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High effectiveness of an adulticide-larvicide formulation for field control of sandflies (Diptera: Psychodidae) in the city of Clorinda, Argentina

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ABSTRACT

In Argentina, *Leishmania infantum* (syn. *L. chagasi*) is the etiologic agent of human visceral leishmaniosis (HVL), and *Lutzomyia longipalpis* (Diptera: Psychodidae: Phlebotominae) is the main vector. The objective of this study was to evaluate the effectiveness and residual effect of two commercial insecticide formulations, one with permethrin and pyriproxyfen as active ingredients (Dragon Max®) and the other with only permethrin (Flop®) for the control of sandflies. Both formulations were applied in chicken coops and other surroundings structures of the peridomicile of urban houses in Clorinda, Formosa (Argentina). Entomological monitoring was carried out weekly for 44 weeks after the intervention. The results showed great effectiveness and residual effect up to 21 weeks post-intervention for Dragon Max®. This result could be explained by the excellent larvicidal activity of the Insect Growth Regulator (IGR) pyriproxyfen against the immature forms of phlebotomines and by the delay on the restoration of the natural threshold of the vector population in treated sites.

1. Introduction

The human leishmaniosis are a group of tropical diseases caused by protozoan parasites from more than 20 *Leishmania* species. Phenotypic diversity within and among *Leishmania* species leads to the existence of three forms of the disease in Humans: cutaneous (HCL), mucocutaneous (HML), and visceral (HVL). Although HCL is the most common form of this disease, HVL is the most serious. The etiological agent for HVL is *Leishmania infantum* (syn. *L. chagasi*) (WHO [World Health Organization], 2015).

The main vector of the region is the sandfly *Lutzomyia longipalpis* Lutz & Neiva, a phlebotomine that is found around the world in tropical and temperate regions (Salomón et al., 2012; Lainson and Rangel, 2005). The female sandflies lays its eggs in different

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places, especially in environments associated with organic matter, heat and humidity, which are necessary for their larval development (Casanova et al., 2013). The females feed on vertebrate blood, mainly on bovine but records of feeding from pigs, equines, humans, dogs, opossums, birds, and reptiles have also been reported (Morrison et al., 1995). This broad feeding behavior leads to the presence of reservoirs of the disease in urban zones, such as the domestic dog *Canis familiaris*. Moreover, even though chickens are refractory to infection of *L. infantum*, they are a food source that attracts *Lu. longipalpis* adults. Consequently, this represents an important risk factor for human health in those households that rear chickens and keep chicken coops in the peridomicile (Salomón et al., 2015; Juan et al., 2016).

The first cases of HVL in South America were recorded in 1998 in the State of Mato Grosso do Sul, Brazil, reaching Asunción, Paraguay, in the year 2000 (de Oliveira et al., 2000; Cousiño, 2006). In Argentina the first human autochthonous case of visceral leishmaniosis was detected in 2006 (Salomon et al., 2008) and most cases reported since then have occurred in the province of Misiones, with only a few being reported in the provinces of Corrientes, Santiago del Estero and Salta (Salomón et al., 2012). In these cases, the vector was *Lu. longipalpis* Lutz & Neiva, the parasite was *Leishmania infantum* Nicolle, and dogs were the most important urban reservoir (Acardi et al., 2010). *Lutzomia longipalpis* has also been found in the provinces of Formosa, Entre Rios and Salta (Salomón and Orellano, 2005; Salomón et al., 2011; Bravo et al., 2013). Due to the dispersal of *Lu. longipalpis* throughout these different provinces and an important volume of pet trade, there are dogs infected with *L. infantum* in most of the country (Salomón et al., 2012).

One of the main strategies for prevention of HVL is vector control through the use of insecticides, generally composed of pyrethroids. Several authors have reported that residual insecticide spraying reduces sandfly density, and therefore leishmaniosis transmission, in various localities of South America (Le Pont et al., 1989; Falcão et al., 1991; Oliveira Filho and Melo, 1994). Hence, the residual application of insecticides in domiciles and in surrounding structures is usually the main preventive practice used to reduce vector transmission in endemic focus areas. In problematic areas of Brazil, chemical control of *Lu. longipalpis* and the elimination of infected dogs are widely used by the Visceral Leishmaniosis Control Program (PCLV) which was developed by the Ministry of Health in 1970 (De Silans et al., 1998). In general, insecticide treatments are not focused on the larval stages of the sandflies because their breeding places are difficult to find (Casanova et al., 2013). Nevertheless, the control of immature stages combined with the traditional treatment for adults would be more effective and sustainable.

