

# Visceral leishmaniasis epidemiologic evolution in timeframes, based on demographic changes and scientific achievements in Brazil

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## ABSTRACT

Visceral leishmaniasis (VL) is a disease of chronic evolution which could be uniformly fatal, if left untreated. Human VL was first described in the Americas in 1913 and in 1936 in Brazil. The number of VL cases in Brazil is increasing steadily in the last three decades. Medical literature highlights this change in the disease epidemiology as a recent urbanization phenomenon, with most of the cases occurring in large cities since 1981, different to that observed previously, like a typical rural endemic. The aim of this study was to create a narrative review of the evolution of VL epidemiology since its first description in Brazil. To describe the process of urbanization of VL, timeframes were created historically consistent with the scientific and public health knowledge obtained about the VL and the demographics changes in Brazil, especially considering the extensive migratory movements in the country due to political or economic events. The first phase of VL was the decades of 30–50 when industrialization triggered internal migration process from countryside to the cities; during this period VL was studied for the first time and described as a rural endemic disease with no relevance to public health. Until the second phase, between the 50s and 80s of the 20th century, demography was characterized by expansion of immigration to the large cities and increase in population density in the suburbs with poor living standards. In this period, there was an advancement in the knowledge of the transmission of the disease being described as the first case acquired in the urban environment. The third phase was characterized by the explosion of cases in Brazilian cities and consolidation of urban endemic transmission. The possibility of urban transmission has been known since the 50s; however, the current phenomenon was due to the creation of ideal conditions for the establishment of transmission cycle in Brazilian cities.

**Key words** Brazil; epidemiology; urbanization; visceral leishmaniasis

## INTRODUCTION

Visceral leishmaniasis (VL) is an endemic disease with a complex clinical course, usually fatal if left untreated. According to the World Health Organization (WHO) 2015 report, it is considered a neglected and emerging disease, endemic in 98 countries with 90% of cases concentrated in Bangladesh, Nepal, Sudan, India and Brazil<sup>1</sup>. In 2010, around 200 million people were at risk of acquiring the disease; while in recent years about 300,000 new cases were registered and between 20,000 and 50,000 deaths occurred annually in the world<sup>2</sup>.

VL in Brazil is a zoonosis caused by *Leishmania infantum* (syn *chagasi*) and transmitted namely by Phlebotominae females of *Lutzomyia longipalpis* species. Two cycles of disease transmission are described, a sylvatic, mainly maintained by wild foxes (*Vetulus pseudalopex* and *Dusicyon thous*) and other domestic, whose main reservoir is the dog (*Canis familiaris*). In both transmission cycles man is regarded as an acciden-

tal host, since so far human infection has not been proved to be able to maintain the transmission<sup>3-4</sup>.

The first case of VL in the Americas was diagnosed in 1913 by a Paraguayan doctor at Asunción from a patient coming from the City of Corumbá in Brazil<sup>5</sup>. However, it was only in 1934, when Penna reported the presence of Leishman-Donovan bodies in 41 tissue specimens analyzed in histopathological examination from post-mortem viscerotomies performed on diseased persons suspected of yellow fever infection coming from the north, northeast and southeast regions of Brazil<sup>6</sup>.

The number of cases of human VL in Brazil has rapidly expanded in the last three decades<sup>7</sup>. This growth was associated to change in the disease epidemiology during the time span and this phenomenon was called disease urbanization since most of the cases occurred in large cities in contrast to the typically rural endemic, as previously believed<sup>8-9</sup>. The objective of this narrative review was to propose a discussion about the changing epidemiological pattern of VL in Brazil by linking up social and demographical information to its scientific landmarks

in order to explain the disease consolidation as an urban endemic.

#### *Social and demographic changes*

A narrative review was carried out based on articles published about VL in Brazil since its first description in a postmortem case in 1934 by Penna<sup>6</sup>. Demographic information was obtained from the website of the Brazilian Institute of Geography and Statistics (IBGE), especially the section of statistics and historical series<sup>10</sup>.

In attempt to explain the process of urbanization of leishmaniasis, timeframes were established with certain historical concordance between the scientific knowledge obtained on VL and the demographic characteristics of the population at that time, especially considering the extensive migratory movements in Brazil as a result of political or economic events<sup>11</sup>.

The first period considered in the study was the decades from 1930 to 1950, when the New State (Estado Novo) consolidated in the process of industrialization of the country mainly concentrated in the southeast region, and when the intense internal migration movements accompanied a vegetative growth in the population. During this migratory period, VL was described for the first time in Brazil and its clinical and epidemiological characteristics started to be investigated.

