doi: 10.5216/rpt.v52i1.74769

REVIEW

VISCERAL LEISHMANIASIS IN BRAZIL: SCENARIOS AND CHALLENGES FOR THE SURVEILLANCE AND CONTROL

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ABSTRACT

Adaptation of the vector and displacement of infected dogs to previously disease-free areas challenges visceral leishmaniasis (VL) control, and leads to geographic dispersion and occurrence in urban and peri-urban areas. Continuous VL control measures over time must be applied with a wide geographic reach, along with better diagnosis practices and timely treatment. The high case-fatality of human VL in areas of recent introduction and its growing association with HIV impose the need for an early diagnosis, treatment and the adoption of active search for human and canine cases incorporated into the routine of periodic home visits by health professionals. The increasing on public rejection of canine euthanasia as a control measure, the limitations of canine therapy with the current available drugs, and the controversies regarding available vaccines for canine protection are discussed. Good prospects on the insecticide-impregnated collars as an effective control measure are emphasized.

KEY WORDS: Leishmaniasis; visceral; epidemiology; public health surveillance; Kalazar.

INTRODUCTION

Visceral leishmaniasis (VL) is considered a neglected tropical disease, and this clinical manifestation of leishmaniasis is responsible for most of the disease's lethality (Bezerra et al., 2018; PAHO, 2021). In the Americas, including Brazil, the protozoa *Leishmania infantum* is the main

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Received for publication: 15/12/2022. Reviewed: 13/1/2023. Accepted: 22/1/2023.

etiologic agent of this zoonosis in humans and dogs, and it is transmitted by the female phlebotomine of the *Lutzomyia* genus, also known as sandfly (Ribeiro et al., 2018; Sousa-Paula et al., 2019). According to the Pan-American Health Organization, Brazil was responsible for 97% of the human cases reported in the Americas in 2021 (PAHO, 2021).

From 1970's onward, a change in the epidemiological VL profile in Brazil was observed, from a typically rural disease to an undergoing process of urbanization (Gualandi, 2013). The first urban epidemics were reported in Rio de Janeiro in the neighborhoods of the west area of the city in the 70s, without previous rural VL (Marzochi et al., 1985), and in Teresina (Piaui State) between 1980 and 1986, when the disease, initially limited to rural areas, expanded to peripheral areas in the city (Costa et al., 1990).

Since then, the disease has been expanding from cities in the Northeast to urban centers in the North, South, Southeast and Midwest regions of the country (de Oliveira et al., 2020). The urbanization of VL and its geographic dispersion to previously disease-free areas poses several challenges related to the displacement of the vector and infected dogs, reinforcing the need of control measures with a wide geographic reach that must be continuous over time.

Although VL still predominates in the Northeast region of Brazil which was responsible for 49.1% of the country's notifications in 2019, autochtonous cases were reported in 24 of 27 Federal Units in the same year (Ministério da Saúde, 2021a). Along with VL advances to previously disease-free areas, there has been an increase trend on case-fatality in Brazil, with an upsurge of 108% on the Global Burden of Disease (GBD) estimates of Years of Life Loss (YLL) between 1990 and 2016 (Bezerra et al., 2018). The lethality rate in 2019 was the highest in the last 10 years, accounting for 9% of the cases, with especial concern towards the infants (<1-year-old) (10.3% lethality) and adults older than 50 years old (19.2%) (Ministério da Saúde, 2021a).

The epidemiology of VL in Brazil and future scenarios rely upon the environmental, biological and social condition (Valero et al., 2021), therefore highlighting the importance of a better understanding about the disease determinants and its impacts on surveillance and control strategies. This understanding may be reached through medical and veterinary sciences combined to establish proper surveillance and control of the disease (Palatnik-de-Sousa & Day, 2011; Hong et al., 2020).

Challenges in surveillance and control measures

Surveillance and control measures of human VL in Brazil are essential and include early diagnosis and treatment, besides the active cases' search. Due to the potential life-threatening disease in areas where canine or human cases have occurred, such actions must anticipate patients' passive pursuit for health treatments through primary health care teams (Marzochi et al., 1985; Marzochi et al., 2009). The active investigation and referral of suspected human cases to Health Units would help to protect patients from the disease's severity and lethality. This is particularly important for those co-infected with HIV, which represented 11% of the diseases' notifications in 2019 with increasing rates in North and Midwest of Brazil (Ministério da Saúde, 2021a). Besides the probable intensification of early diagnosis and treatment, the closer contact between health care teams and local population would promote not only staff training, but the spread of information and prophylaxis awareness to the population.

