Vectors Control Importance on Leishmaniasis Transmission

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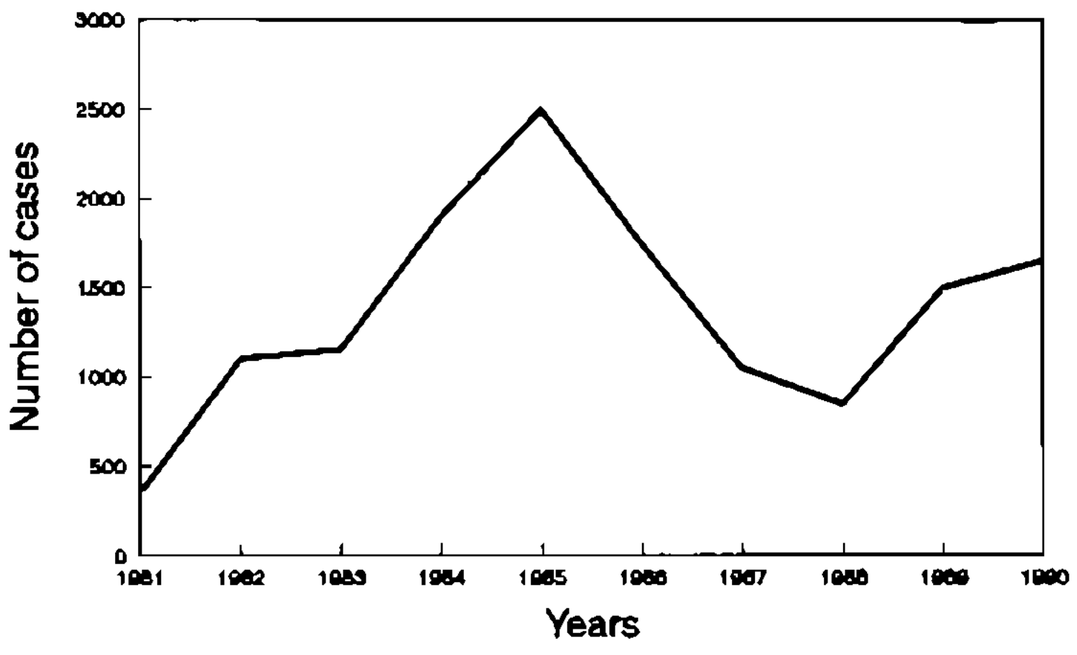
We reviewed the control of transmission of leishmaniasis regarding chemotherapy, reservoirs elimination, vaccination and insect control through the use of chemical insecticides. We also discussed complementary measures like monitoring traps, impregnated bednets and curtains, repelents, pheromones, biological control, etc. A cost comparison of insecticide interventions through the use of products belonging to the four main chemical groups was also done, comparing together conventional formulations versus a slow-release insecticide developed by the Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro. We finally did recommendations on the situation that would justify an insecticide intervention to control sandflies.

Key words: leishmaniasis - sandflies - vector control - insecticides and formulations - entomological evaluation techniques

In Brazil, and in most countries where it is endemic, the control of transmission of leishmaniasis relied mostly on the elimination of infected hosts, mainly dogs, and in chemotherapy through the identification and treatment of infected people. This is true almost only for American visceral leishmaniasis (AVL) to which the Brazilian Ministry of Health has been giving more attention. Cutaneous and muco-cutaneous forms have only been treated by chemotherapy of diagnosed human cases.

Data reported by the Brazilian National Health Foundation (FNS 1993) show an average of 1000 new cases of AVL each year, during the past ten years. However, since 1988 this number is progressively increasing to show 1500 new cases in 1990, the last year for which FNS has the complete set of data (Fig.). If we consider people who have not yet search for assistance or assimptomatics, these numbers will certainly grow. Kala-azar has also spread to larger areas in Brazil showing what is being called the urbanization of this disease. By now, a real bad situation can be exemplified by Terezina, State of Piauí, where active transmission of AVL can be found everywhere, independing of socio-economic conditions of the population, and where some fatal cases have already been registered. This picture indicates that we are loosing control of the situation and much more attention should be given to this disease. Stronger measures are necessary to help the control of transmission. The common or under development tools employed are chemotherapy, vaccination, reservoir and insect control, including the use of insecticides and complementary measures like monitoring traps, bednets and curtains, repelents, pheromones, biological control, insect growth regulators (IGRs), etc.



Number of cases of human kala-azar registered in Brazil between 1981 and 1990 (FNS 1993).

