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Visceral leishmaniasis control in Brazil: time to re-evaluate DDT?

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Summary

Controlling visceral leishmaniasis in Brazil has proven difficult for several reasons, including: 1) limitations in diagnosis and treatment, 2) the failure of the dog culling program, and 3) the short-term residual effect of pyrethroids against the main phlebotomine vector *Lutzomyia longipalpis*. The disease has become more widespread during the last three decades and it now occurs in 21 of the 26 Brazilian states plus the Federal District, and even affects several state capitals and large cities. Although DDT has many environmental drawbacks and possible toxicity to animals, several countries still use this chemical in their public health programs due to its long-lasting effect. Therefore, this study aims to re-evaluate the use of DDT to control zoonotic visceral leishmaniasis.

Keywords

Visceral leishmaniasis; Kala-azar; *Leishmania infantum*; *Lutzomyia longipalpis*; control; DDT; pyrethroids; Brazil

Introduction

Leishmaniasis, a malady caused by several protozoa in the genus *Leishmania*, constitutes the second most important disease caused by protozoa in the world, only second to malaria. Since *Leishmania* was recently found in red kangaroos in Australia (Rose et al., 2004), these protozoa occur in all continents, except Antarctica, and although they are more common in tropical and subtropical areas, there are reports for several European countries (Ready, 2010). Although a role for biting midges on transmission of *Leishmania* in Australia has been suspected (Dougall et al., 2011), their usual

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vectors, the phlebotomine sand flies (Diptera: Psychodidae) that feed from mammals' blood, inject metacyclic promastigotes, which are phagocyted by macrophages, transformed into amastigotes, multiply, then destroy these cells and are phagocyted by other macrophages. If a sand fly ingests amastigotes, they evolve in their digestive tracts, producing infective promastigotes (Fig. 1). Amastigotes can be concentrated in macrophages situated in skin and mucosae, causing potentially deforming lesions, and/or in visceral cells, causing hepatosplenomegaly, fever, anaemia and sometimes death, mostly in undernourished children.

Visceral leishmaniasis (VL) is mostly caused by *L. donovani* Laveran et Mesnil, 1903 in East Africa and in the Indian subcontinent, as an anthroponotic infection, and by *L. infantum* Nicolle, 1908 in Mediterranean area, Central Asia and China and large areas in the American continent, as a zoonotic one, with sylvatic and domestic dogs as main reservoirs (Figure 2). The *Leishmania* causing visceral leishmaniasis in the American continent possibly originated from Spanish and Portuguese settlers although this is still somewhat controversial (Lainson and Rangel, 2005). Lainson and Shaw (2005) presented evidence for an autochthonous disease, present before the migration from Europe, and for the introduction from Europe, proposing the utilization of *L. infantum chagasi* (Cunha and Chagas, 1937) Shaw, 2002 for the parasite in the American continent.

Over the last 30 years zoonotic visceral leishmaniasis (VL or kala-azar) has spread throughout Brazil. Its etiological agent is currently found in 21 out of 26 states, plus the Federal District, and the disease affects medium and large cities, such as Belo Horizonte, Fortaleza, Brasília, Campo Grande, and Teresina (Lacerda, 1994; Silva et al., 2001; MS, 2003; Maia-Elkhoury et al., 2008). Twenty-nine autochthonous seropositive dogs and several imported canine cases were recently reported in Florianópolis, in Santa Catarina, making it the twenty-first state to be affected by the disease (Steindel et al., 2013); it is probable that human cases will soon appear. Recently the main vector, the sand fly *Lutzomyia longipalpis* (Lutz and Neiva, 1912), has been found in nearby Argentinian and Uruguayan provinces (Salomón et al., 2011a, b) and in the Brazilian southernmost states of Rio Grande do Sul (Souza et al., 2009) and Paraná (Santos et al., 2012). Therefore, it is likely that cases will occur in currently unaffected southern areas such as Paraná state and the western part of Santa Catarina state.

A careful review of the literature was carried out on the epidemiology and control of VL and on DDT, using Pubmed and Google Scholar. The key words used were: visceral leishmaniasis, control, insecticides, epidemiology, DDT and/or pyrethroids.

