Strategic Control of *Leishmania* Vectors in Urban Areas

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Phlebotomine sandflies (Diptera: Psychodidae) are the proven vectors of Leishmaniases, a group of parasitic diseases present in at least 88 countries, including over 40 *Phlebotomus* species in the Old World and a further 30 belonging to the genus *Lutzomyia* in the New World. They are present in ecological settings that vary from very humid tropical forest to deserts, from temperate cities situated at sea level to high mountain villages. Despite this diversity all sandfly species share a number of basic features. All are nocturnal, resting during the day in dark, humid microhabitats and able to insert themselves into confined spaces to avoid extremes of temperature or humidity. They generally bite a variety of hosts and should be considered as opportunistic man-biters rather than anthropophilic. Their flight ranges are limited to a few hundred meters. Because of their wide host range, small size and silent, non-hovering flight people in *Leishmania*-endemic areas may be unaware of their presence or role in the epidemiology of the disease, a fact that may compromise leishmaniasis control efforts through community participation.

The more immediate life-threatening form of human leishmaniasis amongst the immunocompetent population is anthroponotic visceral leishmaniasis (AVL) due to *Leishmania donovani* (Laveran and Mesnil) in the Indian subcontinent parts of central Asia and Africa, and zoonotic visceral leishmaniasis (ZVL) due to *Leishmania infantum* Cunha and Chagas (= *Leishmania chagasi*) in Latin America. Both forms are usually fatal in untreated or unresponsive patients. In some countries, sandflies also carry and transmit other pathogenic agents, such as *Bartonella* sp., phleboviruses and some flaviviruses, orbiviruses and vesiculoviruses, causing health problems to humans and domestic animals (Zoonoses).

Despite their small size and delicateness, female sandflies are haematophagous pests, so their control may be required even where they are not active as vectors. Sandfly breeding-sites are generally difficult to find in nature, and therefore control measures oriented specifically against immature stages are not feasible, although the effectiveness of a few biological and chemical agents has been demonstrated in laboratory studies. The vectors of Leishmaniases may theoretically be controlled using genetic or biological means, but at present, there are few effective methods other than chemical control.

Control measures are aimed at reducing sandfly populations and man-vector contact by the use of 1) residual spraying in houses and animal shelters; 2) insecticide treated nets for human use (ITNs); 3) repellents applied on people's skin exposed to sandfly bites, and topical application of insecticides on dogs for prevention of canine leishmaniasis.

1. Residual Spraying of Houses and Animal Shelters

Indoor residual spraying (IRS), i.e., the application of long-acting insecticides on the walls and roofs of all houses and domestic animal shelters in a given area, in order to kill the adult vector that land and rest on these surfaces, has been successfully used in malaria control since the 1940s. The application of IRS is also an important method of controlling the Leishnaniases. In the past, only in some areas residual spraying has been used against these diseases alone. In most cases, the purpose of insecticide treatment of human dwellings has been to control mosquitoes or other insects, the control of sandflies being coincidental. There are several examples of sandflies being affected by control measures directed against other pest species. The malaria control in Italy based on the use of DDT, conducted in the late 40's, reduced significantly the transmission of *Leishmania*.

The same occurred in India, Iran, Syria, and Greece. In Kenya, pesticide use on cotton and its storage in human dwellings caused the suppression of *Phlebotomus martini* as well as the malaria vector *Anopheles gambiae*. In Saudi Arabia, urban populations of *P. martini* were reduced by ground and aerial application of diazinon against synanthropic flies such as *Musca* spp. Nowadays, only two countries from the Americas (Brazil and Paraguay) and three countries from the Eastern Mediterranean Region (Morocco, the Syrian Arab Republic and Islamic Republic of Iran) are reporting the insecticide use for leishmaniasis vector control. (WHO/CDS/NTD/WHOPES/GCDPP/2007.2), mainly for indoor residual spraying. Insecticides most extensively used for leishmaniasis vector control, by class of insecticide in the period 2003-2005, are 1) organophosphate, Chlorpyrifos-methyl; 2) carbamate, Propoxur; 3) pyrethroid, Alphacypermethrin, Cypermethrin, Deltamethrin and Lambda-cyhalothrin.

