick and control of vectors[15]. In relation to mass treatment, Chinese laboratories began manufacturing pentavalent antimony[14], Central Anti-kala-zar Stations were established and over a thousand anti-kala-azar units attended by hundreds of specially trained personnel helped the doctors[2,14]. With this structure, 150 to 200 thousand people were treated from 1951 to 1953 alone[14,18]. Another priority was given to combating the vectors, which began in 1951, since *P. chinensis* was an easy target since at Chinese latitudes, it has only one or two generations per year and lands on walls after feeding. The country started to produce the organochlorine insecticides dichlorodiphenyltrichloroethane (DDT) and gammexane and experiments were conducted that showed their efficiency and prolonged residual effect. DDT became widely used inside and outside houses, and in outhouses and was applied in all households of densely populated villages[14,15]. Although the application was on a large scale, the precise extent of its use in the critical years of the 1950s is not mentioned[2]. Since the 80s, DDT and gammexane have no longer been used and have been replaced by pyrethroids, today restricted to areas of zoonotic visceral leishmaniasis[16,23].

The program for the disposal of dogs in China was as even more difficult to assess than the use of insecticides, since it is not known precisely where and to what extent it was applied, perhaps due to the large variation in the prevalence of canine infection by *Leishmania* in the country (from zero or minimal in the plains and desert to 7% in mountainous areas)[2,12,19]. This heterogeneity led to different interpretations concerning the efficiency of eliminating dogs, because some authors have relegated the core of the success of the control simply to the mass treatment and tothe use of insecticides[14,24,25], while others attributed a relevant role to the elimination of dogs in areas of zoonotic visceral leishmaniasis[2,13,18]. One fact worth noting is that the elimination of the animals was not performed using any definitive selection method, but indiscriminately, killing any dog in sight in endemic areas[24]. To provide some idea of the magnitude of this program, it was estimated that the killing would only be efficient if it eliminated at least 3/4 of all dogs in an area, whether or not evidence of leishmaniasis was available[16]. However, despite the fact that an enormous number of dogs were sacrificed, transmission among dogs resumed four years later[23].

The huge Chinese efforts were rewarded in spectacular fashion, because by 1958, transmission was already entirely interrupted in areas of anthroponotic leishmaniasis[15,19], and this finally became a reality in the 1970s[26], accompanied by reduction to near-extinction of *P. chinensis* from the plains[24], making leishmaniasis a relatively rare disease in China[13]. The annual incidence dropped to around 200-300 cases, restricted to mountainous regions of the north and northwest, where exophilic vector populations continued[16, 24]. After the initial success, complete elimination of kala-azar in the country was predicted to occur by the 1960s[19], but in the 1980s, an increase in the number of cases occurred[23], attributed to the dismantling of the anti-kala-azar network during the Cultural Revolution of 1966 to 1976[2,12].

It is not easy to speculate regarding the effectiveness of the Chinese control program, with its many nuances. A good explanation for the great success in the plains may have been the low force of transmission in those areas, and the dense population, where control was evidently easier and more noticeable. In contrast, in the northwest areas, the high force of infection and more dispersed populations did not enabled such an abrupt drop in the incidence of number of cases, as verified in the lowlands. A great deal can be learned from the striking differences between the success of control in the anthroponotic and zoonotic areas seen in the truly gigantic Chinese control program. Obviously, the control of the anthroponosis cannot be attributed to the elimination of dogs, which leads to the conclusion that the transmission of anthroponotic leishmaniasis in China can only be attributed to mass treatment and the use of DDT and gammexane. The real reason for the success of the Chinese control of anthroponotic leishmaniasis seems to have been the use of organochlorine pesticides that eradicated *P. chinensis,* the main vector in the lowlands. This first lesson should remain. However, the question of what the effect was of the elimination of dogs in the areas of a zoonosis continues. Apart from two studies that showed a reduction in the number of human cases following mass removal of dogs and treatment of people[16], the simultaneous use of organochlorine insecticides in the areas of zoonotic visceral leishmaniasis prevents any definitive conclusion regarding the relative effectiveness of the disposal of dogs. The maintenance of transmission in the highlands demonstrates that the use of organochlorine insecticides did not have the same success in controlling zoonotic visceral leishmaniasis as it did with the anthroponotic disease. However, in spite of the overall success of the Chinese program, what the results most clearly indicate is how difficult it is to control zoonotic visceral leishmaniasis.

