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Comentário

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Visceral leishmaniasis in Brazil: rationale and concerns related to reservoir control

Leishmaniose visceral no Brasil: fundamentos e preocupações em relação ao controle de reservatórios

ABSTRACT

The control of zoonotic visceral leishmaniasis is a challenge, particularly in Brazil, where the disease has been gradually spreading across the country over the past 30 years. Strategies employed for decreasing the transmission risk are based on the control of vector populations and reservoirs; since humans are considered unnecessary for the maintenance of transmission. Among the adopted strategies in Brazil, the sacrifice of infected dogs is commonly performed and has been the most controversial measure. In the present study, we provide the rationale for the implementation of different control strategies targeted at reservoir populations and highlight the limitations and concerns associated with each of these strategies.

DESCRIPTORS: Leishmaniasis, Visceral, prevention & control. Dogs, parasitology. Disease Reservoirs. Zoonoses, prevention & control. Epidemiological surveillance.

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RESUMO

O controle da leishmaniose visceral zoonótica representa grande desafio, particularmente no Brasil, onde um paulatino processo de expansão geográfica da doença vem sendo verificado há mais de 30 anos. Nesse contexto, humanos não são considerados relevantes para manutenção da transmissão. Assim, as estratégias usualmente utilizadas com vistas à redução do risco de transmissão se baseiam no controle das populações de vetores e reservatórios. Dentre essas estratégias, a eliminação de cães infectados, correntemente utilizada no Brasil, tem sido das mais questionadas. Neste comentário, apresentam-se os fundamentos que justificam diferentes estratégias de controle orientadas para a população de reservatórios, assim como os limites e preocupações associadas a cada abordagem.

DESCRITORES: Leishmaniose Visceral, prevenção & controle. Cães, parasitologia. Reservatórios de doenças. Zoonoses, prevenção & controle. Vigilância epidemiológica.

INTRODUCTION

Visceral leishmaniasis (VL) is a major public health problem worldwide, accounting for approximately 200,000-400,000 new cases each year, and a fatality rate of approximately 10.0%.[2] Infection is caused by protozoan parasites of the genus *Leishmania* and transmitted by the bite of female phlebotomine sand flies. There are two major types of transmission cycles: anthroponotic and zoonotic. Anthroponotic transmission, with humans being the sole or major reservoirs of the parasite, occurs mainly in the Indian subcontinent and East Africa. Zoonotic transmission is typically observed in Mediterranean countries and in the Americas, but can also be found in Central Asia, Afghanistan, the Islamic Republic of Iran, and Pakistan.[24] In both types of transmission cycles, the poor and underprivileged are the most affected.[1]

Although anthroponotic visceral leishmaniasis accounts for approximately 80.0%-90.0% of disease burden worldwide, zoonotic visceral leishmaniasis (ZVL) has drawn the attention of public health officers and the scientific community because of its recent spread to urban regions in South American countries. In this region, the disease is caused by the protozoan parasite *Leishmania infantum* (syn = *Leishmania chagasi*), transmitted by *Lutzomyia* sand flies, with dogs being incriminated as the main reservoir of infection in urban settings.[24]

VL was first considered a rural disease in Brazil; however, after the 1980s, the disease has mainly occurred in large cities across the country. The first reported urban outbreak occurred in Teresina, the capital of Piaui state, resulting in 900 VL cases from 1981 to 1985. In the previous decade, this city reported an average of 3.8 cases of VL annually.[5] The disease then further spread to Sao Luis (Maranhao state, MA) and Natal (Rio Grande do Norte state, RN), both large cities in the Northeast region of the country.[a] Since the 1990s, disease has spread out across the entire country, with autochthonous cases reported in 25.0% of the Brazilian municipalities in 21 states. In almost 30 years, the average number of cases reported per year has increased from 1,601 (1985-1989) to 3,816 (2008-2012). Before the 1990s, 80.0%-95.0% of cases occurred in the Northeast region; however, in 2001, for the first time, the proportion of cases autochthonous to that region fell below 80.0%, reaching 50.0% in 2007 and has remained stable till date. This decrease in the proportion of cases reported by the Northeastern states directly corresponds to the introduction of the disease in cities with populations of > 100,000 such as Belo Horizonte (Minas Gerais state, MG), Araguaína (Tocantins state, TO), Campo Grande (Mato Grosso do Sul state, MS), Bauru (Sao Paulo state, SP), Palmas (TO), Cametá (Pará state, PA), Rondonópolis (Mato Grosso state, MT), Três Lagoas (MS), Montes Claros (MG), and Araçatuba (SP). These 10 cities alone were responsible for the 15.0% of the VL cases reported in Brazil from 2001 to 2012. The available data clearly shows that VL is a disease of urban areas and that there are no noticeable signs that its dissemination is under control.

