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Identifying Current and Missing Knowledge in the Control of Pyrethroid-Resistant *Triatoma infestans*, Vector of Chagas Disease

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Abstract

Triatomines are blood-sucking bugs that occur mainly in Latin America. They are vectors of *Trypanosoma cruzi*, the parasite that causes Chagas disease. Chemical control of Chagas disease´s vectors by using pyrethroid insecticides has been highly successful for the elimination of domestic infestation and consequently the reduction of the vector transmission. However, at the beginning of the 2000s a decrease in the effectiveness of the chemical control of triatomines was detected in several areas from Argentina and Bolivia, particularly in the Gran Chaco eco-region.

During the last 15 years, several studies demonstrated the evolution of insecticide resistance in *Triatoma infestans* and established the presence of different toxicological profiles, the autosomal inherence of resistance, the biological costs of deltamethrin resistance, the expression of deltamethrin resistance thorough the embryonic development, and the main mechanisms of resistance (target-site insensitivity and metabolic detoxification of insecticides).

The emergence of pyrethroid resistance coupled with the usual difficulties in sustaining adequate rates of insecticide applications emphasize the need of incorporating other tools for integrated vector and disease control, such as the proposal of the organo-phosphorus insecticide fenitrothion as an alternative chemical strategy for the management of the resistance because it was effective against pyrethroid-resistant populations in laboratory and semi-field trials.

New studies on the current situation of presence and spread of resistant populations of triatomines and the acceptance of the use of alternative insecticides are critical requirements in the implementation of strategies for the management of resistance and for the rational design of campaigns oriented to reducing the vector transmission of Chagas' disease.

Keywords: *Triatoma infestans*, pyrethroid-resistance, biological costs

1. Introduction

Triatomines are blood-sucking bugs that occur mainly in Latin America. They are vectors of *Trypanosoma cruzi*, the parasite that causes Chagas disease or American trypanosomiasis. Chagas Disease is a potentially life-threatening illness transmitted to humans by contact with feces of triatomine bugs. About 6 million to 7 million people are estimated to be infected worldwide, mostly in Latin America where Chagas disease is endemic. This illness is incurable and in its chronic phase may cause damage to the heart and intestines, causing eventually death by heart failure. The cost of treatment for Chagas disease remains substantial (WHO, 2016)

Over 100 species of Triatomine are now recognized, most of them having little epidemiological significance because of their sylvatic habits and consequent rarity contact with humans. However, some species have adapted to live in and around houses and represent highly significant vectors. Undoubtedly, the most important vector species is *Triatoma infestans* in the southern cone countries Argentina, Bolivia, Brazil, Chile, Paraguay, Peru and Uruguay. Other important species are *Triatoma brasiliensis* in northeastern Brazil, *Rhodnius prolixus* and *Triatoma dimidiata* in regions north of the Amazon basin. These species are well adapted to human habitations, generally living in cracks and crevices of poorer quality rural houses, and emerging at night to suck the blood of the sleeping people and domestic animals.

In the absence of vaccines, the transmission of human *T. cruzi* infection can be successfully interrupted by controlling the triatomine bugs in and around the houses where they have their resting places. Since the late 1940s, the chemical control of triatomines has been the main tool for the elimination of the domestic infestation and consequently for the reduction of the vector transmission of Chagas` Disease in Latin America. The insecticides used for the vector control were organochlorines in the 1950s, organophosphates and carbamates in the 1960-1970s, and pyrethroids from the 1980s to the present time. The introduction of the synthetic pyrethroids in the control of triatomines was a major advance in the campaigns to control Chagas disease´s vectors due their high insecticidal activity, low application rates, toxicological safety and rapid environmental degradation. Deltamethrin and cypermethrin were the first pyrethroids successfully used in the field control of *T. infestans* in Argentina and Brazil. Since 1990s, other pyrethroids were used such as beta-cypermethrin, lambda-cyhalothrin and beta-cyfluthrin (Dias, Silveira, & Schofield, 2002).