The experiences of the control strategies for leishmaniasis used in the Transcaucasian and Central Asian Republics of the former Soviet Union are helpful, since they provide information that is very relevant today. In these areas, the disease is only caused by *L. infantum* and affects people and dogs[22,27]. It was an urban disease and affected towns and cities, such as Tbilisi (in Georgia), Yerevan, (Armenia), Kyzylorda (Kazakhstan), and Tashkent and Samarkand (Uzbekistan)[28]. The vectors were *P. chinensis*, which was extinguished, and *P. longiductus* and *P. sminov*[22]. Of particular interest was the situation in *oblast* Kyzylorda, where the proportion of sick children under two years of age reached 92.9%, showing a huge force of infection, similar to the desert regions of northwestern China[21].

In these countries, intervention was also a combination of traditional methods: the detection and treatment of human cases and disposal of dogs, but the main success was achieved only after DDT use for treatment of dwellings in a radius of 500 meters from the microfocus, and in some places, streets and city blocks[22]. Since these measures were implemented, visceral leishmaniasis has also become scarce in the area of the Soviet Union, except in Kyzylorda[22]. In this administrative region, an interruption in transmission occurred in the capital, but there was no response to the control actions in the countryside and no reduction in the number of cases in the region. Although dogs are found naturally infected, a cycle involving coyotes has been verified, which may help to explain the difficulty in controlling the disease. Nevertheless, the main reason for continued transmission in this *oblast* seems to have been the scant use of DDT[21], which was subsequently banned in the Soviet Union in 1970[29]. The control failure in this area indicates that, like China, the interruption of transmission in *L. infantum* foci with a high force transmission may not be possible, even with the use of DDT.

The experience of the Indian subcontinent reveals the astonishing impact that the control of malaria with DDT had on the control of leishmaniasis. In the region of Bihar, India, and in Bangladesh and Nepal, the disease presented epidemic cycles until the end of the 1940s. In 1953, the national program for malaria control began with the use of DDT, reaching its apex in 1958, which led to the disappearance of the vector *P. argentipes* from the interior of houses. Thus, leishmaniasis disappeared and also became rare in India. However, with the end of the Global Malaria Eradication Campaign in 1971, resurgence of the infection was observed, which reached its zenith in 1977, probably affecting a million people, with a fatality rate of about 7%[30,31]. Currently, India has been implementing the use of DDT in the State of Bihar since 1971, but control has not been achieved[32], even though the country plans to eradicate the disease by 2015[33]. Some current studies have compared the effectiveness of residual spraying of insecticides with mosquito nets impregnated with long-term insecticides and with environmental modification, and the best results have been with indoor residual spraying[34,35].

New World

In the New World, some local experiences in Brazil are also relevant to assessing the effectiveness of eliminating infected dogs as a control measure. In this country, the disease is caused by *L. chagasi* (= *L. infantum*), with dogs, foxes, other species of mammals and people as vertebrate reservoirs, and is transmitted by the *Lutzomyia longipalpis* sand fly, which presents both exophilic and endophilic habits. It was a disease of the semi-arid regions where control efforts have been conducted since the 1950s. Despite this, transmission in smaller cities had already been registered. The present phenomenon of large scale urbanization started in 1981, when epidemics hit Teresina and then São Luis, in the mid-north, spread throughout the country to the west and south, affecting several states, including São Paulo and Rio Grande do Sul, and larger cities, such as Belo Horizonte and the capital, Brasilia (**Figure 2**). Moreover, the total number of cases in the country nearly doubled despite all efforts of control[36,37]. The annual cumulative incidence rate increased more discretely, but the mortality rate rose significantly despite medical advances and the development of specific guidelines for the most serious presentation of this disease[38,39]. Recently, urban outbreaks have begun to occur in neighboring Argentina[40]. The situation of leishmaniasis in Brazil is the opposite to that of China, because after nearly 30 years of trying to control the disease, that country had about 10 times fewer cases than China had in 1950 and currently has 10 times more than China now has. This difference is probably due to the successful control of the vast number of cases of anthroponotic visceral leishmaniasis in China, whereas Brazil has tried to control the emergent process of urbanization by prioritizing the selective elimination of dogs.