Urbanization and expansion

One of the earliest studies on the epidemiology and control of zoonotic New World VL was by Leonidas Deane, Maria Deane and Joaquim Alencar in the state of Ceará in the 1950s. They found that VL's transmission was more frequent in foothills and valleys compared with the surrounding drier rural areas (Deane and Deane, 1962). However, the disease also occurred in the suburbs of towns in humid river valleys

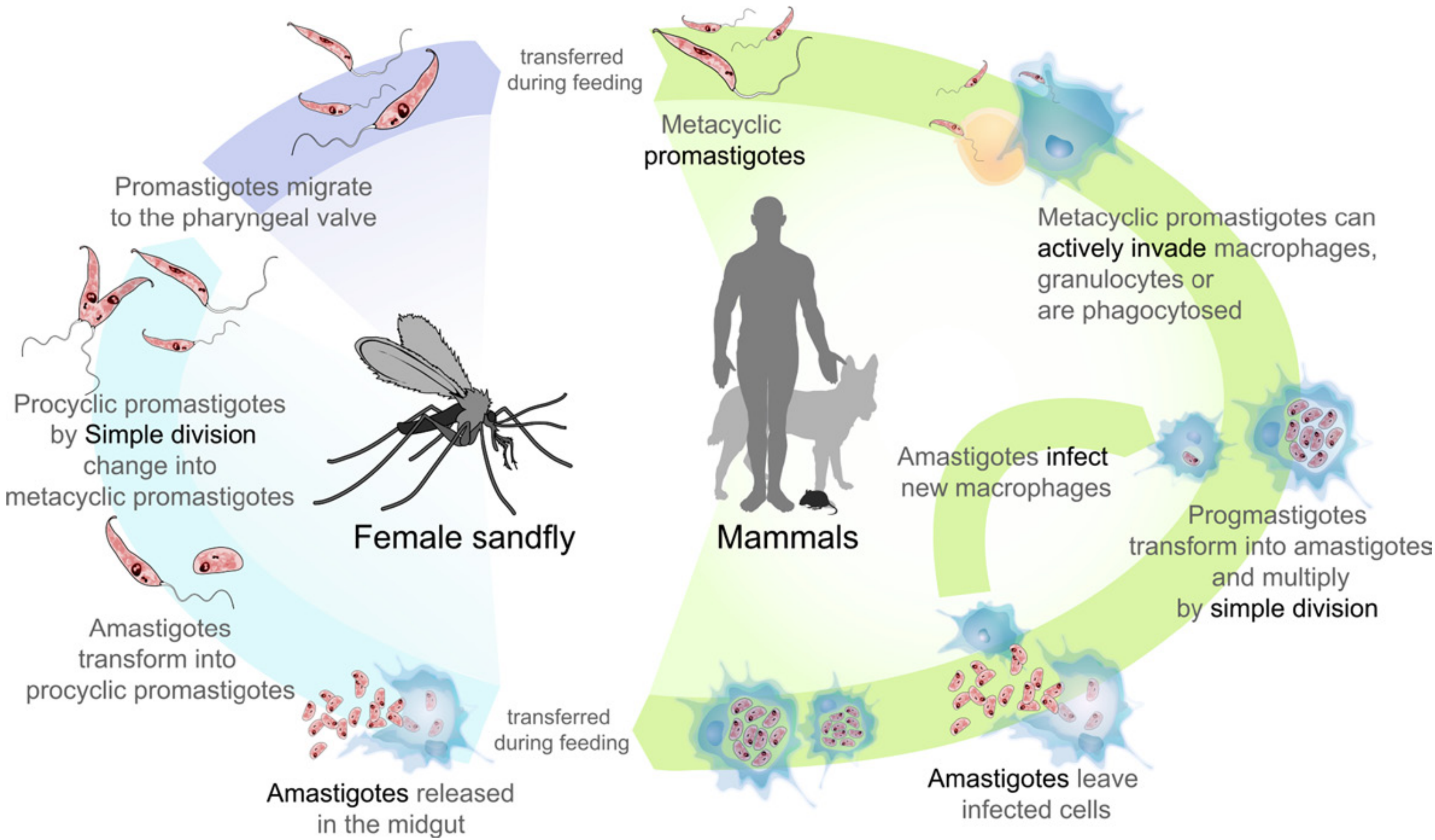

Figure 1. General life cycle of *Leishmania* protozoa. Source: http://upload.wikimedia.org/wikipedia/commons/thumb/e/e0/Leishmaniasis_life_cycle_diagram_en.svg/2000px-Leishmaniasis_life_cycle_diagram_en.svg.png. This figure is published in color in the online version.

