Characterization and speculations on the urbanization of visceral leishmaniasis in Brazil

Caracterização e especulações acerca da urbanização da leishmaniose visceral no Brasil

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Abstract

The available hypotheses or explanations for the urbanization of American visceral leishmaniasis are insufficient. An alternative hypothesis is that changes in the ecology and biology of the vector, Lutzomyia longipalpis *, might explain all the new urban epidemiological features of the disease. To tackle the knowledge gaps in this process, certain key research areas need to be prioritized: the role of dogs in expanding transmission in cities, community trials to evaluate new insecticides, and research on the ecological and molecular determinants of* Leishmania chagasi *transmission. Investment of public funds should focus on the development of a human vaccine, since such a vaccine now appears to be within reach. Even small effects from a vaccine could substantially reduce the impact of the disease, which in the last quarter century has challenged and defeated both the scientific community and the public health field around the world.*

Visceral Leishmaniasis; Urbanization; Vaccines

American visceral leishmaniasis was first recognized in 1913 [1]. It was a typically rural disease. Origins of the disease are controversial, but given the genetic identity with *Leishmania infantum* and their ecological identity (since both are transmitted to canids) some authors believe the disease came from the Old World [2]. Due to the fact that the disease is frequently found in fox and opossum in the Americas, other authors believe it originated on the American continent [3]. This controversy has implications for urban visceral leishmaniasis, given that if it were indeed an exotic disease imported to dogs during the colonial period and that secondarily penetrated the wild environment, transmission could be interrupted by controlling the canine enzootic. This idea favors control of the disease by culling dogs. Unfortunately, hope that the disease can be eradicated has waned after three major intervention trials failed to demonstrate any certainty concerning the impact of this strategy on transmission to humans or even to dogs [4,5,6].

The year 1981 witnessed the beginning of urbanization of visceral leishmaniasis in Brazil, in Teresina, capital of the State of Piauí, where 55 cases were reported, far more than the occasional reports of imported cases over the years [7]. In the following year, the urbanization process appeared in São Luís (Maranhão) and Montes Claros (Minas Gerais), later spreading to various other large cities. Before 1980, nearly all the patients were from rural areas or villages with typical

landscapes (foothills, hollows, or river valleys) [8], although some cases of visceral leishmaniasis had already been reported in smaller towns since the 1950s and even in somewhat larger cities like Sobral and Aracati in Ceará State, Jacobina in Bahia, and Santarém in Pará.

In the 1980s, four new and uncommon events occurred. First, transmission of the disease in fully urbanized areas in larger cities. Second, rapid spread in the Northeast and to various cities in the North, Central-West, and Southeast. After the outbreaks in Teresina/Timon (Maranhão) and the island of São Luís (Maranhão) [9], epidemics occurred in the following order in these cities: Natal (Rio Grande do Norte) [10], Belo Horizonte [11] and Montes Claros (Minas Gerais), Corumbá and Campo Grande (Mato Grosso do Sul), Aracaju (Sergipe), Caxias and Imperatriz (Maranhão), Jequié (Bahia), Araçatuba and Bauru (São Paulo), Várzea Grande (Mato Grosso), Palmas (Tocantins), and now Fortaleza (Ceará), Brasilia (Federal District), and Piracicaba (São Paulo), among others [12], all cities with more than one hundred thousand inhabitants, in addition to a myriad of smaller towns. Third, there was a large proportion of urban versus rural cases. The fourth event was the emergence of large-scale urban epidemics with ten-year cycles [13]. These four characteristics in the distribution of visceral leishmaniasis demonstrate that there was a new large-scale epidemiological event under way, since urbanization changed the eco-epidemiological features of the disease and had a significant impact on the distribution of its related morbidity and mortality in Brazil, with significant health and medical consequences. Between 200 and 300 Brazilians now die of visceral leishmaniasis every year.

One of the changes was in case-fatality, as occurred in Araçatuba and Belo Horizonte, since the rate tends to be higher when transmission occurs for the first time, given that visceral leishmaniasis confers lasting immunity (and creates herd immunity). The force of transmission is thus inversely proportional to age. Therefore, when the population is not immune, patients are older on average, and since the disease is more severe in older individuals, the case-fatality rate in recently affected cities is higher. Additionally, since case-fatality in very small children is also high [14,15] when transmission is very intense in cities that have experienced the disease longer, case-fatality can also increase. However, historical mortality series are needed for further clarification of this issue.