The dynamics of VL and its expression on the Basic Reproduction Ratio (R0) considers the interactions between involved participants in the cycle of the disease (mainly sandflies, domestic dogs, and human populations). Intervention control measures focused in at least one of these factors are tools capable of affecting the transmission of the disease with varying effectiveness degrees (Marzochi et al., 2009; Prestes-Carneiro et al., 2019). VL control has so far failed in Brazil due to several complex factors involving the disease transmission dynamics (Barreto et al., 2011). Besides the difficulties in control implementation and its maintenance during long periods, another challenge is quantifying their impact and effectiveness over the years.

Control of dogs

There have been evidences that the presence of dogs at the domicile and higher dog seropositivity in neighboring areas are associated with human *L. infantum* infection in the Americas (Belo et al., 2013). Although the domestic dog has become a major reservoir for the disease in the context of the rapid urban expansion (Barreto et al., 2011), the culling of infected dogs as a control measure is vastly rejected. Also, considering the conflicting results about the role of culling infected dogs in canine VL control, lawsuit projects prohibiting the euthanasia of animals with leishmaniasis have been discussed in Brazil (Prestes-Carneiro et al., 2019).

Canine culling still seems to be the least acceptable intervention at community level (Romero & Boelaert, 2010; Dantas-Torres at al., 2019) with judicialization by the population and great mobilization of the scientific community to seek alternatives. Reinforcing rejection, studies have shown that only a percentage of infected dogs are infectious to sandflies; besides, dogs that have a natural death are rapidly replaced in nature by others, usually younger and immune naïve, or even by other species of reservoirs, which is an important implication for impairing culling programs success (Courtenay et al., 2002; Dantas-Torres et al., 2018a; Maia et al., 2018). Other aspects related to the scientific rejection are documented failures of controlling human and canine cases trough culling programs (Sousa-Paula et al., 2019), sensibility and specificity variation between commercial serological tests and cross-reactions with other pathogens, such as trypanosomes (Dantas-Torres et al., 2018b; Travi et al., 2018).

Recent evidence of effectiveness and cost-effectiveness sustain the incorporation of insecticide-impregnated dog collars, it impacts the vector population access to the dogs due to their insecticide or repellent potential, hence reducing the prevalence of canine VL which might impact the incidence of the disease in humans (Kazimoto et al., 2018; Silva et al., 2018). Studies using insecticide–impregnated dog collars with deltamethrin, imidaclopridalone or their combination with other insecticides show promising results in Brazil and in other countries, which shows the cost-effectiveness of this strategy (Brianti et al., 2016; Papadopoulos et al., 2017; Shimozako et al., 2017; Assis et al., 2020; de Carmargo-Neves et al., 2021).

The effectiveness of insecticide-impregnated collars in reduce the prevalence of canine VL was demonstrated in some controlled intervention studies. Coura-Vital et al. (2018) evidenced in an intervention study carried out in two regions of Governador Valadares (control and intervention) with a 12 months follow-up, that the effectiveness by intention-to-treat was 48%. In the analysis per-protocol, the effectiveness increased to 63%. Also, the authors emphasize the importance of the uninterrupted use of deltamethrin-impregnated collars to expand the protection against canine VL. Leite et al. (2018) demonstrated in an interventional field effectiveness study in a highly endemic area in Monte Gordo (Bahia-Brazil) that the seroprevalence in the intervention area reduced to 6.0% during the final evaluation versus an increase of 11.0% in the control area and the estimated relative risk (RR = 0.55) indicated protection against canine VL in the intervention area.

In Brazil, the Ministry of Health acquired in 2020 collars impregnated with deltamethrin 4% for subsequent distribution in 16 States, prioritized by their high numbers of human cases, being the first country to officially incorporate the insecticide-impregnated collars as a measure of public health and leishmaniases control (Ministério da Saúde, 2021a; Ministério da Saúde, 2021b).

Despite the insecticide-impregnated collar being an important advancement in control strategy, improvements in durability and safety of the collars should be considered in order to avoid operational difficulties, which includes collar loss (Alves et al., 2018). An alternative could be the development of subcutaneous implantable long-term insecticide/repellent-releasing devices, similar to those used to release hormones in humans. Other viable and available alternatives are spray insecticides at the domicile and peridomicile in highly endemic areas and the human regular use of topic insecticides and insecticide impregnated bed nets even though the lack of compliance and the incorrect use might contribute to unsatisfactory results (Miró et al., 2017; Balaska et al., 2021; Montenegro-Quiñonez et al., 2022). It is also important to limit the dog's access to the peridomicile during the sandflies peak of activity, preferably not allowing dogs to sleep in the backyard, especially if not paved (Leal et al., 2018).