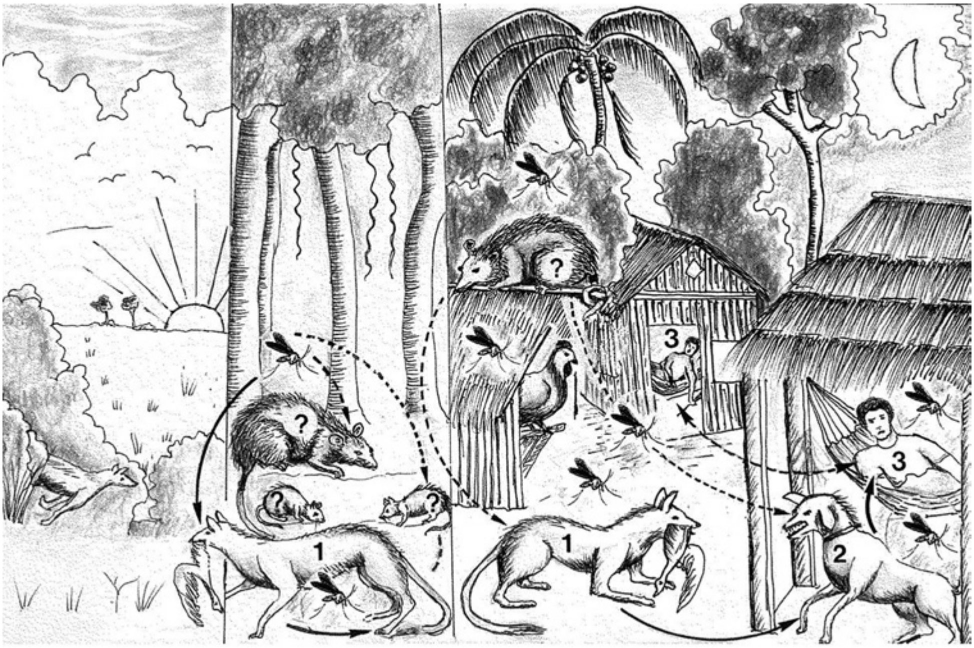

Figure 2. Eco-epidemiology of *Leishmania infantum* in Amazonia: the parasite, originating from a sylvatic source (1) is maintained by silvatic population of *Lutzomyia longipalpis*. Invasion of dwelling places by this sand fly enables the establishment of canine and human infection (2, 3). The domestic dog becomes the major source of infection. Unbroken lines: definite routes of infection; broken lines: possible routes of transmission. Courtesy of Memórias do Instituto Oswald Cruz, from Lainson and Rangel (2005).

(Deane, 1956; Alencar, 1961; Alencar et al., 1962) and cities near the sea (such as João Pessoa) (Guedes et al., 1974).

Although VL's epidemiology is well understood, Brazil has not managed to control this disease efficiently, and its distribution and incidence have increased (Dantas-Torres and Brandão, 2006). From 1984 to 2002, a total of 48,455 human cases were reported in Brazil, 66% of them in four north-eastern states (Bahia, Ceará, Maranhão and Piauí). However, at the end of this period the proportion of cases from these states had decreased while transmission in the southeast and in the Amazon had increased (MS, 2003).

Visceral leishmaniasis is frequently lethal if untreated and kills 200 to 300 people annually in Brazil, and 20,000 to 40,000 worldwide, including *L. donovani* in Indian subcontinent and East Africa (Alvar et al., 2012). It caused more deaths than dengue in 15 Brazilian states from 2001 to 2006 and in five states from 2007 to 2012; nevertheless, dengue attracts more attention from the media and policy makers (Santos et al., 1998). VL is insidious and is difficult to diagnose. Epidemics are decennial, and the disease is especially dangerous to infants, undernourished children, the elderly and HIV-positive individuals.

Lutzomyia longipalpis is the principal vector of *L. infantum chagasi*, although other sand flies, such as *Lu. cruzi* (Mangabeira, 1938) (abbreviated according to Marcondes,

2007) (Santos et al., 1998; Pita-Pereira et al., 2008; Missawa et al., 2011), *Lu. almerioi* Galati and Nunes, 1990 (Savani et al., 2009), *Lu. forattinii* Galati, Rego, Nunes and Teruya, 1985 (Pita-Pereira et al., 2008), *Migonemyia migonei* (França, 1920) (Carvalho et al., 2010), *Nyssomyia neivai* Pinto, 1926 (Dias et al., 2013), and *Ny. neivai* and *Evandromyia sallesi* (Galvão and Coutinho, 1939) (Saraiva et al., 2009) can also be involved in the parasite's transmission. *Lu. longipalpis* is a peculiar species of sand fly, well adapted to both deforested areas and human dwellings (Rangel and Vilela, 2008). Most vector-host contact takes place outdoors in domestic animal shelters, but bites can occur indoors, particularly if insecticides are not used or are used inappropriately. Measles-like dermic reactions caused by multiple bites by *Lu. longipalpis* were noticed in children sleeping in houses, as observed in Santa Rita, state of Paraíba (unpublished observations), during a study on control (Marcondes and Nascimento, 1993). The long-term use of insecticide is essential to provide protection against VL.