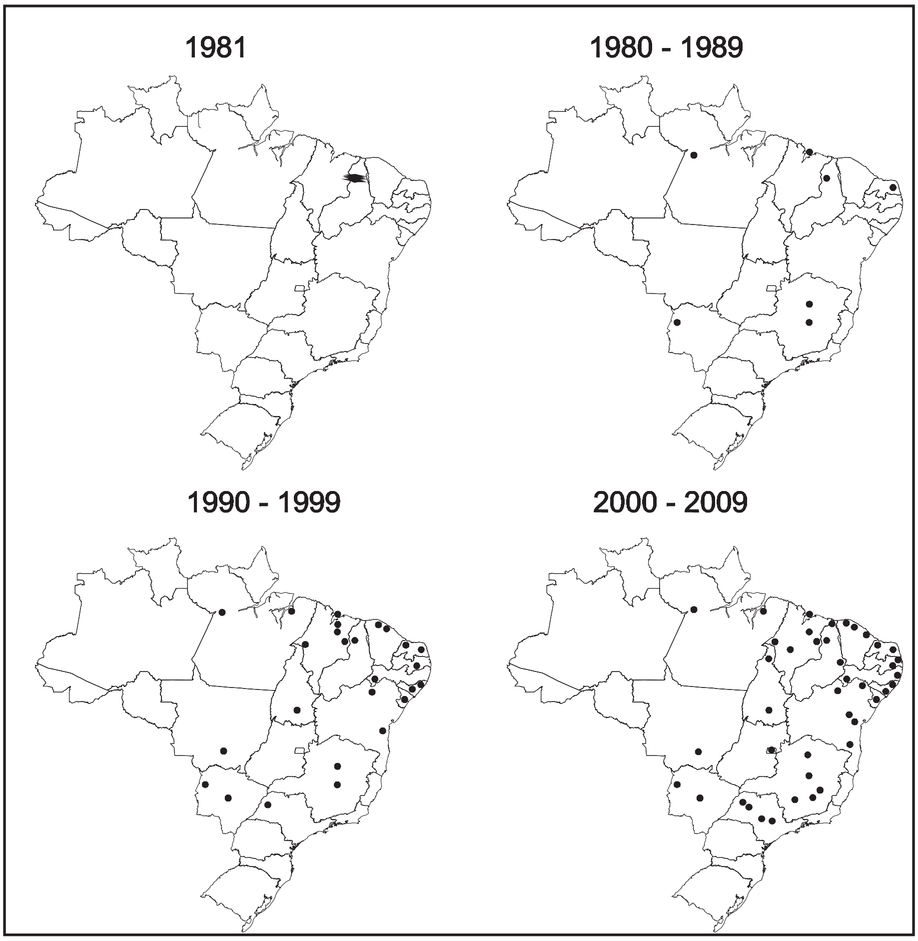

FIGURE 2 - Spread of urban kala-azar in Brazil. Dots indicate cities with more than 100,000 inhabitants with more than ten cases of kala-azar in a year.

The control of leishmaniasis in Brazil began in the State of Ceará, in the semi-arid northeast, in 1953, and just as in China and the Soviet Union, this was based on the treatment of people, the use of DDT and the elimination of dogs. The difference between these countries is that, in Brazil, only dogs with reactive serology were eliminated[41]. In 1953, only one reagent dog was killed, but in 1954 and 1955, the number rose to 42 and was higher than 2,000 in 1960. No analysis of the effect of removing dogs was conducted, but in 14 counties sprayed with DDT, a 58.2% reduction in the incidence of human cases (765 cases before and 320 after) occurred, against an increase of 11.9% in 14 municipalities where only dog culling was carried out (89 cases before and 101 after) (**Figure 3**)[42]. Unfortunately, the use of DDT was discontinued in the 1960s[41]. In any case, DDT proved capable of reducing the incidence of zoonotic visceral leishmaniasis, although the results were a lot less effective than those verified for anthroponotic visceral leishmaniasis in China and India.

The only control experience that was a definite long-term success in Brazil occurred in the late 1960s in the Rio Doce valley, Minas Gerais, in the southeast region. The classical measures were used,