The second period ranged from 1950 to 1980 and was characterized by greater dynamism of industrialization with initial consolidation of manufacturing centers, and also associated with the industrialization of agriculture activity. During this period large scale migratory movement of citizens from the countryside to urban zones occurred. The consequence was that, from the 1960s the proportion of the urban population surpasses the proportion of individuals living in the countryside<sup>12</sup>. The knowledge on VL moves forward with the definition of the role of the wild reservoir and the vector, the sandfly *L. longipalpis*, in transmission dynamics, and the description of the first cases of urban origin<sup>13</sup>.

From the 1980s there was a shift in the Brazilian migration process; after consolidation, urbanization continued to expand to new agricultural zones in the north of the country. The urbanization process in Brazil culminated in the concentration of population in peripheral areas of the cities with poor sanitation conditions. The emergence of urban epidemics of VL was detected in several important cities countrywide and the total number of cases increased steadily. This timeframe epidemiologically marked the disease urbanization and exposed the failure of control measures executed under the responsibility of the Ministry of Health (MoH) and municipalities.

#### *Sparse rural cases without public health concern (Decade 30 to mid-1950)*

The population census conducted in 1940 showed a population of about 40 million people, which crossed 52 million during the 1950s. Since the early 20th century, the population continuously increased, both as a result of increased fertility rates and through the immigration from foreign countries with an input of three million immigrants including Portuguese, Italian and other Europeans.

During this period most of the population lived in rural areas and were employed in commodity agricultural activities (coffee was the major export commodity). The 1929 global crisis had an impact on the Brazilian economy primarily by the breakdown of the coffee market which fostered the beginning of a new cycle of industrialization centered around the City of São Paulo and Guanabara (now the City of Rio de Janeiro). The internal migration of individuals from rural areas and small towns to these urban centers reached to four million people at the end of the 40s.

In 1936, Chagas<sup>14</sup> and his "Committee responsible for the American visceral leishmaniasis studies" described the first alive case of VL in Brazil in a 16-yr-old boy. He was investigated because his brother died from VL, which was confirmed by, histopathological analysis of viscerotomy specimen was by Penna<sup>6</sup> in 1934.

The Committee performed medical assessment of all the individuals who inhabited households with cases of the disease documented by histopathological analysis and the greatest possible number of individuals who lived around the areas with documented outbreaks, insects, domestic and wild mammals were also captured for analysis of the presence the parasite<sup>15-16</sup>. Despite that, the committee found the disease in few patients and the infection in eight domestic animals (seven dogs and a cat). Thus, the researchers concluded that it was a restricted disease limited to rural areas surrounded by forests and epidemiologically characterized by sporadic transmission.

Chagas<sup>14</sup> also implied the role of wild animals in the transmission cycle, considering them as the main reservoirs, and excluded the involvement of man and the domestic dog in the maintenance of the disease in man. They also suggested that sandflies insects could be the vector of VL, despite not having been able to establish this relationship unequivocally.

Indeed, the conclusions of the committee established the theoretical foundations that influenced public health actions and research on the disease in the following decades until the present day. However, for about two decades, VL was considered a disease of no importance from the health point of view, only causing sporadic cases in

regions with low population density and far from major centers. It was only in the 1950s, when the medical reports from the City of Sobral, Ceará state, through the detection of an abnormally high number of cases, alerted the scientific community that VL could have a different epidemiology than was believed.

#### *The establishment of rural endemic*

Until the early 50s VL was considered a medical curiosity in Brazil, just over 40 cases were diagnosed and 240 histopathological examination of viscerotomies specimens were positive for over a decade<sup>13</sup>.

However, the frequent diagnosis of northeastern immigrants with VL in large centers like the University of São Paulo's Hospital, in 1954<sup>17</sup> and clinical communications from Ceará state reporting the existence of several cases from 1953, made Deane and Deane<sup>18</sup>, a member of the formerly Chagas<sup>16</sup> committee, went to the City of Sobral to conduct further investigation about the situation of the disease between 1953 and 1954.

In Sobral, during the period of a few months, they found 188 cases of VL, more than the quadruple diagnosed countrywide at that time. It was possible to carry out the investigation of 177 cases with respect to their clinical and epidemiological characteristics. Deane and Deane<sup>18</sup> were able to modify the existing paradigm about the disease so far. Among its findings were: the first description of wild reservoir, the canid species *Lycalopex vetulus*; the role of the domestic dog as the main source of infection; and the sandfly *L. longipalpis* as the main vector of the disease.

The excellent description of the distribution of the cases in relation to the environment where the diseases spread, demonstrated the importance of vector density in disease transmission<sup>17</sup>. It was found that 3% of cases were acquired in the urban environment, contrasting to what Chagas<sup>16</sup> and collaborators previously stated that VL was an exclusively rural disease<sup>18</sup>.