1.1. Prerequisites for IRS Implementation

The residual spraying campaign depends on the availability of a suitable public health infrastructure, including adequate supplies of insecticide, spraying equipment and trained personnel. Ideally, such personnel should be trained in insecticide application, monitoring techniques and interpretation of sampling data, as well as safety techniques. The effectiveness of residual spraying may depend on the degree to which sandflies have adapted to man-made environments, as well as the total area treated. Thus sandfly/leishmaniasis control by this method will be much more effective in urban situations, where every house and animal shelter is treated, than in rural areas, where relatively few, widely dispersed dwellings are sprayed and the insects that bite man and his domestic animals represent a small proportion of the total vector population. In rural areas where large areas must be covered and suitable spraying equipment is available (including aircraft modified for crop-spraying) application of insecticides as aerosols may represent a viable alternative to residual treatment of houses or animal shelters.

2. Chemical Repellents

The use of insect repellents or protective clothing in areas where *Leishmania* transmission is extra-domiciliary may be the only prophylactic measures available. They should be considered for use by people who are only temporarily at risk of *Leishmania* infection, such as tourists, soldiers on manoeuvres or hunters. Among the synthetic chemical repellents, the gold standard is N, N-diethyl-3-methylbenzamide (DEET), which is highly effective against haematophagous insects, well documented and in use for more than 50 years. Its efficacy has been proven against *Leishmania* vectors. During the last 10 years a new piperidine compound [1-piperidinecarboxylic acid, 2-(2.hydroxyethyl)-1-methylpropylester], known as KBR 3023, has been developed and its efficacy has been recently demonstrated against *Phlebotomus duboscqui*. Laboratory tests on human volunteers, to evaluate the efficacy of NeemAzal® (34% Azadirachtin and 57.6% limonoids) and Neem oil, compared to that of 20% KBR 3025 commercial formulation (Bayrepel, Bayer, Germany) against the bite of a well known anthropophilic species, *P. papatasi*, showed 100% protection by KBR 3023 until the 7th hour.

3. Preventative Measures for Dog

Although certain wild animal species may be involved in the epidemiology of ZVL, domestic dogs appear to be the principal reservoir host of *L. infantum* throughout the world. In rural areas, even significant densities of a specific vector could be not relevant for the *Leishmania* transmission force since, being a catholic feeder, this vector may feed on other domestic animals unsusceptible to *Leishmania* infection. On the contrary, in urban area the competent vectors can feed only on two main hosts, human and dog resulting in an increasing trend and urbanization of CanL. Thus, much of the focus on control of ZVL is currently placed on dog, particularly the search for a canine vaccine. Waiting for an effective vaccine, preventing sandfly bites is a priority to protect dogs from leishmaniasis and to reduce the risk of human infections too. Research has been carried out on chemical compounds to be used on dogs as an effective measure in controlling CanL in endemic areas. In particular, the impact of mass use of deltamethrin-impregnated dog collars on the incidence of CanL has been evaluated. Recently, a combination of imidacloprid 10% and permethrin 50% has been developed in a spot-on dermal or topical formulation in order to provide treatment for, and prophylaxis against, ticks, fleas, mosquitoes and phlebotomine sandflies.

3.1. Laboratory and Field Evaluation

Collars

It has been demonstrated that deltamethrin-impregnated collars exert a potent anti-feeding effect on *P. perniciosus* and kill up to 60% of the insects within 2 h of exposure. In Iran it was found that dogs wearing collars were bitten by about 80% fewer *P. papatasi* than unprotected animals. The collars have also an anti-feeding and insecticidal effect against both *L. longipalpis* and *L. migonei*, New World vectors of ZVL and CL parasites respectively. Based on the results of laboratory evaluations, it has been suggested that, at least in the Mediterranean and Middle East subregions, this measure could be expected to protect dogs from most sandfly bites and retain a protective and killing effect for a complete biting season. Given the long-term effect of collars (up to 34 weeks), it has been suggested that supplying them to the majority of dogs in a *L. infantum* focus would reduce contact between vectors and reservoirs sufficiently to reduce the risk of infection for both dogs and humans. A village-based intervention trial carried out in the Campania region of Italy during two consecutive transmission periods has shown that collars confer up to 86% protection against *L. infantum* infection in pet dogs. A study performed in Iran indicate that use of dog-collars significantly reduced ZVL incidence in both dogs and children.