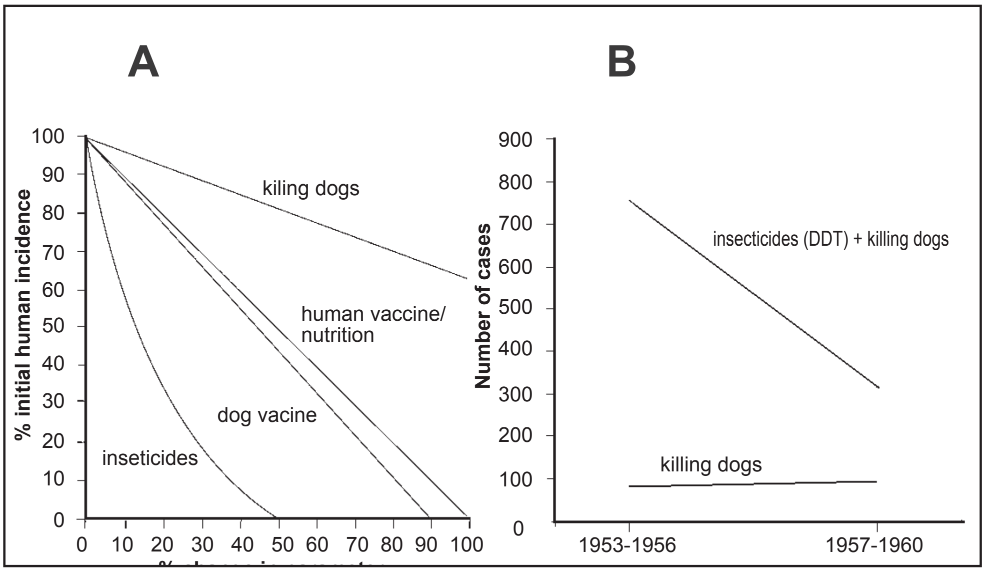

FIGURE 3 - Theoretical and observed efficiency of control measures for zoonotic kala-azar. In A, the theoretical efficacy starting from a given initial human incidence and according to the variation of the parameters that are critical for each measure; data from Dye, 1996. In B, the observed variation of human incidence in Ceará, Brazil; data from Alencar, 1961.

including the application of DDT, for about 10 years. Beforehand, up to 40% of dogs were seropositive. The incidence fell from 169 cases in 1965 to zero in 1978 and in subsequent years[43]. However, despite the continuity of the program, but with the help of pyrethroids instead of DDT, infection among dogs is reemerging[44]. Another successful experience in Brazil occurred in a small outbreak in Rio de Janeiro, between 1979 and 1985[45], where they used organochlorines, followed by pyrethroids. However, there was no interruption of the transmission.

The application of control measures on a large scale in Brazil was secondary to the epidemic outbreaks that started the process of urbanization and expansion of the disease in the early 1980s in the state of Piauí. Similarly to India, actions against other diseases had some repercussion on leishmaniasis, since limited spraying with DDT for malaria seems to have protected against the intense transmission of leishmaniasis (in the outbreak of 1981-1986). Furthermore, in those municipalities with extensive spraying with gammexane for Chagas' disease, the incidence of leishmaniasis was the lowest[46]. However, gammexane was never used for leishmaniasis and the indoor use of DDT for this disease was minimal. Instead, the use of organophosphates and later, ultra-low volume pyrethroids, was predominant[41]. Aside from the observations in the 1950s, there has never been a controlled study of the use of insecticides for leishmaniasis by *L. chagasi* anywhere in the world. Nowadays, Brazil is the only nation with a large-scale program of systematic elimination of dogs to control zoonotic visceral leishmaniasis.

THE IMPORTANCE OF DOG INFECTION FOR HUMAN KALA-AZAR

Neither the role of dogs in the transmission of *L. infantum* to humans, nor the benefits of disposing of dogs have ever achieved consensus in the literature[15,47,48]. However, the evidence suggests that infections in humans and dogs are interdependent, although transmission between dogs may be independent of the presence of sand flies and not associated with human infection[49]. As a general rule, where transmission of *L. infantum* among humans occurs, it also occurs among dogs[19,23,50]. In one study, the highest prevalence of infection among dogs was not associated with the highest incidence among humans[51], but in two other studies in Brazil and in a third in Iran, this association was shown[52-54]. These discordant results demonstrate that the association between human and canine infections is not strong and suggest that the infections between the two hosts may have distinct dynamics, with a more complex relationship than previously thought. The existence of a sylvatic host transmitting the disease to both humans and dogs, as observed in Central Asia, cannot be discarded. In Brazil, this common source may well originate from the outskirts of cities, as indicated by the association of the human disease with peri-urban vegetation[55].

An indirect way of analyzing the dependence between the infection in humans and the infection in dogs is to assess the presence of dogs as a risk factor for humans. Even thou, the results are also inconsistent (**Table 1**). Five cross-sectional studies suggest that dogs are risk factors. Two of them, in the Old World, show that both the number of dogs and the rate between dogs and humans increase the risk of seropositivity in children[52,56]. Another study, involving multi-level analysis, showed that the presence of dogs may increase the risk of clinical manifestation[54], while another showed that the presence of dogs (and poultry) increases the risk of seroconversion[57]. Yet another study showed that the time that a dog remains in a home increases the risk of skin reactivity to *Leishmania*[58]. However, longitudinal studies revealed borderline or conflicting results. Two case-control studies showed no significant association between the presence of dogs and the disease among people[59,60], although the risk of the disease was slightly higher among those domestic groups that lived with dogs. Another cohort study showed a contradictory association, depending on whether the outcome was measured using skin reaction or serology[61], while yet another reported no association between the presence of dogs and the development of the disease in people[62]. These fairly ambiguous results suggest that studies that can measure the proportion of the flow of parasites to humans from a canine source have yet to be developed[63]. In order to achieve this, it is essential to conduct specifically designed cohort studies.