Thanks to a coordinated multi-country program in the Southern Cone countries (Tropical Disease Research/World Health Organization, TDR/WHO) the transmission of Chagas disease by vectors and by blood transfusion has been interrupted in Uruguay in 1997, in Chile in 1999, and in 8 of the 12 endemic states of Brazil in 2000. Similar control multi-country initiatives have been launched by TDR/WHO in the Andean countries and in Central America, and rapid progress has been recorded to ensure the interruption of the transmission of Chagas disease by 2005 as requested by a Resolution of the World Health Assembly approved in 1998. Argentina, Bolivia and Paraguay were expected to be free of transmission by 2005 (Moncayo, 2003). Unfortunately, Bolivia and Argentina had serious difficulties in controlling the disease in the Gran Chaco geographical area mainly due to the evolution of insecticide resistance in of intra and peri-domestic field populations (collected from infested houses) of *T. infestans*

Recently, Mougabure-Cueto & Picollo (2015) reviewed toxicological, evolutionary and ecological aspects related to the evolution of insecticide resistance in triatomines, including theoretical concepts leading to understand this particular scenario of pyrethroid resistance. Later, Dávila Pessoa et al. (2015) structured a review based on a literature search of all articles from 1970 to 2015.

The present report summarized the current knowledge and the main gaps in knowledge for the potential application of alternative insecticides in the management of pyrethroid resistance in vectors of Chagas disease.

2. Current Knowledge

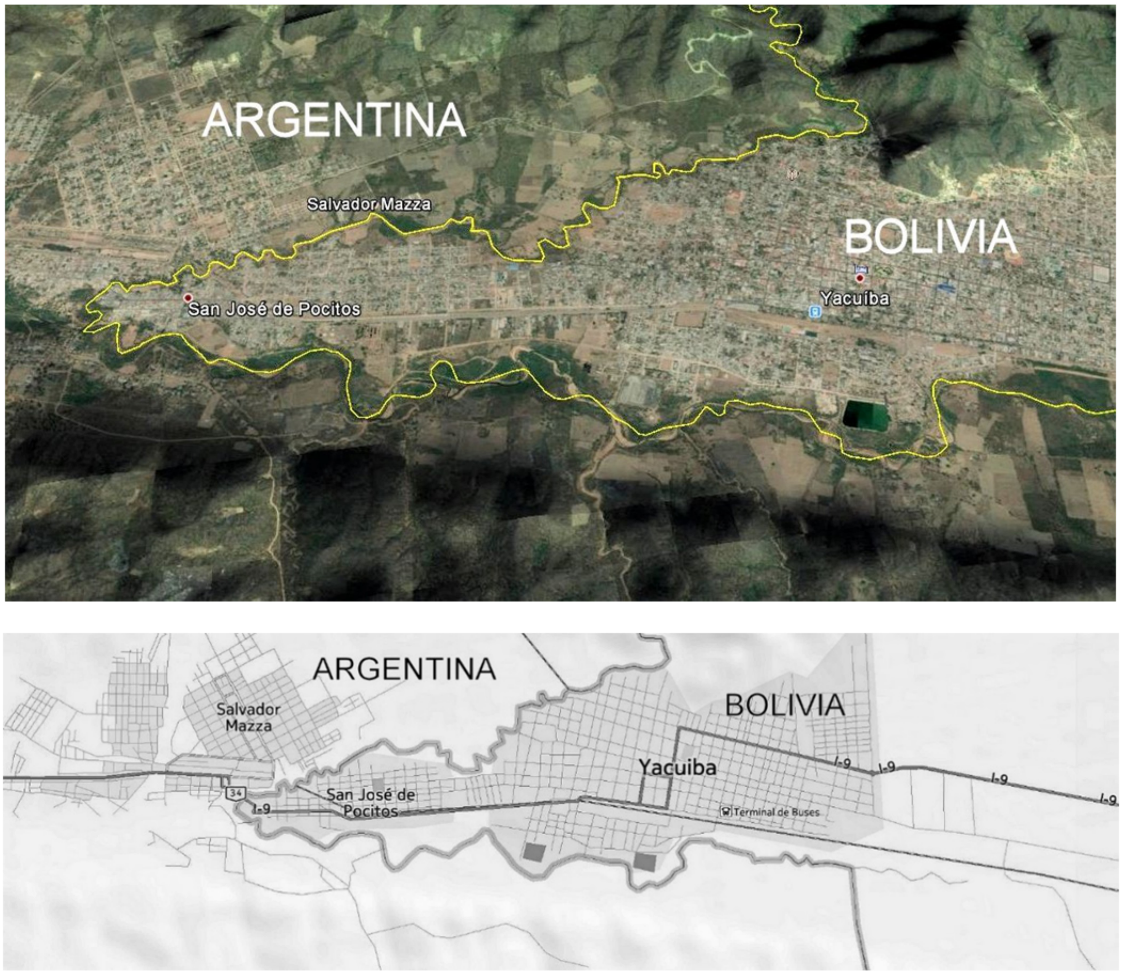
2.1 Detection of Insecticide Resistance in Triatomines