At least three cities have conducted studies on the spatial characteristics of visceral leishmaniasis in the urban setting. Research in Jequié did not show either an urban pattern associated with canine visceral leishmaniasis or characteristic clusters of canine infection cases [16]. In Belo Horizonte, cases of human and canine visceral leishmaniasis were clustered, but no typically urban feature was defined [17] except for altitude [18].

In Teresina, cases were clustered on the urban periphery in areas bordering on green forest areas or pastures; the latter appeared as independent risk factors in relation to type of housing, crowding, and socioeconomic status [19]. Houses with more residents located in areas with higher incidence of the disease were also at increased risk [20]. While the type of housing construction and water supply were not related to incidence, lack of sewerage or regular garbage collection were associated with increased incidence. Finally, a multilevel analysis showed that socioeconomic status (poverty) and increased vegetation were associated with higher incidence of the disease in humans and amplified the association with canine infection before and during the human epidemic [21].

This observation of an association with periurban green areas indicates that the urban transmission cycles depend on a relationship with the sylvatic environment. There are two reasons for this dependence: (1) a simple increase in the degree of contact between sources of infection and susceptible individuals mediated by increased exposure to the vector *Lutzomyia longipalpis* on the periurban outskirts and (2) the suggested existence of a sylvatic transmission cycle linked to the urban peripheries through wild mammals, namely *L. chagasi* reservoirs inhabiting the vicinity of urban areas, like fox and opossum. In fact, we recently described the presence of high levels of antibodies against *Lu. longipalpis* saliva in fox specimens from the periphery of Teresina with evidence of natural infection [22].

Thus, the scenario for the dynamics of urban visceral leishmaniasis transmission appears to be that of a sylvatic disease among fox, transmitted on the urban peripheries to dogs, which in turn apparently amplify and transmit it to humans living in marginal areas, under poor socioeconomic conditions with precarious urban services. However, this pattern does not rule out transmission under better socioeconomic conditions in central areas of cities, as occurs in Teresina and Belo Horizonte, or occasionally among humans [7,17].

At any rate, these conclusions are limited by the lack of knowledge with more robust evidence, since not even the role of dogs has been clearly established. On the one hand, while prior or current spatial correlation between canine seroprevalence and the incidence of human visceral leishmaniasis [18,21] may indicate that the human disease depends on canine infection, it may also

merely show that both human and canine infection result from a common source. This would reemphasize the concept of urban dependence on sylvatic transmission cycles of *L. chagasi*.

A socioeconomic approach has dominated the explanation for the urbanization of visceral leishmaniasis. It has been speculated that drought in endemic regions has facilitated epidemics by leading to the emigration of humans and infected dogs to cities, subject to deforestation and degraded living conditions [7]. This is an attractive hypothesis, because it is also supported by the observation that the highest incidence in cities occurs on the urban outskirts and in poor neighborhoods, where most rural migrants concentrate.

However, this explanation failed to stand up over time. For example, visceral leishmaniasis succeeded in entering cities like Araçatuba and Campo Grande that had not undergone rapid and chaotic urban growth and were not surrounded by slums, and where the epidemics were not limited to the periphery. Neither was there an exceptionally intense migratory flow concurrent with the beginning of the epidemic in these cities, as occurred in Teresina and São Luís, where the epidemics were preceded by regional droughts and rapid spread of slums. It its also necessary to explain why cities that experienced a strong migratory flow from endemic rural areas, like Recife (Pernambuco) and Salvador (Bahia), were not hit by epidemics.

Thus, the hypotheses or explanations presented thus far in relation to the urbanization process fail to elucidate the entire phenomenon and are therefore insufficient. New explanations are needed for the urbanization of *Lu. longipalpis* and ease of transmission. For example, changes in the ecology and biology of *Lu. longipalpis* could explain all the urban epidemiological features.