TABLE 1 - Studies investigating the risk of the presence dogs in relation to the acquisition of human visceral leishmaniasis or asymptomatic infection with *Leishmania infantum*.

Study designs	Units of analysis	Exposures	Outcomes	Results*	References
Intervention	Individuals	Dog collars with insecticides	Serology (a) Montenegro skin test (b)	↑ risk (a) & no risk (b)	Gavgani et al, 2002
Cohort	Individuals	Dog ownership	Disease	No risk	Nascimento, 1996
Cohort	Individuals	Dog ownership	Serology (a) Montenegro skin test (b)	↓ risk (a) & ↑ risk (b)	Caldas et al, 2002
Cohort	Individuals	Dog ownership	DNA hybridization (a) DNA hybridization plus serology (b)	↑ risk (a) & no risk (b)	Moreno et al, 1998
Case-control	Individuals	Dog ownership	Disease	No risk	Navin et al, 1985
Case-control	Individuals	Dog ownership	Disease	No risk	Costa et al, 1999
Mixed ecological	Census tract	Previous canine seroprevalence	Disease	↑ risk	Werneck et al, 2006
Mixed ecological	Urban clusters	Previous canine seroprevalence	Disease	↑ risk	Oliveira et al, 2001
Cross-sectional & ecological	Individuals	Dog ownership & size of dog population	Serology	↑ risk (both)	Gavgani et al, 2002
Cross-sectional	Urban area	Dog ownership ≥ 3 years	Montenegro skin test	↑ risk	Gouvês et al, 2007
Cross-sectional	Individuals	Dog ownership	Serology	↑ risk	Kotkat, 1996
Ecological	Neighborhood	Canine seroprevalence	Disease	No risk	Costa et al, 1995

* risks with p value ≤ 0.05.

While it is intuitive to believe that dogs are significant reservoirs because they are more competent at infecting sand flies than people[47, 63-68], other parameters that depend on the vectors (vectorial capacity) are much more significant for the basic reproductive number of the disease (e.g., the number of secondary cases emerging from an infectious case) and, therefore, for the incrimination of reservoirs. For example, some observations and mathematical models show that the importance of a reservoir is regulated not only by its competence in infecting vectors, but also by the parameters that measure a) the degree of exposure of vertebrate hosts to vectors and b) the vector daily mortality. Both parameters have a nonlinear (quadratic and exponential) effect on the transmission of the disease[69,70]. This means that small efforts aimed at controlling vectors can have strong results concerning the transmission of the disease. In contrast, since the competence of the vertebrate reservoirs at infecting the vectors has a merely linear effect on transmission, proportionally much greater efforts are needed to control the reservoirs, thus demonstrating why the strategy of removing reservoirs is less efficient than controlling vectors. Indeed, Dye[71] and Burattini[72] modeled the impact of different strategies on the transmission of leishmaniasis and showed that the elimination of vertebrate reservoirs is much less efficient than vaccines, nutritional interventions or the use of insecticides (**Figure 3**).