Chemical control of triatomine vectors using pyrethroid insecticides has been highly successful for the elimination of domestic infestation and consequently the reduction of the vector transmission. However, at the beginning of the 2000s a decrease in the effectiveness of the chemical control of triatomines was detected in several areas from Argentina and Bolivia. In 2002, high resistance to deltamethrin correlated with field control failures was detected in *T. infestans* in the neighboring areas of Salvador Mazza (Argentina) and Yacuiba (Bolivia) (Figure 1). At the same time, the Health Authorities for Vector Control of Argentina reported ineffectiveness of the application of deltamethrin and other pyrethroid insecticides in infested houses of this endemic area. This study (Picollo et al., 2005) reported the first case of pyrethroid resistance at a high enough level to cause control failures in field populations of *T. infestans*.

Surprisingly, some *T. infestans* populations of the neighboring areas of S. Mazza (Corralito, San Carlos, Banda Sur) were susceptible or presented moderate to low levels of deltamethrin resistance (M. D. Germano et al., 2010). Subsequent studies demonstrated that *T. infestans* from different dwellings of resistant areas presented different toxicological phenotype to deltamethrin, that is some houses hosted resistant insects and other houses hosted susceptible insects (Mónica Daniela Germano, Picollo, & Mougabure-Cueto, 2013). These toxicological differences were justified by the highly structured *T. infestans* populations, that is to say the significant genetic differentiation from insects of neighboring dwellings (Marcet et al. 2008; Pérez de Rosas, Segura, Fichera, & García (2008); Pérez de Rosas, Segura, & García (2007).

Further studies demonstrated high levels of deltamethrin resistance associated with field control failures in field populations (collected from infested houses) of *T. infestans* from a locality of the Argentinean Chaco province (La Esperanza), an area far from the first focus of high resistance detected in 2002 (M Germano, Picollo, Spillmann, & Mougabure-Cueto, 2014) (Figure 2). Similarly to what was observed in S. Mazza, *T. infestans* populations of a neighboring area (Pampa del Indio, Chaco) located 40 km from La Esperanza, presented significantly lower levels of resistance to deltamethrin despite their geographical proximity (Gurevitz et al., 2012).

In 2010, most domestic *T. infestans* populations along the geographical distribution of this vector in Bolivia were resistant to deltamethrin. High resistant ratios, from 6 to 491, were established in field insects sampled in human dwellings in the center and south areas of this country, where the National Program for Control of this vector had reported chemical treatment failures. These results demonstrated high resistance to deltamethrin widespread in Andean and non- Andean regions of Bolivia (Lardeux, Depickère, Duchon, & Chavez, 2010).



Top: Satellite image of Salvador Mazza and Yacuiba (modified from Google Earth, 2016).

Bottom: Political Map (Modified from HereWeGo Maps, 2016) irregular bold line denotes countries limits.

Figure 1. First areas where resistance to deltamethrin correlated with field control failures of *T. infestans*.

Figure 2. Geographic location of deltamethrin-resistant *T. infestans* in Argentina and Bolivia

The toxicological and biochemical studies on insecticide resistant in field populations of Argentina and Bolivia, demonstrated different mechanisms (Santo-Orihuela, Vassena, Zerba, & Picollo, 2008; Toloza et al., 2008). These studies identified at least three resistant profiles named Ti-R1, Ti-R2 and Ti-R3, for the Argentinean Acambuco, and the Bolivian populations Entre Ríos and Mataral respectively (Roca-Acevedo, Picollo, Capriotti, Sierra, & Santo-Orihuela, 2015; Gonzalo Roca-Acevedo, Picollo, & Santo-Orihuela, 2013) (Figure 3).

Ti-R1 exhibited medium resistance level to deltamethrin in nymphs and eggs (RR=32.5 and 28.6), and pyrethroid-esterases played a pertinent role in deltamethrin resistance.

Ti-R2 exhibited high deltamethrin-resistant nymphs (RR=173.8) and low fipronil- resistant (RR=12.4). Pyrethroid esterases were implicated in resistance, and eggs showed medium resistance level to deltamethrin (RR=39.1).