Previous studies have evidenced the effectiveness of permethrin on adult insects of *Lu. longipalpis* under laboratory conditions (Juan et al., 2014), as well as the effectiveness of the larvicide pyriproxyfen on their immature forms (Juan et al., 2016). Pyriproxyfen is a growth regulator in insects and it's characterized by its selectivity for specific species, with a considerable safety profile towards the environment and non-specific organism, including mammals (Mulla et al., 2003). This chemical compound is juvenile hormone analog (JHA) which suppresses embryogenesis, metamorphosis and the emergence of adult insects (Koehler and Patterson, 1991). Although there are no previous studies from Argentina on the use of pryriproxyfen specifically for sandflies, its effectivity has been evaluated in other Diptera insects of public health importance (Seccacini et al., 2014; Harburguer et al., 2014; Seccacini et al., 2008). In addition, a new formulation (EC: emulsifiable concentrate) containing the pyrethroid permethrin and the larvicide pyriproxyfen showed promising effectivity in the control of sandflies under field conditions (Juan et al., 2016). However, the comparison of the effectivity of this formulate with the traditional permethrin treatment remains unknown. Therefore, the main objective of this study was to compare the effectiveness of the adulticidal-larvicidal formulation and a similar formulation containing only the adulticide in the control of *Lu. longipalpis* and other species of sandflies under field conditions. This study could represent a significant contribution to improve vector control of the main vector of HVL.

2. Materials and methods

2.1. Study site

The field trial was carried out in the city of Clorinda (Formosa, Argentina) (25° 17′29″S 57° 43′06″O), located 4 km from the border with the Republic of Paraguay and 115 km from Formosa (the capital city of the Province). Clorinda is the second most important city in the province of Formosa and has just over 98,000 inhabitants.

2.2. Insecticide formulations

The two commercial insecticide formulations used in this study were Dragon Max® and Flop® (Chemotecnica S.A., Argentina). The emulsifiable concentrate (EC) formulation Dragon Max® contains two active ingredients, the pyrethroid permethrin (Juan et al., 2016) and the insect growth regulator (IGR) pyriproxyfen (2%). The emulsifiable concentrate (EC) formulation Flop® contains a single active ingredient, the pyrethroid permethrin (10%). Both formulations contain the same concentration of permethrin and are composed of a similar mixture of coadjuvants.

2.3. Capture and identification of phlebotomines

Adult sandflies were captured using REDILA-BL minilight traps. The effectiveness of these traps in the capture of sandflies has already been previously demonstrated (Fernández et al., 2015). Each sample point consisted of a minilight trap placed in the peridomicile or near a chicken coop, and it was placed under the roof at 1.5 m above the ground. These traps were placed around 6:00 p.m. and kept until the next morning at around 8:00 a.m. This was performed during two consecutive nights a week for a total period of 44 weeks post-treatment. Insects captured were analyzed in the laboratory using a stereomicroscope in order to separate sandflies from other insects.

2.4. Selection of sample point and insecticide treatment

The sample points were selected considering the points that registered the greatest abundance of sandflies in previous sample rounds that had been conducted by Fundación Mundo Sano during three years (2012–2014) as part of a Sandfly Surveillance Program in the same locality (Gomez-Bravo et al., 2017). Additionally, for this study, new points were included in order to be able to have enough points to compare control and intervention sites. Five points were selected for treatment with Dragon Max® and five points were selected for treatment with Flop®. First of all, the family of each household was informed about the objective of the study, the treatments that would be applied in each case and a written consent was obtained from a responsible adult. The formulations were applied with a 10 l manual spray backpack (model 1165-4, Guarany, Sao Paulo, Brazil). An average flow of 1135 ml/min was used to obtain a dose of 100 mg of permethrin and 20 mg/m^2 of pyriproxyfen for the Dragon Max® formulation, and 100 mg/m^2 of permethrin for the Flop® formulation. The spray was applied evenly in order to cover the soil and the walls of the chicken coops. The surrounding plants and the trunks of the trees were also treated reaching coverage up to 2 m in height and a radius of 3 m around each of the coops. These distances were chosen based on the observed behavior of the phlebotominae, which tend to stay close to their food source and rarely fly at a height of more than 1.5 m (Santini et al., 2010).