Available control strategies for visceral leishmaniasis

The cost-benefit ratio of VL control for north-eastern Brazil was calculated as 1:200 (Akhavan, 1996). In Brazil, the disease has been controlled through the culling of dogs, the treatment of infected human hosts and the spraying of insecticides in houses and peridomiciliary shelters (Deane, 1958). Dog vaccination, protection and treatment, and the use of bednets impregnated with insecticides have also been tested as alternatives for control.

In the Indian subcontinent and East Africa, where humans are the only VL hosts and the agent is *L. donovani*, the treatment of human cases could help disease eradication programs (Bern et al., 2010), such as the program in India and Bangladesh (Chowdhury et al., 2011). However, in areas of zoonotic VL, this strategy is of little help, since most human infections are possibly acquired from other animals (although the vectors can get infected from humans, this host is of lower competence) (Costa et al., 2000). Anthroponotic transmission is of particular concern for patients co-infected with HIV, who are highly infective to sand flies for longer periods of time (Molina et al., 1994).

The strategy of dog culling is beset with difficulties: the low sensitivity and specificity of tests (Courtenay et al., 2002); delays in culling; the refusal to authorize culling and the rapid acquisition of other dogs (Moreira et al., 2004). Culling is controversial and it has only persisted due to the political distortion of scientific data, not because of its efficacy (Costa, 2011). Although 137,143 dogs (seropositive and stray dogs) were killed from 1981 to 1990 (Lacerda, 1994), the increase in VL distribution and incidence during this period indicates that this measure had an arguable effect. Dog culling was shown to be the least efficient measure when compared with the use of insecticide (the most efficient) and canine vaccination (Dye, 1996).

Canine vaccination was first proposed in 1995 (Tesh, 1995; Romero and Bolaert, 2010). Although some vaccines are already on the market, mathematical models indicate that this type of vaccination may not be as effective as human nutrition/vaccination (Dye, 1996). Treating dogs is an ineffective strategy, because relapses are frequent, and although the treated dogs may clinically improve, they can be reinfected by sand flies (*Phlebotomus perniciosus* Newstead, 1911) soon after treatment (Alvar et al., 1994). Furthermore, although treatment with a liposome formulation of meglumine antimoniate reduces the possibility of *Lu. longipalpis* becoming infected, it does not eliminate it (Ribeiro et al., 2008).

The protection of dogs against sand fly bites using pyrethroid-impregnated collars was found to be effective in Italy (Maroli and Khoury, 2004; Vulpiani et al., 2010), especially when the transmission force was high (Maroli and Khoury, 2004). Its advantage over dog culling increases with transmission rate (Maroli et al., 2001; Vulpiani et al., 2010). This strategy would be useful in Brazil if adequate coverage were obtained. However, it would be difficult to protect stray dogs, and, as a public health measure, requires enormous government subsidies and organization (Reithinger et al., 2004).

Deltamethin-impregnated bednets provided good protection against *Lu. longipalpis* for people sleeping on covered beds and even for those who were uncovered but in the same room, in a study on Marajó Island, in Brazil's Pará state (Courtenay et al., 2007). However, in the Argentinean province of Misiones, it was not effective since adults stayed outside in backyards until around midnight during the summer, when *Lu. longipalpis* is active (Santini et al., 2010). Similar difficulties related to hours of activity were reported in the Marajó study (Courtenay et al., 2007). It is vital to obtain information about the hourly activity of VL vectors and human behavior when choosing an adequate protection strategy. For impregnated nets to work as a strategy, the community must actively participate, which is less important for indoor residual spraying (IRS); also, funds need to be available to buy nets and they must be well maintained. A study in Bangladesh reported good compliance and a high reduction of bites when impregnated bednets were used, indicating that this is an important complementary measure for sand fly control (Mondal et al., 2010). Bednets also significantly reduced indoor sand fly populations in India and Nepal (Picado et al., 2010).