What are the potential control measures that could be employed for addressing this problem? For ZVL, prompt diagnosis and treatment of human cases, although essential for avoiding human deaths due to the disease, would not be a solution because humans do not play an important role in its transmission.[15]

[a] Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Manual de vigilância e controle da leishmaniose visceral. Brasília (DF); 2006.

Unfortunately, no registered human vaccine against *L. infantum* is available currently. Therefore, for preventing further transmission, control programs against VL should rely on measures that focus on the vector and reservoir populations.

The use of vector control and reservoir management as intervention strategies against ZVL is based on previous findings that the incidence of human infection is directly related to the number of infectious dogs and the efficiency of sand flies in transmitting the parasite from dogs to humans (also known as the vectorial capacity).[8]

Assuming that infectious dogs play an essential role in transmission to humans in an urban setting, an effective control strategy should be capable of decreasing the incidence of infection in the canine population. A key parameter for measuring the transmission potential of an infectious disease is the basic reproduction number (R_0).[3] For ZVL in the canine population, the R_0 might be conceived as the average number of new infections due to an infectious dog when introduced into a reservoir population fully susceptible to infection.[8] Therefore, it could be inferred that the disease could be eradicated among dogs (and consequently in the human population) if the R_0 of *L. infantum* in the dog population is decreased to < 1. Therefore, the potential effectiveness of any intervention against ZVL can be gauged from its impact on the R_0 of infection in dogs.

The R_0 can be determined on the basis of the vectorial capacity of the sand fly population in transmitting infection to dogs, on the duration of the infectious period, and on the probability of transmission to a susceptible individual during a single contact.[10] The vectorial capacity is a combination of the entomological parameters affecting transmission such as vector density, the rate of female sand fly bites in dogs, the life expectancy of sand flies, and the extrinsic incubation period of *L. infantum* in sand flies.[8] In Brazil, Quinnell et al[14] estimated an R_0 of approximately 6, i.e., an infectious dog when in contact with a population of fully susceptible dogs causes the appearance of an average of 6 new infections.

In theory, vector control is considered by far the most potentially effective strategy against vector-borne diseases, mainly because R_0 is very sensitive to the mortality rate of the vector.[10] However, the putative higher effectiveness of vector control for ZVL is hampered by operational problems and the high cost associated with sustaining large-scale insecticide spraying, the limited knowledge regarding sand fly ecology and biology in urban areas, and the need for an extensive entomological surveillance system that could estimate the size of the vector population.[12,16] In this setting, focusing on the reservoir population seems an attractive alternative, particularly because for ZVL, the domestic dog is reasonably accessible in urban areas.

One can devise various strategies for controlling the ZVL reservoir population. Killing infected dogs is by far the most commonly used approach, and is a pillar in the VL control program of the Brazilian Ministry of Health.[a] Other possible strategies include dog vaccination, treatment of infected dogs, insecticide-releasing dog collars, and topical insecticides.

All of these strategies might be effective because they would interfere with the parameters that determine the R_0. Removing the source of infection from the environment by killing infectious dogs, for instance, would work by decreasing the average duration of the infectious period. Treatment of infectious dogs would also shorten their infective stage and there would be no need to remove these animals from the community. A dog vaccine that builds immunity against infection would decrease the pool of susceptible dogs. Alternatively, a vaccine might not impede infection but may limit the parasite burden, decrease disease severity, and increase the survival of infected dogs. In this situation, although infected, the probability of transmission by a vaccinated dog would probably be diminished. Topical insecticides and dog collars impregnated with insecticides would decrease transmission by increasing the mortality of sand flies.