Most of the diagnosed cases were children aged 0–9 yr. These findings were reinforced by the report of local physicians and residents of previous epidemics of a disease with a clinical picture similar to VL, killing most of the children. This observation posed the hypothesis that the disease presented itself as endemic, which interspersed with epidemic cycles, causing high morbidity and mortality among children<sup>18</sup>.

The work of Deane and Deane<sup>18</sup> anticipated the possibility of urbanization of the disease, a fact that became a public health problem 30 yr later<sup>19</sup>. Additionally by including VL among the health priorities of the country when they demonstrated that it was not a disease with

sporadic occurrence, but an endemic disease predominantly rural at that time, with potential for urbanization and of great social impact; the MoH was compelled to create a national disease control programme<sup>20</sup>.

This timeframe was marked from the demographic point of view, due to population and vegetative increase and huge rural exodus towards the large cities. It was reported that in the 1960s >11 million people have moved toward the urban centers with greater power of attraction, as a result of the industrialization process. It was also in the 1960s, when the proportion of individuals living in cities exceeded those living in the countryside (Fig. 1)<sup>12</sup>.

Since then, new cases have been detected in various states of the northeast, especially Piauí, Bahia and Pernambuco. Sporadic cases have also been reported in Goiás and Mato Grosso and Mato Grosso do Sul in the centralwest region<sup>21–23</sup>. In the end of 1970s, the rural region of Vale do Rio Doce, Minas Gerais, had become endemic, preceding the establishment of urban VL in the capital Belo Horizonte in the following decade, even though control measures taken by the government to at the time seemed to quell the outbreak<sup>24</sup>.

#### *The 1980s and the consolidation of disease urbanization*

Since the 1950s, the VL was treated as rural endemic disease; control measures were applied discontinuously aiming vector and domestic reservoir control, with prioritization in rural areas<sup>20</sup>. From the 2nd half of 1970 the urban areas, especially in large cities, had received large numbers of people from rural areas due to environmental conditions (the successive droughts in the north-

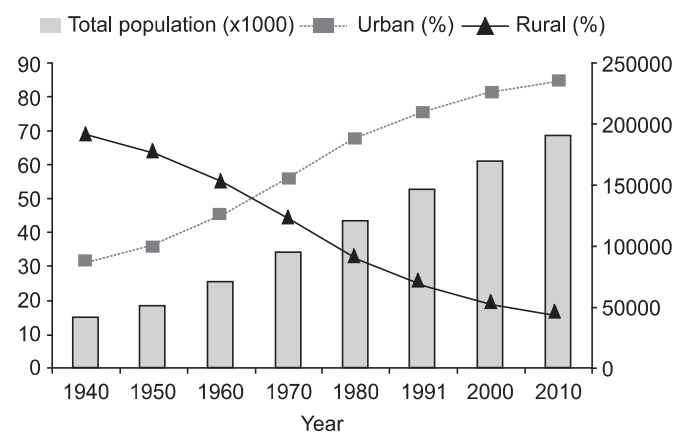


Fig. 1: Brazilian population census from the 1940s and the proportion of population living in urban and rural areas. Right axis (Y) is the absolute number of peoples in the population (x1000) and the left axis (Y) is the proportion (%) in urban/rural zones countrywide. Source: Instituto Brasileiro de Geografia e Estatística (IBGE), Brazil.

east) and unfavourable social conjecture. At the same time there was a significant increase in natural population of the urban areas from the decade of 1960. The last population census in 2010 revealed that the proportion of the population in these areas reached 85% of the total population (Fig. 1).

In the southeast, the States of Minas Gerais, Rio de Janeiro and Espírito Santo, began to show major outbreaks of the disease from the 1980s, away from the old endemic areas of the northeast. In the City of Rio de Janeiro, beginning in late 1970 and extending over the years 1980–90, there were dozens of cases of human VL and hundreds of canine VL in peri-urban and urban areas of the city, during which strong measures were also adopted that managed to control the occurrence of new human cases<sup>25</sup>.

Until 1990, 53,480 cases of VL were reported in Brazil and the northeast region accounted for 90% of them<sup>7</sup>. In 1981, VL epidemics in Teresina, Piauí's state capital, was reported. During a six month period, 1059 cases were diagnosed with an incidence of 190 cases/100,00 inhabitants<sup>26</sup>. There were also outbreaks in São Luís (capital of Maranhão), Belo Horizonte (capital of Minas Gerais), Campo Grande (Mato Grosso do Sul capital) among other large cities<sup>27–29</sup>.