Ti-R3 exhibited low deltamethrin-resistant nymphs (RR=17.4), and medium fipronil-resistance (RR=66.8). Pyrethroid esterases showed increased activity, and eggs presented low deltamethrin resistance (RR=8.4).

The classification of the pyrethroid-resistance in these *T. infestans* populations from Argentina and Bolivia did not allow the generalization of only three profiles; additional locations would be able to show combinations of different resistance mechanisms. The evolution of resistance in *T. infestans* might be more complex than expected, reflecting the insecticide pressures and genetic structures of the populations. Scientific evidence of different resistance profiles in field populations from Argentina and Bolivia suggested an independent evolutionary process, mainly based on local environmental and genetic differences of natural populations (Mougabure-Cueto & Picollo, 2015).

The current scenario is very different from the one in which the Southern Cone Initiative of Tropical Disease Research/World Health Organization (TDR/WHO) based its plans for the elimination of *T. infestans* using pyrethroid insecticides 25 year ago, exhibiting multiple bug populations showing high or incipient levels of pyrethroid resistance in Argentina and Bolivia. The emergence of insecticide resistance coupled with the usual difficulties in sustaining adequate rates of insecticide applications emphasize the need of incorporating other tools for integrated vector and disease control.

The three resistant profiles were identified according to the toxicological and biochemical characteristics of the studied resistant populations (Germano et al. 2012).

Figure 3. Geographical location of three resistance profiles in resistant Triatoma infestans of the Gran Chaco area

2.2 Inheritance of Insecticide Resistance

The mode of inheritance of deltamethrin resistance was studied in field populations of *T. infestans* from the resistant area of the north Argentina. The response of susceptible male crossed with resistant female (SR) and resistant male crossed with susceptible female (RS) hybrids to deltamethrin was intermediate between the highly resistant and the susceptible parent colonies, indicating some degree of semi-dominance for resistance (Cardozo et al., 2010; MD Germano, Vassena, & Picollo, 2010). Moreover, lack of significant differences between the resistance ratios of the reciprocally mated insects indicated no sex linkage on this trait, thus the *T. infestans* resistance was controlled by autosomal inherited factors.

The genetic basis of the resistant phenotype indicated that, under pyrethroid selective pressure, the resistant genotypes could be easily spread to susceptible insects from resistant individuals, posing a major threat to vectorial control of Chagas disease.

As was demonstrated for other insect species, deltamethrin resistance in *T. infestans* was associated with biological costs. A reproductive cost of resistance was expressed as a lower fecundity in the resistant colony in a way of a shortening the second and third nymph stage and an extension of the fifth stage. These costs were associated to a maternal effect, since these effects were demonstrated in females and their offspring, regardless of the male with whom they copulated (Mónica Daniela Germano & Picollo, 2015).

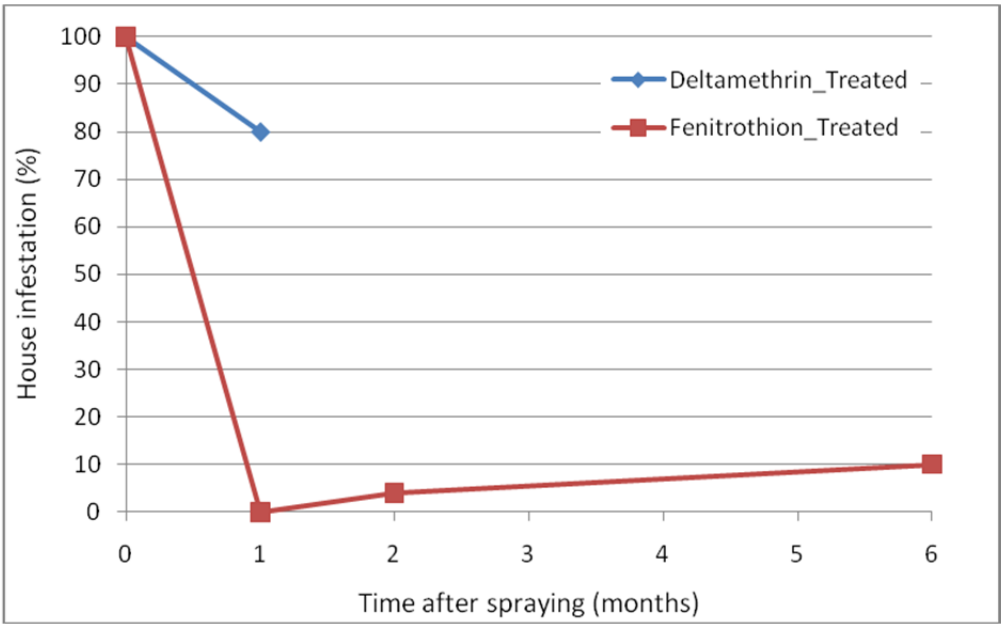
Variation in life cycle traits can be a key to enhance the management of resistant *T. infestans* in infested areas. The described differences in reproductive output and development could possibly lead to lower growth rates in the resistant insects, hence delaying resistance evolution or allowing its reversion in heterogeneous populations. Including such information in management programs could be decisive for insecticide rotation organization or a future reinstatement of pyrethroid spraying in areas were field control failures have been detected.