Spot-on Formulations

The repellent and insecticidal activity of a spot-on formulation (imidacloprid 10% and permethrin 50%) against bites from *P. papatasi*, *P. perniciosus* and *L. longipalpis* has been demonstrated experimentally, and it has therefore been speculated that it could be effective in protecting dogs against CanL. The efficacy of this formulation was evaluated in the field as a control measure to prevent CanL in dogs in an endemic area of southern Italy. The results clearly showed that the spot-on formulation is effective in preventing CanL in the field. Other formulations such as a solution containing permethrin 65% has been shown to be effective against the sandfly bites (*P. perniciosus*). Prevention of sandfly attack was also demonstrated for a permethrin/pyriproxyfen combination.

4. Use of Insecticide Treated Nets

Insecticide-treated bednets (ITNs) are easy to use and require less technical and capital resources to implement, compared to other vector control methods. They are cost-effective, which has led to their extensive implementation by countries on a large scale. ITNs represent currently a key malaria control strategy, but low insecticide re-treatment rates remain problematic. The development of mosquito nets pre-treated with insecticide, Long Lasting Impregnated Nets (LLINs) is a solution to the difficulty of the re-impregnation of conventional nets. Two main methods are used for producing LLINs: 1) incorporation of insecticide into fibers, and 2) surface treatment of net fibers or finished nets. Olyset and Permanet nets are currently the two commercially produced bednet with permethrin 2% incorporated in polyethylene fibres. K-O TAB 1-2-3 is the formulation of deltamethrin complimented with a binding agent for converting existing nets into LLINs.

4.1. Community-Based Trials

In urban and rural settlements of Sanliurfa City, SE Anatolia, Turkey, a large-scale field trials performed in an endemic focus of cutaneous leishmaniasis using K-O TAB (deltamethrin tablet formulation) showed high efficacy of impregnated bednets. Results showed significant ($P<0.05$) reduction in cutaneous leishmaniasis incidence in the intervention areas from 1.87 % to 0.035% in Yenice and from 2.3% to 1.32% in Suru. To control visceral leishmaniasis (VL) in eastern Sudan, Médecins Sans Frontières distributed 357000 insecticide-treated bednets (ITN) to 155 affected villages. Regression analysis of incidence data from 114 villages demonstrated a significant reduction of VL by village and month following ITNs provision. The greatest effect was 17-20 months post-intervention, with VL cases reduced by 59% (95% CI: 25-78%). An estimated 1060 VL cases were prevented between June 1999 and January 2001, a mean protective effect of 27%. A community-based intervention trial (KALANET), funded by European Union, and aimed to assess the efficacy, the acceptability and the cost-effectiveness of LLINs in the prevention of visceral leishmaniasis is ongoing in *L. donovani* endemic areas of the Bihar region that extends on both sides of Indian-Nepalese border.

5. Conclusions

Although effective in urban areas with high concentrations of sandflies, residual spraying programmes require suitable equipment and trained personnel. As such large-scale interventions based on residual spraying of insecticides are no often longer sustainable in most situations. In rural areas where dwellings are more dispersed and surrounded by large, untargeted "reservoir" populations of sandflies, residual spraying of houses may be both impractical for logistic reasons and ineffective. ITNs may offer the best solution in rural areas where transmission is largely intradomiciliary. This measure has the advantage that it can be employed at the individual household level and affords collateral benefits such as privacy and control of other biting insects such as mosquitoes, fleas and bedbugs. More focalised measures are required which may require increased community participation and education in preventative measures against leishmaniasis. Inadequate control may merely increase the mean age at which leishmaniasis is acquired, possibly increasing the severity of the disease. Improved information on aspects such as biting behaviour and resting/breeding sites would make delivery of existing compounds more efficient, resulting in lowered costs of interventions, higher efficacy and fewer detrimental effects to the environment.

Speaker Information

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