2.5. Evaluation of treatment results

Both treatments were applied on the 17th of November 2015 and the traps were evaluated weekly during the entire 44 week period in order to determine the presence of sandflies. Temperature values during the experimental period were recorded using thermohygrometers (model 30.5005, TFA, Wertheim, Germany) in each treated site. Pretreatment results were taken from the historical average of capture in the same sites during the month of December for the years 2012, 2013 and 2014 (Gomez-Bravo et al., 2017).

2.6. Data analysis

The average number of sandflies captured in each treatment and the maximum and minimum temperatures per week post-treatment were recorded in order to analyze the temporal effects of the formulations on the population dynamics. To analyze the variation in the abundance of captured phlebotomines, Generalized Linear Models (GLM) with Poisson distribution errors and log as a link function were used. The effectiveness of Dragon Max® and Flop® were compared by analyzing the sum of captured phlebotomines in treated sites during 21 weeks post-treatment. To determine any differences between the sites treated with Dragon Max® or Flop® and the same places 3 years prior to insecticide treatment (historical data from 2012 to 2014), the average captured sandflies from each site during the month of December were compared.

GLMs were conducted using the lme4 (Bates et al., 2013) and MASS packages (Venables and Ripley, 2002) from R software (R Core Team, 2013). In both cases, the Poisson model showed over-dispersed data, so a negative binomial distribution of the data was assumed for the analysis (Zuur et al., 2009). Tukey's multiple comparisons were performed using the multcomp package (Hothorn et al., 2008) from R software.

3. Results

The abundance curve of the households treated with Dragon Max® was always below the curve of the households treated with Flop® during the entire analyzed period (Fig. 1). In addition, the households treated with Dragon Max® did not show the presence of any sandflies for several weeks. The differences between the two treatments were greater during the first 21 weeks post-treatment, when the mean abundance of sandflies varied from 4 to 79.8 in the Flop® treatments and from 0 to 1.8 in the Dragon Max® treatments, while both abundances started to follow similar tendencies starting week 25 post-treatment. Taking into account the descriptive analysis, we considered only the first period of 21 weeks for further statistical test. Finally, in the coldest weeks of the intervention period (25 and 30 week post-treatment) both treatments presented low abundance values (Fig. 1).

The sum of captured sandflies during the 21 weeks post-intervention in those sites where Dragon Max® was applied was significantly lower than in the sites were Flop® was applied (p-value = 5.87e−06, θ of the negative binomial distribution = 0.81) (Fig. 1).

The average of captured sandflies during December was significantly different between sites treated with Dragon Max®, Flop® and the historical data (p-value = 0.01179, θ of the negative binomial distribution = 0.82). In accordance with the previous analysis, the average of captured sandflies from sites treated with Dragon Max® was significantly lower than the sites treated with Flop®. Furthermore, the average of sandflies on sites treated with Dragon Max® was significantly lower than the historical data. Finally, no differences between the historical data and the sites treated with Flop® were found (Fig. 2).