Sand flies are so small that their biting activity is not usually influenced by non-impregnated bednets; however, such bednets do reduce the biting rate of *Ph. argentipes* Annandale and Brunetti, 1908 and the Human Blood Index by 85% and 42.2%, respectively (Picado et al., 2009). No information is available for *Lu. longipalpis*, although one study suggested that non-impregnated bednets reduced their landing rate (Courtenay et al., 2007).

Indoor residual spraying of insecticides

Although several control measures, such as dog collars, canine vaccination, impregnated bednets and even the use of biological enemies of sand flies should be evaluated, Indoor Residual Spraying (IRS) continues to be an essential part of VL control (WHO, 2010). However, the efficacy of IRS, including its cost and period of protection, needs to be taken into account.

Protecting human houses and annexes (henhouses, pigsties, stables etc.) with long-lasting insecticides should be the priority for VL control. IRS was better at controlling

Ph. argentipes when compared with deltamethrin-impregnated bednets and plastering of walls (evaluated through the use of light traps) (Das et al., 2010).

Two vectors of *L. peruviana* Velez, 1913 were controlled by IRS using λ-cyhalothrin in the Peruvian Andes (Davies et al., 2000). The sand fly populations (mainly *Ny. intermedia* and *Mg. migonei*) decreased for several months in houses that were a focus of dermal leishmaniasis in the Brazilian state of Espírito Santo after they were sprayed with deltamethrin, and all of the *Ny. intermedia* were killed when forced to come into contact with treated surfaces (Falcão et al., 1991). The Brazilian Ministry of Health has decided to use pyrethroids that remain active for three months to control *Lu. longipalpis* (MS, 2003).

However, several studies found no difference in sand fly capture between treated and untreated surfaces in houses sprayed with deltamethrin (Santini et al., 2010; Marcondes and Nascimento, 1993), cypermethrin (Barata et al., 2011a) or λ-cyhalothrin (Sillans et al., 1998; Feliciangeli et al., 2005), after seven days and also after three months. Barata et al. (2011b) observed variable and non-significant effect of cypermethrin spraying on populations of *Lu. longipalpis*, but no control group was utilized.

In Bolivia, deltamethrin significantly controlled *Lu. longipalpis*, but not *Lu. nuneztovari anglesi* Le Pont and Desjeux, 1984 (which is a more sylvatic sand fly) for a nine-month period (Le Pont et al., 1991), a result that differs from other studies. F Le Pont (2011- pers. commun.) believed that the results of this Bolivian study were not remarkable ("pas brilliant") and stated that *Lu. longipalpis* is a difficult species to control through insecticides, when compared to more anthropophilic and endophilic species, such as *Anopheles gambiae* Gilles, 1902. Failures to control *Lu. longipalpis* have been reported (Costa, 2008).

Results about insecticide efficiency must be analyzed in terms of seasonal fluctuations of populations, comparing treated houses to a control group with the same characteristics (quantity of potentially infective bites, condition and time period). Comparing quantities collected in different years (Barata et al., 2011a) or seasons (Barata et al., 2011b) could be misleading, due to possible annual and seasonal differences, as was reported for *Ny. umbratilis* in Pernambuco state (Balbino et al., 2005). Although light traps are useful for sand fly collection, the ideal method is to compare quantities of sand flies trying to bite (adequately protected) humans in randomly distributed groups of houses with and without the use of insecticide.

Pyrethroids, which have a long-lasting activity at low doses for triatomine bugs (Marcondes, 1989; Marcondes and Pinto, 1989), were also efficient in controlling bedbugs (Moore and Miller, 2006) and mosquitoes, but resistance has also been reported (Hemingway and Ranson, 2000; Vassena et al., 2000; Rodriguez et al., 2007).

Due to limitations of IRS, mostly related to the need for smooth surfaces and repeated spraying, a durable lining (Zero Vector® Durable Lining) impregnated with deltamethrin is being tested for malaria control in Angola and Nigeria (Messenger et al., 2012), with promising results. When this plastic lining was compared with Oliset lasting nets (LN) in experimental huts (Chandre et al., 2010), the bednets were found to be significantly better. It has not yet been tested for sand fly control. However, its low acceptance in urban areas (Messenger et al., 2012) and its high cost could preclude it from being used in Brazil. This lining, as well as other methods tested for malaria control (Raghavendra et al., 2011), should be tested for VL control, but differences in the biology of vectors, house conditions and human populations must be taken into consideration.