These theoretical uncertainties have led to the need for tests to assess the effect of removing dogs on the transmission of kala-azar to humans. Four intervention trials were conducted in Brazil (**Table 2**). To some extent, all of them evaluated the effect of selective elimination of seroreactive dogs. The outcome of the first of these trials was seroconversion of humans, conducted in two rural areas. No difference between the areas of intervention and control (20% vs. 22% and 26% vs. 27% respectively) were verified after periods of 6-months and 1-year[73]. The second study compared the effect of the elimination program with the incidence of pediatric cases in two urban districts and showed that the annual incidence was lower in the intervention areas than in the control areas (5/1,000 vs. 20/1,000), but due to several factors, the authors could not attribute the protective effect to the elimination of dogs[74]. Another study expanded the sample size and used random allocation of interventions and factorial design to evaluate seroconversion. The study area consisted of 34 plots measuring about 200 x 200m in one neighborhood, where the interventions took place in the internal 100 x 100m area, leaving a buffer of 200m between each intervention area. Due to the ethical considerations, all houses were sprayed indoors with a synthesis pyrethroid, included those within the buffer area. Thus, the following additional interventions were compared, and were randomly assigned as: a) spraying in residential outhouses; b) selective removal of seroreactive dogs; c) spraying in residential outhouses and selective removal of seroreactive dogs; d) no other intervention apart from indoor spraying. After six months to one year of intervention, the incidence in the area where the removal of dogs was conducted with indoor spraying (but not outdoor spraying) fell from 46% to 16.1%. However, this effect of eliminating dogs disappeared (40% to 37.9%) in the area where removal of dogs was conducted with simultaneous indoor and outdoor spraying. No reduction also occurred when only additional outdoor spraying was conducted. The three main problems in this study were the large proportion of non intervention-buffer areas (which corresponded to 75% of the study area), the loss of up to 46% of the studied population and the allocation of an indoor spraying fund, which hindered the assessment of the effect of elimination of dogs in the absence of insecticide use[75]. An additional study compared the strategies of: a) no intervention, b) spraying with pyrethroid insecticide, and c) area under the combination of insecticide spraying and screening with the elimination of seropositive dogs, in three districts of Feira de Santana in Bahia State. After a year, the seroconversion incidence densities were, respectively, 3.02, 2.86 and 1.65 per 100 children-years. The differences were not statistically significant to distinguish the effect on transmission[76]. Although all the studies presented significant problems, it seems that there is a dubious, tenuous and evanescent trend of additional protection by removing dogs, but far less than the theory predicts.

CONFLICTS BETWEEN SCIENCE AND CONTROL PROGRAMMES

Science and public policy do not always agree or go hand in hand. Incorporation of scientific knowledge into policy depends on political, economical and ethical issues, the grade of scientific evidence and agreement between scientists and even on the corporative interests of decision-makers[77]. Due to the worsening of the situation of zoonotic kala-azar in Brazil and the lack of scientific consensus, choosing the best health policy for the control of the disease has been prone to disregarding or misinterpreting the available science. Moreover, the strategy of killing dogs is hampered for numerous reasons, such as the low accuracy of the methods in assessing the infectivity of dogs, the intensity of efforts needed to remove the dogs, the replacement of animals[48] or simple refusal of owners to hand over their valuable and cherished creatures. Knowing these difficulties, the Pan American Health Organization (PAHO) commissioned a systematic review to evaluate programs aimed at the control of kala-azar. The conclusion was that "*in spite of all these limitations, the relevant number of reports could be reviewed in detail, showing no strong evidence for a significant impact on VL transmission for any of the interventions reviewed. Canine culling seems to be the least acceptable intervention at community level for obvious reasons and has low efficiency due to the high replacement rate of eliminated dogs with susceptible puppies and other cultural obstacles*"[9]. This last evaluation, despite the limitations of the studies analyzed, finally showed that the hypothesis of Adler and Tchernomoretz has no empirical support. The review was then presented to a panel of consultants as part of the "*Project for the establishment of a regional cooperative research agenda in the field of neglected diseases*" convened by PAHO, the World Health Organization (WHO), TDR and BIREME for a consensus meeting, which was also attended by representatives of health ministries of Latin American countries with leishmaniasis transmission. The meeting was held in September 21-22, 2009, in Foz do Iguaçu, Parana, Brazil, and agreed with the systematic reviews conclusions that programs of systematic killing of dogs to control kala-azar lacked evidence in the literature as related to the protection of humans (PAHO, a still unpublished report).

In order to clarify the process of constructing guidelines for controlling neglected diseases, the linking of scientific evidence to the maintenance of the dog killing programs to control kala-azar will be discussed in the following paragraphs. On the following day, also in Foz do Iguaçu, a meeting was held by the chiefs of programs for visceral leishmaniasis control of the Southern Cone (Meeting regarding Surveillance, Prevention and Control of Visceral Leishmaniasis in the Southern Cone of South America) and they decided to recommend the culling of infected dogs, allegedly supported by the participants of the previous research agenda meeting, despite the fact that a position paper had not written or approved, and in clear opposition to the findings of the systematic review[78]. About 10 days after the panel convened by the PAHO, the Ministry of Health of Brazil consulted a forum of experts to assess the ban on the treatment of dogs that had been determined by the Health Ministry in 2008[79]. Members of the Forum reaffirmed the ban, also in plain disagreement with the conclusions of the systematic review. The

TABLE 2 - Results of the main published intervention studies for the control of zoonotic kala-azar.