Ecological changes with attractive biological repercussions would be those that explained the invasion of cities by *Lu. longipalpis* and increased the vector's capacity to transmit *L. chagasi*. Sand flies have quite eclectic eating habits, such that they seek to circulate between animal shelters and human dwellings, between the peridomicile and the sylvatic environment. The females are non-autogenous and require blood meals for oviposition and to complete the life cycle [23]. They only require feeding on blood a few times in their lives, and thus, like males, use plant sap and nectar as their main sources of energy and water [24]. The existence of a plant that particularly attracts *Lu. longipalpis* or that somehow provides protection against predators could explain the vector's proliferation in areas where this plant were abun-

dant. In addition, it would have to be found in the urban context, particularly in cities affected by visceral leishmaniasis epidemics. Plant species that could meet these characteristics are the acacias. Importantly, the visceral leishmaniasis epidemic that devastated Sudanese populations in the 1980s and 90s occurred in acacia forests [25], and the species *Acacia podalyriifolia* (Mt. Morgan wattle or Queensland silver wattle) is widespread in Brazilian cities and is recommended by landscapers for urban tree-planting [26].

Together with the vectorial mortality rate, another element that determines changes in vectorial competence is the duration of the extrinsic incubation period. This period includes the time ranging from the vector's infective bite until the arrival of metacyclic promastigotes in the proboscis. Transmission thus depends on the probability of survival until the end of the extrinsic incubation period, which has an exponential repercussion on the number of secondary events in relation to each index case, the so-called basic reproduction number for infection (R_0) [27]. Plant sugars appear to modify the sand flies' success in transmitting *Leishmania* [28]. If, besides providing attractive food or protection for *Lu. longipalpis*, the sap or nectar of acacias or other plants were capable of shortening the extrinsic incubation period of *L. chagasi*, the resulting exponential increase in R_0 would provide an additional explanation for the occurrence of urban epidemics.

Genetic changes in *Lu. longipalpis* populations may have the same impact as ecological alterations. Candidate molecules that present gene polymorphisms with repercussions on *L. chagasi* transmission would be those that influence the protozoan's development in the vector's digestive tract. Lipophosphoglycan (LPG) is a *Leishmania* surface glycoconjugate that participates in adhesion to the intestinal wall [29]. If populations of *Lu. longipalpis* associated with urban epidemics have evolved with polymorphisms in the LPG ligand gene so as to allow rapid and efficient development of *L. chagasi*, the epidemics would be explained. The only flaw is not explaining the spread of *Lu. longipalpis* to areas where it did not exist before. This would require the polymorphism to result in some adaptive advantage.

Unfortunately, measures to control *L. chagasi* transmission have not shown satisfactory results, and programs to cull seroreactive dogs [4,5] and non-controlled trials using modern insecticides have proven ineffective [14]. The only measure that reduced transmission was a trial with DDT 50 years ago in rural areas of Ceará State [30]. This trial at least illustrates that although dog-culling programs have apparently failed, there could be

some hope for visceral leishmaniasis control using insecticides in crisis situations, such as at the beginning of urban epidemics. In addition, evidence is needed to incriminate poor conditions in urban services, and to show that investments to improve basic sanitation could have an impact on distribution of the disease in cities.

Key knowledge is still lacking, and certain research lines need to be prioritized to fill this gap. Research on the role of dogs in amplifying transmission of the disease in cities is particularly pressing. Insecticide trials are important to assess whether new insecticides can have an impact similar to that obtained with DDT. The investigation into ecological or molecular determinants that participate in *L. chagasi* transmission merits specific attention. Efforts with public investments should be made to develop vaccines for humans, since a viable vaccine appears to be within reach, given that few vaccinated individuals become ill when infected [31]. Even modest vaccine results could substantially reduce the impact of this disease, which in the last quarter century has challenged and defeated both the scientific community and the public health field around the world.

Resumo

As hipóteses ou explicações apresentadas até o momento para o processo de urbanização da leishmaniose visceral americana são insatisfatórias. Uma hipótese alternativa é a de que mudanças na ecologia e biologia do vetor, Lutzomyia longipalpis, *poderiam explicar as feições epidemiológicas urbanas da doença. De forma a suprir lacunas no conhecimento sobre esse processo de urbanização, destacam-se algumas linhas de pesquisa prioritárias: a investigação do papel de cães na amplificação da transmissão da doença nas cidades, ensaios de campo com novos inseticidas, investigação dos determinantes ecológicos ou moleculares que participam da transmissão de* Leishmania chagasi. *Esforços com investimentos públicos devem ser feitos para o desenvolvimento de vacinas para humanos, pois uma vacina não parece estar tão distante. Resultados vacinais mesmo modestos podem reduzir substancialmente o impacto dessa doença que, no último quarto de século, desafiou e venceu a ciência e a saúde pública mundo afora.*

Leishmaniose Visceral; Urbanização; Vacinas

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