2.3 Alternative Chemical Control for Pyrethroid-Resistant Populations

Considering that the prevention of Chagas disease is based on the control of the vector mainly by insecticides, it was necessary to select insecticides with alternative modes of action to that of pyrethroid for controlling resistant populations. Fenitrothion and imidacloprid showed high lethal effect on susceptible and resistant *T. infestans*, but ivermectin, flubendiamide, indoxacarb, amitraz and spinosad did not show effectiveness. Thus, fenitrothion and imidacloprid were considered as alternative compound for chemical control of this vector (Carvajal, Mougabure-Cueto, & Toloza, 2012).

Of both insecticides, fenitrothion was chosen for field trials in a pyrethroid-resistant area of Argentina (Chaco province) because it had been authorized by the Ministry of Health for its use in the National Campaigns for the control of Chagas´ vectors. After the treatment, the percentage of infested houses was reduced from 100 to 0%, and remained below 10% for 6 months, demonstrating the effectiveness of fenitrothion in deltamethrin-resistant triatomines (Picollo & Germano. personal communication, 2015) (Figure 4).

To optimize the management of insecticide resistance in *T. infestans*, it is indispensable that new insecticides are available for control programs in South America, especially those with alternative modes of action to pyrethroids and organophosphates.



Deltamethrin curve covers up to the first evaluation, when infested houses were sprayed with fenitrothion to ensure population safety.

(Picollo & Germano. personal communication, 2015)

Figure 4. Percentage of infested houses before and after fenitrothion (red line) field spray

2.4 Target-Site Insensitivity

Pyrethroids exert their insecticidal action on the insect nervous system by modifying the normal function of voltage-gated sodium channels in the membranes of excitable cells. Knockdown resistance (kdr) is the reduction in the sensitivity to pyrethroids caused by point mutations in the sodium channel gene. Most resistance-conferring mutations were found in domain II of this large membrane protein, particularly in the region comprised between trans-membrane segments IV and VI (IIS4–IIS6 region). This mechanism of resistance has been reported in several insect species of economic and sanitary interest (Soderlund & Knipple, 2003).

The presence of a resistance-conferring mutation (L1014F) was confirmed in the sodium channel of a pyrethroid-resistant population of *T. infestans* from Madrejones and Campo Largo, two small localities near the focus of high resistance detected in northern Salta, Argentina, and a pyrethroid-resistant population from Entre Ríos, in southern of Bolivia (Fabro et al., 2012; G Roca-Acevedo et al., 2015). Later, a new pyrethroid resistance-conferring mutation (L925I) was identified in the sodium channel of *T. infestans* from El Mala, a little locality in the Argentinean Gran Chaco region. Unlike L1014F mutation that was identified in many insect species from different families, L925I mutation has been identified only in hemipterans (Capriotti, Mougabure-Cueto, Rivera-Pomar, & Ons, 2014; Sierra, Capriotti, Fronza, Mougabure-Cueto, & Ons, 2016).

It is important to emphasize that the highest levels of resistance in *T. infestans* field populations were determined by alterations in the site of action of pyrethroid insecticides (Mougabure-Cueto & Picollo, 2015). The presence of kdr mutations differs in frequency among resistant populations. An increased frequency of the kdr resistant allele is correlated to high resistance to pyrethroid insecticides in other species (Huang, Kristensen, Qiao, & Jespersen, 2004). For example, Ndiath et al., (2012) demonstrates that in *An. gambiae* the allelic frequency of the resistant allele in homozygosity was very low, and after 4 years of insecticide treatment went from 2% to 18,7% ,with lower sensivity to pyrethroid insecticides.