DDT in vector-transmitted diseases

After the discovery of DDT's long-lasting insecticide effect during the Second World War, it was widely used to control several pest insects. It reduced the annual incidence of malaria in India in the 1960s, from 75 million to 100,000 (a 99.8% reduction) (Sharma, 2003). In Sri Lanka, cases fell from 2.7 million to 17 cases in 1963, but increased to 500,000 by 1969, with downgrading of priority of control and emergence of resistance (Curtis, 2002). No VL cases were registered in India during the application of DDT (Sanyal et al., 1979; Mukhopadhyay et al., 1996), probably because *Ph. argentipes* is very endophilic. However, when DDT spraying was reduced, this vector repopulated the country and VL re-emerged. When DDT was suspended, there was a resurgence of malaria (Curtis, 2002). DDT has been routinely utilized in malaria control campaigns in India (Sanyal et al., 1979; Mukhopadhyay et al., 1996). Corradetti (1949) observed a great reduction on quantities of *Ph. perfiliewi* Parrot, 1930 biting in houses at Abruzzo, Italy, but many insects continued to bite in the open, and in one occasion they entered in a treated house, but died soon after contacting the walls. The transmission of oriental sore was entirely interrupted in the treated zone (Corradetti 1952).

It was thought that some populations of malaria vectors became resistant because after houses were sprayed they started biting cattle (probably due to the presence of DDT in house walls); however, even taking this resistance into account, DDT spraying continued (Curtis, 2002).

Since *Lu. longipalpis* is not a strictly endophilic sand fly (Lainson and Rangel, 2005), resistance could be a consequence of DDT utilization for other purposes, but this is not likely to happen in Brazil, due to the prohibition of use of DDT. Even though insecticides may fail to control VL, the prevention of sand fly bites in houses is probably effective for disease control, except when extra domiciliary exposure is usual, as in Marajó Island (Courtenay et al., 2002) and northeastern Argentina (Santini et al., 2010). Resistance to DDT was reported for *Sergentomyia shortii* Adler and Theodor, 1927, and *Ph. argentipes* in India (Kaul et al., 1994; Kishore et al., 2006), and *Ph. papatasi* (Scopoli, 1786) in Iran (Rashti et al., 1992).

In Brazil, DDT reduced populations of sand flies and incidence of cutaneous leishmaniasis (Nery-Guimarães and Bustamante 1954) and was utilized until 1964, with good results. The usage of DDT was resumed in 1980, in response to an increase of VL incidence in urban areas (Monteiro et al., 1994), but was progressively replaced by pyrethroids from 1989 to 1992, when its application was discontinued (Alexander and Maroli, 2000). In the East of the State of Minas Gerais, the incidence of VL was greatly reduced by many years after utilization of DDT together with the elimination of seropositive dogs (Magalhães et al., 1980), but the effect of each measure separately was not evaluated.

Alencar (1963) compared the incidence human VL in 14 municipalities in the State of Ceará that underwent DDT spraying and dog culling with that in other 14 municipalities in which the only measure was dog culling, during 10 years; both groups included municipalities of all regions of the Ceará. DDT was utilized in the municipalities with higher VL prevalence, and the reduction was much higher in them (67.7% in periods of four years and 83.1% in those of two years) than in those not receiving DDT (respectively 25.4% and 45.6%). Alencar (1961) cited the efficacy of DDT spraying in the reduction of VL incidence and emphasized the need of spraying in the rainy season to get better results.

Data from early control measures showed that the application of DDT reduced populations of *Lu. longipalpis* for several months (Costa et al., 1990) and lowered the VL transmission rate in municipalities with a higher incidence, while dog culling was inefficient (Deane, 1956). Additionally, the number of human cases fell during a VL epidemic in the Brazilian state of Piauí (Costa et al., 1990) in municipalities that widely used DDT.

The susceptibility to organophosphates and pyrethroids of two Brazilian *Lu. longipalpis* populations was tested. It was concluded that the two populations differed in terms of detoxification (Alexander et al., 2009).