Observing the present situation of chemotherapy we must look to the past to see that not much progress has been achieved since sodium antimonyl gluconate started to be used in the treatment of Kala-azar in China, 50 years ago. According to Croft and Neal (1989) the drugs used nowadays are still the pentavalent antimonial derivatives of "Solubstibosan" - the sodium stibogluconate "Pentostan" (Wellcome) and meglumine antimoniate "Glucantime" (Rhonepoulenc). New alternatives such as the pyrazolopyrimidines allopurinol and allopurinol riboside,

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the antifungal imidazole ketoconazole and the 4-methyl-8-aminoquinoline WR602 have been or still are under study. However, it is not expected that pharmaceutical companies will support the high cost of development of a new drug due to the limited market. This mean that in the near future the continuation of use the antimonials, even with the toxicity problems and limited efficacy, is likely to occur.

Regarding vaccination, it is known that leishmaniasis infections give life-long protection against new infections, what is a strong demonstration that a vaccine is possible. However besides all studies performed and progress achieved, a safe and efficient product that can be recommended for human mass protection is not available (Liew 1989). Field trials of a dog vaccine are presently being performed in Brazil, which gives hope of imunization of these reservoir hosts instead of their elimination.

Any strategy for leishmaniasis control is likely to include mammal reservoirs control. In spite of poorly documented and rigorous evaluation of consequences for humans of operations directed solely to the elimination of infected dogs, this method seems to be effective in certain circumstances (Ashford 1989). Recently Badaró et al. (1994) reported a new method for the fast diagnosis of AVL (Dipstick) that takes only 30 seconds. This method when applied to dogs could make the elimination of hosts much more effective, avoiding the period of time necessary for processing the diagnostic in the laboratory and coming back to the same place. A dog vaccine, still under development, would be wellcome to avoid all the constraints generated by the elimination of pets or valuable animals. It is also worthwhile to think about the use of systemic insecticides in dogs that would eliminate biting sandflies, avoiding transmission to man and other animals, even if not protecting the treated dog itself.

The lack of well designed and performed field assays against flebotomine sandflies is still one of the main constraints in the evaluation of vector control actions in the transmission of leishmaniasis. In general there are only assumptions in this respect referring to the consequences of malaria control programmes and, furthermore, referring only to insect density and not on the impact on clinical disease.

Eggs, larvae and pupae of sandflies have rarely been found in nature turning the biology of these insects in natural conditions poorly understood. Studies performed in India by Smith et al. in 1936, in Panama by Hansen in 1961, in Sudan by Quate in 1964 and again in India (Dhiman et al. 1983) collecting soil samples indoors or outdoors, allowed the identification of some preimaginal stages. Even the use of emergence traps in a more recent study done by Bettini in Italy (Killick-Kendrick 1989) resulted in little help when referring to the possibility of using antilarval measures. According to Dhiman et al. (1983) *Phlebotomus papatasi, P.argentipes* and *Sergentomyia babu* lay their eggs preferentially in the loose soil close to the floor surface in the corners inside the houses, but can also be found in cattle sheds. In these conditions it seems that it would probably be worthwhile treating the soil near the walls with a control agent even though it is the same residual insecticide being used for adult control, probably rendering the treatment more effective not allowing adults to come up from young stages.

Referring to biological control through the use of entomopathogens, from which *Bacillus thuringiensis israelensis* (B.t.i.) and *B. sphaericus* are already known, and *Clostridium bifermentans malaysia* and *B. t. medellin* are other promising bacterial species under study, there is at present no hope of use. The last report on this matter from WHO (1993) does not even mention the possibility of use of these tools for sandflies control. However it is a matter of fact that sandfly larvae are susceptible to B.t.i. The problem remain in putting both, bacteria and larvae, in close contact in real natural conditions in a cost-effective manner, due to the poor present knowledge of young stages of sandflies in nature. The same situation is appliable to the IGRs, including juvenile hormones, precocenes and chitin inhibitors.

An alternative approach to the control of transmission of leishmaniasis is the use of bednets or curtains, to avoid sandflies biting. This has been an important approach for malaria control all over the world (Rozendaal 1989). However as sandflies are tiny insects, those nets and curtains should have a too fine mesh, which would result in discomfort due to poor air circulation. Itoh et al. (1986) has developed and tested a wide mesh treated with insecticides, that could avoid most of bites by mosquitoes transmitting malaria. Maroli and Lane (1989) and our group (Oliveira Filho et al. 1994) performed preliminary studies on the effects of permethrin impregnated large mesh nets respectively on *Phlebotomus and Lutzomyia*, showing significant results that can recommend this technique as a complementary approach to other measures of insect control.