Gellatly et al., (2016) showed that in the human head louse *Pediculus capitis*, a high frequency of kdr-type mutations lowers the effectiveness of permethrin formulations. Moreover, Raab et al., (2016) explained that in a building infested with the bed bug *Cimex lectularius*, there were 8 genetic clusters with no gene flow between them, and 40% of the insects were homozygous for two concomitant kdr mutations, responsible for the decrease in effectiveness of the insecticide.

This mechanism seems to be one of the most important in the decrease in susceptibility to pyrethroid insecticides in other insect's species.

This information is useful for monitoring the presence and spreading of resistant populations, a critical requirement for the implementation of strategies for resistance management, and for the rational design of campaigns oriented to the control of Chagas' disease transmission

2.5 Metabolic Detoxification of Insecticides

Resistance to pyrethroids in a variety of insects has been associated with increased oxidative metabolism mediated by cytochrome P450 monooxygenases and esterases (Oppenoorth, 1985). Increased activity of P450 monooxygenase and specific esterases were identified as contributive mechanisms in field pyrethroid-resistant *T. infestans* from northern Argentina (Salta and La Rioja Provinces) and southern Bolivia (Yacuiba and Entre Ríos) (Mónica Daniela Germano et al., 2012; Santo-Orihuela et al., 2008). Moreover, the increase in activity of pyrethroid esterases was found throughout the embryonic development of an Argentinean (Campo Largo) and a Bolivian (Entre Ríos) population, both resistant to deltamethrin (G Roca-Acevedo et al., 2015; Gonzalo Roca-Acevedo et al., 2013). Gene amplification, and/or altered gene regulation are another phenomena that may be present in resistant insects with increased esterase activity (Ffrench-Constant, Daborn, & Le Goff, 2004).

The partial reversion of resistance levels using enzymatic inhibitors (piperonyl butoxide for P450 and triphenol phosphate for carboxylesterase) or the slightly significant differences in enzymes activities revealed that the enhanced metabolism evolved as resistance mechanism, but do not fully explain the high resistance to pyrethroids in *T. infestans* and suggested the contribution of altered site of action as the main mechanism in very high resistant populations.

3. Analysis of Main Gaps in Resistant *T. infestans* Information

The insecticide resistance has been recognized as the main reason for the persistence of *T. infestans* in the Gran Chaco from Argentina and Bolivia. Although several mechanisms of resistance were assessed in these populations, undoubtedly mutations in the sodium channel gene had been associated with the highest levels of resistance to pyrethroids.

The ineffective field treatments due to high resistance to insecticides produced an increased number of infested houses and consequently an increased risk of Chagas transmission in some localities of Argentina and Bolivia. The organo-phosphorus insecticide fenitrothion was proposed as an alternative chemical strategy for the management of the resistance because of was effective against pyrethroid-resistant populations in laboratory and semi-field trials. Moreover, the fenitrothion had been approved by the Ministry of Health of Argentina for its use in National Campaigns for the Control of Chagas Disease Vectors. Actually, the translation of these semi-field trial results as operational tools for the chemical field control of pyrethroid-resistant *T. infestans* brought the emergence of the following issues to be solved:

1) Which is the current situation of resistance to pyrethroids in field populations of *T. infestans* throughout the endemic area of Argentina and Bolivia, especially in the Gran Chaco eco-region?

2) Which is the spreading and frequency of kdr alleles in field populations of *T. infestans* throughout the endemic area of Argentina and Bolivia, especially in the Gran Chaco eco-region?

3) How far from the detected resistant focus (dwellings and small localities) is necessary to extend the application of the fenitrothion alternative insecticide, that is to say what is the extent of the resistant focus to the neighboring villages.

4) Commercial fenitrothion is an organophosphorus insecticide usually formulated as wettable powder (instead of the flowable deltamethrin commonly used for triatomines control). Therefore new protocols are necessary for the proper preparation and implementation of this alternative insecticide.

New studies on the current situation of presence and spread of pyrethroid-resistant populations of *T. infestans*, and the acceptance of the use of fenitrothion as alternative insecticide, are critical requirements in the implementation of strategies for resistance management. We emphasize the need to ensure a constant, enduring control and eternal surveillance of the pyrethroid-resistant triatomines at the political and at the community level, to ensure a rational design of campaigns oriented to reducing the vector transmission of Chagas' disease.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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