Canine treatment

Canine treatment with pentavalent antimonials has been carried out in Europe since the 1950s, but the use of this medicine for the treatment of human VL to manage diseased animals is prohibited in Brazil, due to the possibility of inducing *Leishmania* drug resistance in the country (Ministério da Saúde, 2008). In 2016, miltefosine has been approved for canine VL treatment in Brazil (Brasil, 2016). To this date, no therapeutic regimen has been shown to be completely effective for canine leishmaniasis, especially since the parasitological cure is still a challenge to achieve. However, some studies have demonstrated that miltefosine in combination with allopurinol, offers a safe, convenient, and effective alternative treatment option for canine leishmaniasis (Miró et al., 2009; Ribeiro et al., 2018). However, the main issue regarding the drug treatment is that it requires clinical, laboratorial and parasitological accompanying of the dogs, which makes a high-cost treatment and non-accessible therapy for most of the population. It also requires the animal to have a tutor committed to the life-long treatment (Ribeiro et al., 2018). In addition, both infected and non-infected dogs must still use impregnated collars and be kept in areas sprayed with insecticides, and despite of the treatment, not only as a prophylaxis to contamination, but also as a mean to avoid the reservoir role of animals at the beginning of the treatment that still carry a high parasite level on the skin.

Canine vaccination

Canine mass vaccination is another strategy to be discussed as a promising control measure treatment in Brazil, yet it is limited in robust scientific evidence due to the insufficient number of randomized controlled field studies. Furthermore, immunoprophylaxis by Leish-tec® vaccine is the only approved in the country and it presents contradictory results. Thus, this measure needs more scientific evidence before its recommendation as a public health measure. Grimaldi et al. (2017) evidenced that after two transmission cycles completed, the cumulative incidence of infection did differ significantly ($p = 0.016$) between the vaccinated (27%) and non-vaccinated (42%) dogs. The study also demonstrated that 43% of vaccine recipients developed disease over time. Regina-Silva et al. (2016) evidenced a significant reduction of VL cases in the vaccinated group dogs. The efficacy was estimated according to parasitological results (71.4%; $p=0.001$; risk ratio=0.287), by adding results of xenodiagnosis and parasitological exams (58.1%; $p=0.002$; risk ratio=0.419). Among the animals that converted to a positive anti-A2 serology, efficacy reached 80.8% ($p=0.001$; risk ratio=0.192). Also, xenodiagnosis has detected a reduction of 46.6% ($p=0.05$) in transmission to sand flies from vaccinated animals presenting anti-A2 positive serology.

Some concerns around the immunoprofilaxis for canine mass vaccination include the limitations regarding effectiveness of the vaccines in prevent infection, although they succeed in lowering parasite levels and clinical symptoms, also some vaccines could possible indiscriminate serological tests between vaccine elicited antibodies and those produced upon infection (Miró et al., 2017; Dantas-Torres et al., 2018a). New scientific evidences on canine vaccination are needed, since this strategy could be useful in endemic areas of VL in Brazil.

FINAL COMMENTS

New investments should be directed towards the reduction of human and canine VL cases and fatality in both rural and urban areas. The cases and death control requires continuous actions and complementary strategies depending on the location and epidemiological situation. The most likely factors for the establishment and expansion of urban VL are rural-urban migration (human and canine population) from an endemic area to a disease-free area; disorderly cities growth (environmental changes), adaptation of *Lu. longipalpis* to the urban environment (possible introduction by road and rail transport by organic fertilizers, cereal residues and ornamental plants containing sandflies' eggs, larvae and pupae) (Marzochi, 2016).

Canine leishmaniasis precedes human cases, so there is no endemic urban VL without infected dogs and sandflies involved in the area. Surveillance of the occurrence of canine and human cases through active search is essential. Thus, considering that infected, symptomatic and asymptomatic dogs, present *Leishmania infantum* in all the body surface (Madeira et al., 2004), the biggest challenge to control is to recognize the condition of the dog as a real source of infection or not. This distinction might be harder on dogs that are treated, vaccinated and/or using insecticide-impregnated collars, especially those kept in the domestic environment with judicial authorization despite their serological status.

We should consider that the current evidence does not support the maintenance of euthanasia as a control measure in terms of effectiveness. However, evidence do not rule out that euthanasia might be a possibility in poorer areas where treatment is not a feasible alternative. Due to treatment high cost, for dogs without a tutor that could take responsibility for its continuity, euthanasia might ensure animals can be released from pain and suffering from the disease. Therefore, responsible ownership measures should be better implemented and target tutors whose dogs are undergoing treatment. Also, the lack of quantitative evidence regarding combined components (human, animal, environment) contributing to disease scenarios of transmission remain as a public health problem. Integrated one health approaches must consider scientific evidence that contemplates these different aspects in order to propose more effective strategies for its resolution.

ACKNOWLEDGMENTS

MCAM is grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq: Bolsa de Produtividade Sênior, Processo No. 308889/2017-7. GRA is grateful to Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES, for the doctoral scholarship.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest or financial ties to disclose.

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