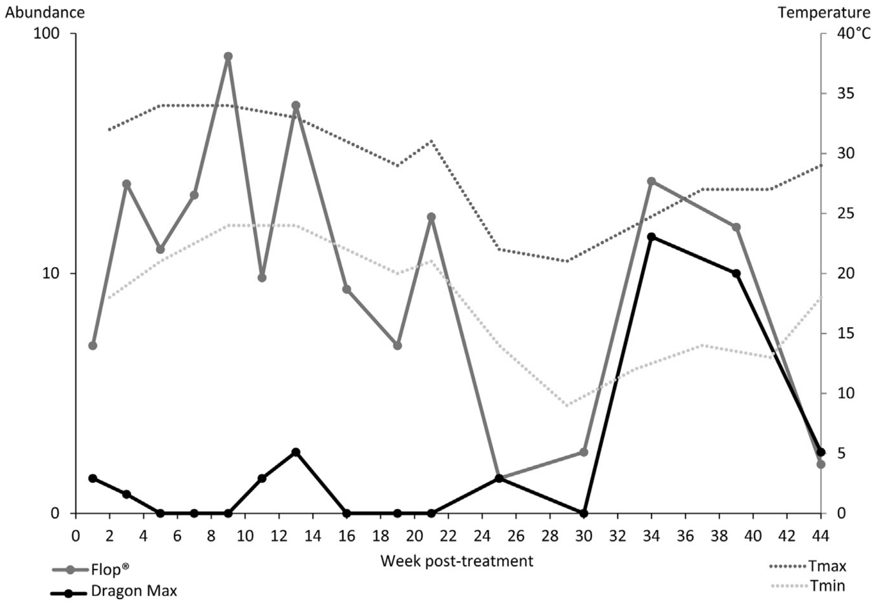

Fig. 1. Average number of sandflies captured of from each treatment arm in logarithmic scale and the maximum and minimum temperatures (°C) per week post-treatment

4. Discussion

This study shows that the Dragon Max® formulation is more effective than the Flop® formulation for sandflies control. This difference was observed during the first 21 weeks after the application of the treatments. In addition, only Dragon Max® showed a decrease in the abundance of sandflies in comparison with the historical data of the same sites without treatment. A similar result was found by Juan et al. (2016) who determined that the application of Dragon Max® resulted in a significant decrease in the number of sandflies for two weeks post-treatment. The abundance of sandflies captured presented high variation, especially after Flop® treatment. This trend was also reported in several studies from untreated cities of Argentina, Colombia and Brazil (Morrison et al., 1995; de Melo Ximenes et al., 2006; Fernández et al., 2010; Quintana et al., 2012; Fernández et al., 2013). Further studies are necessary to determine the biological and environmental reasons for this natural variation. Moreover, the number of sandflies for both treatments sites remained low on weeks 25 to 30 post-treatment. Low values of abundances registered in these weeks could be due to the decrease of temperatures during this period, in which the maximum and minimum temperatures were below 25 °C and 11 °C, respectively (Fig. 1). The influence of temperature on the field abundance of sandflies is well known (Morrison et al., 1995; Santini et al., 2010; de Melo Ximenes et al., 2006), however, the influence of the temperature on the activity and population parameters to predict field outbreaks remains unclear. This knowledge could be useful to improve control actions.

Treatment with Dragon Max® showed an important reduction of sandflies abundance whereas treatment with Flop® did not, and this effect was maintained during 21 weeks post-treatment. It cannot be ruled out that in the Clorinda area where this

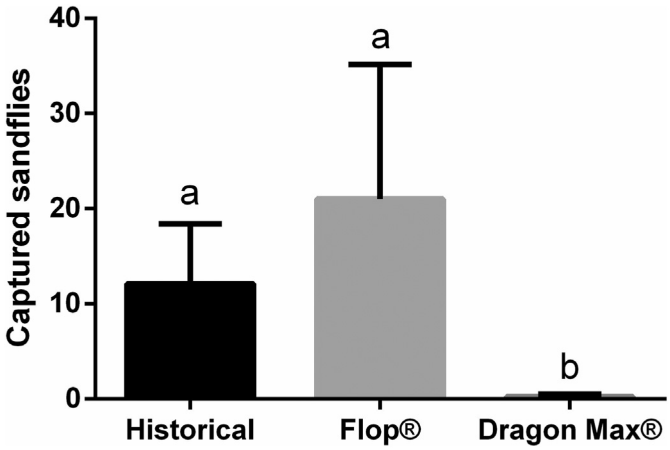

Fig. 2. Sanflies captures during December for each treatment (Average Standar Error). Different letters indicates significant differences (p<0.05)