Exposures	Outcome	Time of follow-up	Results*	Main limitations	References
No intervention (a) Dog culling (b)	Seroconversion	Six months & one year	No protection	Non-random allocation	Dietze et al, 1996
No intervention (c) Dog culling (d)	Disease	One to four years	Protection in the first two years**	Non-random allocation	Ashford et al, 1997
Indoors, outdoors & animal pens spraying with pyrethroids (baseline) (a) Indoors spraying + dog culling (b) Indoors, outdoors & animal pens spraying with pyrethroids + dog culling (c) Indoors spraying (d)	Seroconversion	Six months to one year	- Protection of indoors spraying + dog culling - No protection of indoors, outdoors & animal pens spraying with pyrethroids + dog culling - No protection of indoors spraying	- High loss of follow-up - 3/4 of the study areaunder indoors, outdoors & animal pens spraying with pyrethroids - No non-intervention baseline	Costa et al, 2007
No intervention (baseline) (a) Indoors & outdoors spraying with pyrethroids (b) Indoors & outdoors spraying with pyrethroids + dog culling (a)	Seroconversion	One and two years	No protection	Non-random allocation	Souza et al, 2008

* effects with p value ≤ 0.05. ** the authors refused to claim a cause effect relationship between the exposure and the outcome.

prohibition was based on the agreement that a) the infected dogs must be the source of *L. infantum* for humans and other dogs, b) any treatment would be inefficient in reducing infectivity, c) could also lead to drug resistance and d) hinder the cooperation of the population with the program of systematic elimination of animals. This reaffirmation is a more extreme measure than systematic elimination, because it prevents all attempts to rescue the infected animals that are identified in routine screenings and whose owners try to save them with treatment, even with no scientific evidence that killing them will protect people. Currently, a legal measure for strengthening the policy of killing of all seropositive animals is being developed by the Ministry of Health and the Brazilian Legal Advisory and Consulting Office (Parecer/CODELEGIS/CONJUR/GABIN/MS/LP N 1243/2009). Furthermore, far more extreme measures of reservoir control can be predicted due to the recent movements towards destroying pups and endangered wild canines. Therefore, it is clear that the Brazilian government will not take into account the conclusions of the systematic review.

There are serious problems concerning the validity of the conclusions of this forum of dog treatment consulted by the Ministry of Health of Brazil, since it pursued no international recommended norms for elaborating guidelines[80-83]and the following neutrality issues were incurred: a) the participants were selected through criteria that were not made public; b) there was bias in the convening of the components, because it was already public knowledge that a large number of the participants were in favor of canine elimination and potential participants who were known to profess an opposing opinion were not invited, which led to bias in the spectrum of opinions; c) there was no expert in development of guidelines among the members of the forum and some of the participants had no expertise in epidemiology and leishmaniasis control (despite being distinguished scientists), which are fundamental requirements for the development of guidelines[81]; and d) the decisions were not preceded by a systematic review, as the brief literature that was consulted did not follow the rules of this type of evaluation of evidence[80], the only systematic review available[9] was not cited and the forum omitted publications with results that could lead to different conclusions, according to the citations mentioned in **Table 1**. This suggests that participants did not have access to the systematic review and to what went on in Foz do Iguacu, despite the presence of members of the Ministry of Health and the PAHO at both meetings. Thus, by not using international recommendations for the construction of systematic reviews and the development of guidelines, the case for banning the treatment of dogs to control leishmaniasis in Brazil reveals a systematic loss of scientific neutrality for the recommendation of a highly debatable health measure[83].

There are numerous reasons for ignoring the science that is oriented towards health policy[77], and some seem plausible in this case. One would be the fragility of knowledge concerning the control of leishmaniasis, as revealed in the systematic review[9]. Another is the territorial expansion of the disease and increase in incidence and mortality[36,37], which generates expectations and pressures on decision makers. Third, the lack of alternatives with recognized effects regarding zoonotic visceral leishmaniasis, which, in the face of political pressure may push the decision-makers to take irrational attitudes. A fourth possibility would be conflicts of interest. Even without considering possible lobbies and research groups interested in vaccines and tests for the diagnosis of dogs or of collars with pesticides, other undefined factors, such as traditions or past recommendations based on control measures used in other programs, such as rabies, may be influencing decision makers negatively and leading to resistance to changes in the policy for the control of visceral leishmaniasis. This could be created by the perceived threat of innovations, because changes in the decisions taken could possibly be interpreted as past mistakes and may have implications in relation to the prestige of the institutions and within the institutions.