Between 1998 and 2005, information obtained from the National Notifiable Diseases Surveillance System (NNDSS), showed that VL was detected in 34.2% people of Brazilian municipalities with an average fatality rate of 5.5%. The most affected age group was that of the children under 10 yr, with the proportion of 56.7% of total cases, showing that in Brazil, despite the epidemiological changes, it is still a disease typically linked to childhood<sup>19</sup>.

## CONCLUSION

The first evidence of the epidemiology of VL emerged from the analysis of the Chagas<sup>16</sup> expedition to the north and northeast of Brazil in 1936. The fact that they found few cases exclusively in rural areas made them to conclude that it was an endemic disease of low impact and geographically restricted. These findings influenced public health actions for decades halting disease monitoring and control.

The few cases diagnosed *in vivo* country wide from 1934 to 1955 might have resulted from the little interest raised by the disease and because of the unavailability of diagnostic methods at that time. The fact is that the VL was considered a disease of purely academic interest in Brazil during this period, which halted the execution of an adequate response by the health authori-

ties in the same intensity as carried out in the control of yellow fever.

Only two decades after the description of the first case in Brazil and four decades after the first description in South America, VL transmission dynamics was almost completely described by Deane *et al*<sup>13</sup> in 1955. At this point these researchers demonstrated the existence of disease transmission in urban areas and that the main factors for the occurrence of the disease are the population concentration and favourable environmental conditions to “an exuberant proliferation of the transmitter”.

As soon as the Brazilian sanitary authorities realized that VL actually was a public health problem due to high morbidity and severity especially in children, the MoH created a department for disease control in the 1950s. Nevertheless, the program was interrupted in the 1960s, which later resumed its activities in the 1980s, yet with a high degree of discontinuity, even facing the worsening of the epidemiological situation of the country with the emergence of urban epidemics<sup>20</sup>.

From the 1930s, internal migration from rural to urban areas displaced large populations to the newly industrializing cities; a phenomenon due to which the proportion of inhabitants in urban areas exceeded to the country side since the 1960s. This process did not find the necessary urban planning in order to accommodate this magnitude of people. The occupancy of peripheral areas of the cities with high population density and the maintenance of habits linked to rural areas like breeding (chickens and dogs) in backyards were important factors that favoured the establishment of the VL transmission cycle in the urban environment<sup>12</sup>.

The urban epidemics of VL in Brazilian cities were recorded from the beginning of the 1980s. In 1981, the increase in the number of cases in the City of Teresina, Piauí alerted to the problem, that until then was not considered as a priority, taking into account the extinction of control activities in the 1960s<sup>26</sup>. From thereon, the literature referred this process as the VL urbanization in Brazil. Nevertheless urban cases were reported earlier by Deane *et al*<sup>13</sup> in Sobral, Ceará state, who also stated that the disease occurs as a result of favourable conditions, which indeed existed in the majority of Brazilian big cities at that time, and still do.

Negligence of disease control and the health and social problems caused by lack of urbanistic planning for accommodating the immigrant population in urban zones resulted in development of the optimal conditions for the occurrence of high grade disease transmission in several cities country wide. The reports of a rural epidemics in Vale do Rio Doce, Minas Gerais, in the 1970s and a periurban/

urban epidemics in Rio de Janeiro in the decades from 1980 to 2006 reinforce the need for continued efforts in prevention and urban planning to the control of VL<sup>24–25</sup>.

Limitations of this review are primarily related to publication bias; though major databases and libraries were sought, all the literature could not be included, especially those that were in thesis or book formats. However, the systematization of the evolution of the epidemiology of VL in Brazil in phases based on scientific and demographic landmarks appears to be unprecedented work and contributes to the analyses of timeframes when there was a failure in disease control.

The current complexity of the transmission mechanisms of urban VL represent new challenges and require new strategies and approaches for its control. Control programmes should not only consider the biological factors linked to the transmission cycle of the disease, like reservoir and vector control, but also its social interrelations and the impacts in economic development of affected nations. This review proposed this approach through the discussion of the role of faster and unplanned movement of human populations to urban zones<sup>30–31</sup>.

The control of VL in Brazil has no easy solution, current strategies are difficult to implement under existing social and political conditions resulting in progressive increase in the number of cases and territorial expansion of the disease in the last 40 yr<sup>32</sup>. It is clear that intervening solely in disease transmission dynamics is not sufficient to achieve the control objective and that there is need to establish a minimally adequate urban planning in Brazilian cities allied to economic and social development<sup>31, 33</sup>. Undoubtedly, 60 years of negligence in controlling the disease and uncontrolled and poor urban growth make the adoption of these “alternative” measures extremely costly and difficult to implement, considering the social and political impacts involved. However, this will be the price to be paid in order that not only the VL, but also other vector-borne diseases become real medical curiosities in the tropics.

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