Insect repelents are only palliatives mostly used by persons on their skin when entering an endemic area to stay a few days. To prolong their usually short duration they should be formulated in an oil base. The most common active ingredient is DEET (n-Diethyl-m-toluamide) but there are some others, including synthetic

pyrethroids in low concentrations, used for the impregnation of clothes.

Some kinds of monitoring traps are already in use, like CDC light traps, and those based on it, animal baited traps and sticky traps. Nowadays pheromone traps are under study but they are not yet available (Ward et al. 1990).

As phlebotomines young stages cannot yet be cost-effectivelly controlled in practice, the few papers published refers to adults control and some of them deal with insecticide resistance mainly to DDT in areas generally treated for malaria control.

The first report on the use of insecticides against sandflies in Brazil was done by Nery-Guimarães and Bustamante (1954) in a focus of ACL in the State of Rio de Janeiro. Five years after periodic domiciliary spraying with DDT they noticed a decrease in both the sandfly population and disease incidence. Seyedi-Rashti and Nadim (1975) reported the re-establishment of cutaneous leishmaniasis in some areas of Iran after the cessation of DDT spraying for the control of vectors of malaria.

In an attempt to reduce transmission of *Leishmania braziliensis guyanensis* in a periurban rainforest, Ready et al. (1985) sprayed the lower part of trees with DDT. They reported, 11 months after, that these places were no longer occupied by *Lu. umbratilis*. In Bolivia Le Pont et al. (1989) reported the control of *Lu. longipalpis* from dwellings and chicken houses until nine and ten months, respectively, after one deltamethrin treatment.

Falcão et al. (1991) studied the effect of deltamethrin in the sandfly population (mainly *Lu. intermedia* and *Lu. migonei*) of an area of State of Espírito Santo in Brazil. Application of 25mg a.i./m^2 of a 5% flowable formulation, on the internal and external walls, roofs and buildings plus the trees within 10m from the houses promoted a reduction in the number of sandflies captured inside houses, but not in the peridomicilium, during a period of 12 months.

More recently Rashti et al. (1992) showed increased tolerance, or maybe resistance, of *Ph. papatasi* to DDT in Iran, even in areas where the application of this insecticide has been discontinued for more than 15 years. This is not the first time resistance has been reported on this part of the world, with many references already been made in India.

In an informal report Silans (1991) showed through the bioassay of treated house walls, exposing *Lu. longipalpis* at intervals until six months post-treatment, the comparative results of the residual effect of DDT, deltamethrin and cypermethrin. The only one that kept residual effect enought to kill 100% of the sandflies after six months over mud surfaces was DDT, applied as wettable powder at 2g a.i./m^2. Deltamethrin 5% FW sprayed at 25mg a.i./m^2 and cypermethrin 20% WP sprayed at 125mg a.i./m^2 didn't achieve this performance.

The last Technical Report released by WHO (1990) on the control of leishmaniasis, reported data collected on insecticides, formulations and doses, probably derived from the literature and practice on the control of other insect vectors (Table). If not precise these data can help us to make the assessment of part of the products that could be used nowadays and at which cost/ratio when compared with the commonly used DDT. We added to this Table the results obtained with the Slow Release Emulsifiable Suspension (SRES) formulation developed in the NPPN-UFRJ when used against triatomines. We also compared cost of operations, based on the real costs determined during the campaigns against Chagas'disease vectors in Brazil (Oliveira Filho 1989). DDT is still one of the most cost/efficient products in use, being cheaper than the representatives of organophosphorus, carbamates and pyrethroids. The only exception was for the organophosphorus malathion or fenitrothion when formulated in the slow-release formulation PVA based, developed in our laboratories, which gave an estimated cost ratio of 0.9, becoming cheaper than DDT, due to its long residual effect (Oliveira Filho 1988, Oliveira Filho & Melo 1994a). Deltamethrin would be the third product of choice, however WHO data assume six months residual effect for deltamethrin over mud, what it is not in accordance with most of data available (Silans 1991).

Anyway, as there are no conventional formulation that can resist in non-protected peridomicilium, the advantage of the SRES in obvious because its film coating of the surfaces assure its presence for longer than anyother. This will certainly save operational work and with the same spraymen larger areas will be allowed to be treated, turning this kind of treatment even more attractive. This have to be proven in real field situation, comparing concomitantly other candidate products. By now a field trial is aproved and will be supported by WHO/TDR in India, in collaboration with the Rajendra Memorial Institute of Medical Sciences-Patna (India). Another field assay is being planned, together with FNS, PAHO and WHO/TDR, to happen in northeastern Brazil. In recent laboratory experiments Oliveira Filho and Melo (1994b in press) showed that the dose of this slow-release formulation and also of some other insecticides in conventional formulations can still be reduced when compared with those recommended for the control of other vectors like those of Chagas'disease and malaria.