Restrictions for DDT use

Due to concern over the high quantities of DDT that were used in agriculture, its high persistence in the environment and accumulation in the food chain (Carson, 1962), this chemical was banned for several of its uses, initially by developed countries and then by most countries, and a total ban has been proposed (Attaran et al., 2000). DDT's use in agriculture, mainly in cotton and rice cultures, which was associated with the increased use of insecticide during the "green revolution", probably caused resistance in some vectors (*Anopheles sacharovi* Favre, 1903, *A. albimanus* Wiedemann, 1820, and *Simulium damnosum* Theobald, 1903) (Mouchet, 1998). Its discontinued use was certainly helpful in preventing this resistance. DDT continued to be used in sub-Saharan Africa and some Southeast Asian countries due to the serious malaria problem in these places (WHO, 2011).

The Stockholm Convention proposed the elimination of 12 chemicals or classes of chemicals, including DDT (Curtis, 2002), so production of this insecticide is now highly restricted. In India, 20% of the total of 5,000 metric tons used for vector control in 2005 was used for VL control. By 2007, the use of DDT in India had fallen by a quarter, to 3,750 metric tons (Van den Berg, 2009). Brazil banned DDT use and storage in 2009. The executive power was given a two-year deadline to assess the environmental and sanitary impact of this ban on malaria control in the Amazonian part of Brazil (http://www.jusbrasil.com.br/legislacao/231528/lei-11936-09 [accessed 11 June 2012]).

DDT tends to accumulate in the soil and is absorbed by plants and animals, even when used for indoor residual spraying against cutaneous leishmaniasis and malaria (Vieira et al., 2001; Van Dyk et al., 2010). One study found that although its concentration in the soil was low, it was twice the FAO limit in chicken eggs, seven years after spraying (Vieira et al., 2001). Contamination in parts of India where this insecticide had not been used was attributed to the fact that DDT destined for IRS was illegally diverted to agricultural use (Curtis, 2002), a practice that needs to be stamped out.

A small proportion of DDT sprayed on walls will certainly pollute soil and water. However, the pollution caused by spraying one house (2 g/m^2, 0.5 kg/house) is approximately 0.04% of the amount caused by spraying a 100-hectare cotton field, which receives 1,100 kg in four weeks (Attaran et al., 2000). The possibility of soil contamination from indoor application was considered negligible (Curtis and Lines, 2000), and DDT's degradation in the soil of a Sudanese tropical cotton field was very fast (El-Zorgani, 1976).

Although the association between DDT and cancer has been extensively studied, no definite association has been found (Safe, 1997), except in some malaria workers who were highly exposed to this insecticide (Cocco et al., 1997), but no data existed on individual exposure levels, so a thorough analysis was not possible (Safe, 1997). The carcinogenicity of DDT was based on a higher serum concentration of the DDT derivative, DDE, in patients dying of cancer when compared with healthy controls; however, this was attributed to the release of DDE from body fat in emaciated patients (Sharma and Singh, 2008). DDE has not been confirmed as an etiologic agent for breast cancer, and high exposure to dietary bioflavonoids should be taken into account (Safe, 1997); a recent meta-analysis of 68 studies indicated no association between exposition to DDT/DDE and breast cancer (Ingber et al., 2013).

DDT's influence on hormonal and reproductive physiology has also been suspected and investigated, but no causal links have been observed (Rogan and Shen, 2005). While a study in Mexico found a reduced sperm count in those exposed to DDT (Ayotte et al., 2001), a similar study in South Africa found no significant difference (Dalvie et al., 2004a, 2004b). Reduction in sperm mobility and insufficient sperm chromatin condensation was associated with non-occupational chronic exposure to DDT in Mexico (De Jager et al., 2006) and these and other effects on sperm were noticed in male patients in South Africa (Aneck-Hahn et al., 2007). The decline in sperm counts in European men, which was attributed to DDT contamination, continued even after DDT usage had decreased, and it was difficult to separate the effect of DDT from other pollutants (Sharpe, 2010). Therefore, chronic exposure to DDT is not definitely associated with damage to health and needs to be more thoroughly studied.

Acute DDT poisoning has been associated with several neurological symptoms. People who consumed fish from the Great Lakes in the United States had higher blood concentrations of DDE than those who did not consume fish, but the impairment of cognitive functions was not significantly associated with DDE blood levels in a study in South Africa (Dalvie et al., 2004). Several studies have shown different effects on growth, the lactation period, damage to blood cells and other effects in humans (Curtis and Lines, 2000; Rogan and Chen, 2005).