Formal recommendations for the elaboration of further guidelines regarding other subjects of the diseases caused by *Leishmania* and many other tropical diseases are also are in use in Brazil[39,84-88], which would seem to confirm the widespread nature of distorting scientific evidence. In any case, perhaps the most important factor that has led to noncompliance with the formality of adherence to scientific evidence appears to have been a lack of institutional culture for fostering scientific integrity. This system of evaluating scientific evidence for public policy is governed by the promotion of systematic reviews and by the development and adoption of formal guidelines[77]. If this climate of integrity had already been established, it is unlikely the science would have been misinterpreted. Lastly, the loss of neutrality during the interpretation of the scientific information that occurred within the State itself was probably facilitated by the fact that zoonotic visceral leishmaniasis is a neglected disease that affects the least expressive part of the population and whose control and research depend almost entirely on the bureaucracy of the State.

CONCLUSIONS

Beside the three strategies used, the treatment patients, the use of indoor residual insecticides and the elimination of dogs, three other strategies for the control of zoonotic visceral leishmaniasis have been assessed. In Iran, a trial took place involving control by impregnating dog collars with deltamethrin in nine control villages and nine intervention villages paired by the prevalence of previous seropositivity and immunity was measured after one year of observation. A 43% reduction in the incidence of the infection (measured using serology) was determined, but the reduction in the incidence of DTH was not significant[52]. In Sudan, a vaccine against leishmaniasis was tested that consisted of autoclaved *L. major* plus BCG, which was compared with BCG. Protection only occurred in 6%, but the group that began to present DTH presented a lower incidence of the disease[89]. Finally, the effect of mosquito nets impregnated with insecticide is currently under assessment in India[90]. Excellent reviews regarding the use of insecticides and vaccines for leishmaniasis have been published[91-94] and should be consulted. Therefore, there are promising efficient alternatives for the control of leishmaniasis besides the traditional measures that widen the horizon of the fight against this disease.

Since the zoonotic kala-azar is now a threat to other South American countries, the decision over what to do based on the conclusions of the systematic review has become urgent and imperative. Given that there is no hard evidence on how much dogs contribute towards human infection, or on the effect of insecticides, particularly organochlorines, and there are no analyses of the operational obstacles to control measures used in large-scale urban environments, and since the biological, social or ecological events that led to urbanization and the spread of leishmaniasis are absolutely unknown[36], investment in research that addresses these problems must be a priority. Finding vaccines seems to be an immediate challenge. A recent international symposium identified the priorities for advancing the development of vaccines and this allows agencies to develop a view of crucial investments in the sector (Working Group on Research Priorities for Development of Leishmaniasis Vaccines: PLoS Neglected Tropical Diseases, in press). As a final point, the resumption of economic growth in emerging economies that are endemic with kala-azar, puts pressure on nations like Brazil, India and Iran to take on responsibilities of science and technology and to promote serious investments in the development of vaccines of a quality adequate for use in humans. Despite the great controversy surrounding the use of DDT, because of its persistence in the environment and toxicity[29,95,96], tests should be urgently conducted concerning its application to control urban kala-azar. Until then, the most that can be done would be a gradual, scheduled and monitored demobilization of the elimination of dogs, accompanied by extensive independent testing and evaluation of different strategies for spraying and other alternatives, such as the effect of vaccines already licensed for dogs, or collars and mosquito nets impregnated with insecticides.

Tropical and developing countries should also take advantage of this lesson given by the systematic review[9] on the control measures for leishmaniasis and its political consequences. They should seek the best available scientific knowledge, based on the best evidence, to obtain the best public health programs. Indeed, article 43 of the International Health Regulations[97], of which Brazil and many endemic countries in neglected diseases are signatories, require scientific evidence for policy development aimed at public health in one of its clauses. Moreover, the World Health Organization, like many other organizations, provides guidelines for the development of consensus[98]. Thus, the stimulus for policies aimed at promoting integrity[99] is an easily achievable goal and essential for the formation of scientifically neutral environments. Therefore, the lesson of zoonotic kala-azar can be useful for a quality review of current recommendations for public health in different countries.

The awakening of the conservationist movement and the rights of minorities, coupled with the recognition of complex feelings among mammals has substantially changed the moral relationship between human beings and animals[100, 101]. Within this change in the ethics of relationships with other living beings, dogs are one of the most sociable and affectionate species and cannot be regarded as morally irrelevant beings that can be disposed of without causing irrefutable harm to humans. Thus, progressively more accurate and sensitive human values imply the requirement of reputable and firm scientific justification in order to be morally valid, which has never been the case with any program for the disposal of dogs for the control of leishmaniasis. Finally, some good may come from the confused knowledge and decisions of the past, since the thousands of dogs needlessly sacrificed may at least serve to encourage a revolution in scientific quality and in the ethics of health policies aimed at neglected diseases.

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CONFLICT OF INTEREST

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