TABLE

Cost comparison of insecticide interventions of various products and formulations in the recommended doses (Oliveira Filho 1989, WHO 1990)

Inseticide and formulation[a]	Dosage (ga. i./m^2	Residual effect on mud (months)	Approx cost/ tonne (US$)[b]	Insectic. cost ratio (DDT=1)	Cost/ house 18 months + insectic operat. (US$)[c]	Insect.+ operat. cost. ratio (DDT=1)[d]
DDT 75% WP	2.0	6	3,000	1.0	42.0	1.0
Melathion 50% WP	2.0	3	2,100	2.1	84.6	2..0
Fenitrotion 50% WP	2.0	3	7,500	7.5	117.0	2.8
Propoxur (20%EC)	2.0	3	9,300	23.2	211.5	5.0
Deltamethrin (2.5%WP)	0.025	6	25,000	3.1	54.7	1.3
Permethrin (25%WP)	0.125	3	30,000	3.7	94.3	2.2
Melathion or Fenitrotion (10% SRES)	2..0	18	5,400[d]	13.5	39.0	0.9

[a]: WP: wettable powder; EC: emulsifiable concentrate; SRES: slow-release emulsifiable suspension (NPPN).
[b]: international prices reported by WHO, not including freight.
[c]: cost of a visit US$ 12,00/house (250m^2 estimated treated area/house).
[d]: Brazilian price (Ilharabrás, Sorocaba, SP).

Of course even if an insecticide is very effective against sandflies this do not mean that it should be applied in every situation. During the two last meetings on leishmaniasis that happened in Brazil (Natal 1991 and Recife 1993) the discussions among the experts lead to some general recommendations to help decision making. In short terms that would be the presence of autoctonous human cases of AVL and of *Lu. longipalpis* in the same area, the only situation that would justify an insecticide intervention, together with the other tradicional measures. The application should be residual, covering walls and roof surfaces inside the houses, the eaves outside, all the peridomiciliary structures and tree trunks that often harbour domestic animals like chickens.

The methods of evaluation should be standardized. To assess the effect of control measures on sandfly populations many standard sampling methods can be used to measure population densities. Of course all of them refer to adult population due to the strong difficulties found in the capture of young stages in nature. According to the World Health Organization (WHO 1990) the mostly used are:

Man-landing rates - Expressed as number of sandflies/person/hour, where collectors working in pairs sucks into glasstubes the adults coming to bite each other. Catches are made at night in previously set dates, in the same sites, during the same period of time. The collectors, preferentially selected among local population, should have had a previous infection and already recovered from it, to avoid the risk of becoming infected.

Light traps - Expressed as number of sandflies/trap/night, where CDC light traps are fixed at previously decided places and left running from before nightfall untill just after dawn. Catches can be greatly affected by the species. They differ in their response to light, and the place where the traps are installed, accordingly to the endophilic or exophilic behaviour. Protected places (houses, chicken houses, stables, etc.) are preferred for being less affected by weather changes and intervals between observations can be longer.

Active catches - Expressed as number of sandflies/person/day, where all sandflies inside a given place are caught by skilled collectors. This method can only be used for endophilic sandflies

and must be done as repetitive as possible (same days of the week, same buildings and, if possible, same persons).

Knock-down catches - Expressed as number of sandflies/room/night, where those insects are collected after spraying selected places with an apropriate insecticide (generally a synthetic pyrethroid). It is also used only for endophilic sandflies. The floor and furnitures of a room are covered with papers or plastic sheets, the place is sprayed generally at dawn, and all insects falling on to the sheets are collected.

Sticky-paper traps - Expressed as number of sandflies/m^2/night, where the flies are captured onto pieces of paper or cards recovered with oil (castor or engine oil), grease or a non-drying glue, placed overnight in possible resting places. These traps, measuring around 20x25cm can be fixed in supports or onto the walls, should be used in the same numbers and exposed area on every ocasion to make the results quantitative.

Pheromone traps, e.g. for *Lu. longipalpis* - Can also be added to WHO list, however they are still under development (Ward et al. 1989, 1990).

For all the techniques mentioned the specimens must be identified because usually more than one species are caught.

It must be recognized that no universal strategy is likely to be effective against all kinds of leishmaniasis, even when dealing with the same *Leishmania* species. Primary health care services should be involved in control measures, allowing popular participation but respecting local traditions. Recurrent effort may be needed in many circumstances what means the need of continuous supply of funds. Controlled areas must be surveyed on a long term basis to avoid the reinstallation of transmission.

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