Debate over DDT use for malaria control tends to be divided into three viewpoints: those who are anti-DDT, those who have moderate views and those who are pro-DDT (Bowman et al., 2011). Its usefulness for controlling malaria is recognized, but the benefit in reducing mortality needs to be balanced against the risks to human health and environmental pollution (Rogan and Chen, 2005). However, until a better alternative becomes available, DDT is considered the best option (Rogan and Chen, 2005). Other alternatives for control, such as "Zero Vector® Durable Lining" (which has been successfully tested for malaria control) are probably more expensive. Since many countries have tried to eliminate the use of DDT, most factories are now closed, except for one in India, so there would be some difficulty to test and reintroduce DDT. If the decision is taken to utilize this insecticide, production will need to be stimulated.

Visceral leishmaniasis: why not DDT?

Controlling VL through the use of traditional prophylaxis (treatment of human patients, killing of infected dogs and IRS) has proven difficult, and the replacement of DDT by pyrethroids has probably contributed to increased transmission and failure to control it. Therefore, DDT should be carefully re-examined as an alternative for control. Although DDT has certain limitations (its effect on the environment and suspected toxicity to humans), it does not necessarily need to be thrown into the "garbage can of history", and may prove useful for VL control in Brazil.

Complete information for each region must be compiled to establish which season and year is most dangerous for infection of humans and dogs in order to utilize insecticides efficiently. For example, in French Guiana transmission by *L. guyanensis* Floch, 1954 occurs during several months of the year, but mainly during the first half of November, between two rainy seasons (Le Pont, 1982). The utilization of an insecticide with long-lasting effect on sand flies reduces the need for detailed knowledge about seasonal fluctuation.

Bacillus thuringiensis var. *israelensis* De Barjac, 1978 (B.t.i.) would be potentially useful for the control of *Lu. longipalpis*, due to its toxicity for immature forms of this species (Wermelinger et al., 2000) and of other species (Yuval and Warburg, 1989). However, the knowledge on breeding places of these insects, which are very scattered, is still incipient. As a matter of fact, the analysis of 1,523 soil samples in the Brazilian state of Bahia produced 64 sand flies, of which 40 were *Lu. longipalpis* (Sangiorgi et al., 2012). Several additional operational limitations have jeopardized the utilization of these bacteria for the control of sand flies (Amóra et al, 2009).

Other alternatives for VL control in Brazil should be analyzed. Although studies on pheromones, courtship behavior and the taxonomy of *Lu. longipalpis* species complex are promising, these methods still have a long way to go before they can be used for VL control. While more definitive solutions for the control of VL are obtained, some efficient and urgent measure needs to be taken to save lives (Dantas-Torres and Marcondes, 2008).

A proposal for using DDT in the control of visceral leishmaniasis in Brazil

Outcomes such as human incidence of VL, the density and natural infection of *Lu. longipalpis* in and around houses and serum positivity among humans and dogs should also be assessed. *Lu. longipalpis* can bite chickens and dogs, both of which play a role in VL epidemiology; the former as a feeding source and the latter also as a reservoir (Alexander and Maroli, 2002; Lainson and Rangel, 2005). The epidemiological role of chickens is complex and needs further investigation, to decide whether spraying their shelters is actually useful (Alexander and Maroli, 2002). Contamination of soil and water should be controlled by not spraying surfaces that are excessively exposed to rain and wind, such as external surfaces of henhouses and kennels. Since the efficiency of IRS may be influenced by several operational shortcomings, as reported in Indian and Nepalese control programs using DDT or λ-cyhalothrin (Chowdhury et al., 2011), these should be carefully analyzed and addressed.

Workers who apply DDT (as with any other insecticide) must be adequately trained and protected. They must be taught how to avoid contaminating rivers and other bodies of water when they wash their spray pumps. The population, food and domestic animals must also be protected from contamination.

Probably because the task of VL control has been decentralized, staff are hired for short periods and then dismissed at the end of "transmission season" in several Brazilian cities, a policy that hampers efficient control of visceral leishmaniasis and other diseases. Such studies should be complemented by a long-term analysis of the contamination of soil, water, plants and animals by DDT and its products (DDD and DDE). Insecticide should be manipulated with extreme caution, not only in tests, but also during routine use, to protect workers, food and domestic animals. Rigorous supervision will probably prevent the illegal diversion of DDT for agriculture or personal utilization, possibly a result of the low wages paid to sprayers (Curtis and Lines, 2000). The degradation of DDT in soil through aerobic-anaerobic associations (Corona-Cruz et al., 1999) should also be evaluated.

In conclusion, carefully designed evaluations of DDT's efficacy compared with other insecticides and dog culling should be urgently funded and developed.

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