experience was carried out, sandflies may have developed some degree of resistance to pyrethroid insecticides which would explain the ineffectiveness of permethrin in the Flop® formulation. In Argentina there are no government control actions for sandfly control, but the municipal authorities of Clorinda has been carrying out campaigns for the control of the *Aedes agypti* mosquito for several years in the entire city, with spatial permethrin treatments (Masuh et al., 2003). This pressure with permethrin in or near the areas where the field experience was conducted could have caused some type of resistance to this pyrethroid in sandflies. However there is very little information on pyrethroid insecticide resistance cases in Phlebotomine sandflies and most of them correspond to old word species, The greatest number of cases have been reported for DDT in different areas of India and Iran for *Phlebotomus papatasi*, *Phlebotomus argentipes* and *Sergentomyia shorttii* (Alexander and Maroli, 2003; Sharma and Singh, 2008; Dhiman and Yadav, 2016; Yaghoobi-Ershadi, 2016). With respect to pyrethroids, evidences of permethrin resistance were informed for *Phlebotomus argentipes* and *P. papatasi* in some areas of India (Amalraj et al., 1999; Gomes et al., 2017). The only precedent of pyrethroid resistance that we find in new word species is from a study in Venezuela where this insecticide is used to control sandflies (Mazzarri et al., 1997). Therefore, taking into consideration the lack of evidence of insecticide resistance in our region, it is unlikely for the ineffectiveness of the Flop® formulation to be due to resistance mechanisms. A more plausible explanation could be a short residuality of the insecticide in the environment and the rapid recolonization of treated areas by sandflies, which is characteristic for this insect (Santini et al., 2010).

Differences in the effects of the treatments could be explained by the action of (IGR) pyriproxyfen, a larvicide present in the Dragon Max® formulation be due to presence of the IGR. A laboratory bioassay showed that the post-embryonic development of *Lu. longipalpis* exposed to pyriproxyfen is interrupted in the pupal stage avoiding the emergence of adult insects (Juan et al., 2016). Results along this same line were obtained for *Aedes aegypti* using a similar formulation (Lucia et al., 2009), where the effect of the pyriproxyfen inhibition was recorded during 6 weeks post-treatment, in contrast with the 21 week effect observed in the current study. Therefore, the long lasting effect of Dragon Max® treatment observed in this study could be due to a distinct extended effect of the larvicide on sandflies breeding sites, which could be combined with a delay in recolonization, but it could also be due to the concentration of pyriproxyfen in the Dragon Max®. However, further studies are needed to clarify the main reason for the long lasting duration of the effectivity of pyriproxyfen treatment on sandflies. Finally, the sandflies captured on the first month post-treatment in sites treated with Dragon Max® were lower than those collected in the past (historical data), while the captures in sites treated with Flop® did not present differences. The lack of significant effects for the Flop® treatment could represent a confirmation of previous results, in which it was observed that only one week is needed to restore the population to pre-treatment levels for a similar permethrin formulate for *Lu. longipalpis* and *Ae. aegypti* (Santini et al., 2010; Lucia et al., 2009). These results support the hypothesis mentioned above that the difference is explained by the pyriproxyfen present in the Dragon Max® formulate. Thus, this study provides evidence on the effectiveness of the larvicide in controlling sandflies in peridomestic areas.

In order to evaluate the effectiveness of the two formulates in an urban area we registered sandflies abundance during 44 weeks. Long-term field studies are important to assess the effectiveness and duration of control strategies. The results presented herein disagree with a previous recommendation discouraging the residual spraying to control urban foci due to the lack of evidence of residual effectivity (Salomón et al., 2015). Our study suggests that spraying with an adulticide-larvicide formulation results in long-lasting control of the sandflies. Moreover, the very low residuality of permethrin shown by the Flop® formulation emphasizes the need to conduct future studies on the control effect of larvicide treatments with pyriproxyfen formulations as well as studies to determine the susceptibility or resistance of the sandfly species of this region to larvicides and adulticides for public health use. Furthermore, an integrated program control that combines the spraying of an adulticide-larvicide or larvicide formulation in peridomiciles with prevention methods like personal protection, environmental management and health education, would be an effective strategy to prevent HVL.

Declarations of interest

None.

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