Unfortunately, some of these potential control strategies are not yet available or require additional scientific evidence for proving their effectiveness.[20] There are dog vaccines in Brazil that have shown to be immunogenic and decrease symptoms and mortality of vaccinated dogs;[4,7] however, there is no solid evidence that the transmission from vaccinated dogs to sand flies has been decreased to a level that would effectively and significantly protect humans from infection.

Treatment of infected dogs has been used for a long time in the Mediterranean countries and seems to provide some temporary benefits to dogs, although no parasitological cure has been achieved.[21] Previous studies have shown that treated dogs have a lower parasite burden and rate of transmission than non-treated infected dogs.[19] However, there is no data on its effect on transmission to humans. In addition, for assessing the potential effect of such approach, the fact that these infected dogs will continue to transmit the parasite across its community should be considered. Because of the absence of an effective parasitological cure, treatment needs to be repeated periodically, which in turn could increase risk of drug resistance.[24]

Topical pour-on insecticides may act as a repellent and an insecticide and might decrease the prevalence of infection in the canine population; however, its effects on human outcomes have not been explored.[22] The relatively short-term effect of this intervention and the consequent need for frequent reapplication is an issue that needs to be addressed before further evaluation in large community trials.[15]

Dog collars impregnated with insecticides have shown to increase mortality of sand flies and decrease both the prevalence and incidence of canine infection.[22] A clustered randomized trial in Iran showed also that such intervention resulted in a 43.0% decrease in the odds of infection in children.[9] However, the absence of results showing its effectiveness from large community intervention trials in Brazil associated with the reported high rate of collar loss[17] and high price are some limitations to its large-scale application.

Reasons for the ineffectiveness of dog culling include the lack of accurate tests for identifying both canine infection and infectiousness, the fast replacement of destroyed dogs by a new susceptible dog population that are rapidly infected in highly endemic areas, the long interval between identification of a seropositive dog and its removal from the environment, and the high cost of sustaining a program requiring constant vigilance and well-trained personnel.[13,15,20] A simulation study based on mathematical models for VL transmission to humans have shown that dog treatment and dog vaccination are ineffective for decreasing human disease, and that dog culling is less effective than insecticide-releasing dog collars and vector control. This indicates the need for increasing the natural mortality rate of dogs by 1,000-fold for significantly decreasing human prevalence.[18]

An article on this issue of *Revista de Saúde Pública*[11] emphasizes an important and often overlooked problem with the strategy of culling seropositive dogs: the high proportion of uninfected dogs that test positive for Leishmania-specific IgG antibodies. The substandard specificity of tests used for identifying infected dogs in the field lead to the sacrifice of many false-positive dogs, particularly when the prevalence of infection in the dog population is low. For instance, in a realistic scenario in which the prevalence of canine infection varies from 10.0% to 20.0%, a test with a 90.0% sensitivity and specificity can lead to a respective 50.0% to 30.0% of the tested dogs being false positive and incorrectly sacrificed. The above sensitivity and specificity are similar to the proposed strategy of the Brazilian VL control program[b] of combining the use of the Dual-Path Platform for screening and ELISA for confirmation. Therefore, an ethical issue is raised against the culling strategy, particularly considering the lack of scientific evidence supporting such intervention. Considering these issues and the conclusion of another simulation study indicating that culling alone is not an effective control strategy in areas with high levels of transmission, the guidelines of the Brazilian VL control program should be revised.[6]

Despite strong theoretical models suggest that a certain intervention might be effective, it is essential for considering that its impact will essentially depend on the spatial variability in transmission rates.[23] VL is considered a disease in which the conditions for transmission depend mostly on local factors. When such focal transmission is the rule, an intervention program will be more effective when targeting groups at higher risk. Therefore, the choice of control measures to use against VL should be based on the specific context to which it will be implemented.

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