Insecticide Resistance in Triatomines

Gastón Mougabure-Cueto and María Inés Picollo

Abstract The control of Chagas disease vectors has been based principally on spraying dwellings with insecticides. This strategy reduced the geographic range and infestation prevalence of major vectors leading to the interruption of disease transmission in several areas from endemic regions. However, triatomine survival after spraying pyrethroid insecticides, mainly in the case of *Triatoma infestans* (Hemiptera: Reduviidae), has become more frequent in the last two decades. Insecticide resistance emerges as one main explanation for these chemical control failures. This chapter reviews the evolution of insecticide resistance in triatomines. Resistance to pyrethroids was first detected in *T. infestans* in the 1990s. But, it was only in the 2000s that resistance associated with control failures was described for the latter species in Argentina and Bolivia. Different resistant profiles were demonstrated for *T. infestans* suggesting that resistant foci originated independently. The main resistance mechanisms (i.e., enhanced detoxification, target-site modifications, and reduced penetration) were described for this species. Resistance to deltamethrin in *T. infestans* was shown to be controlled by an autosomal and incompletely dominant character. The resistance evolving in *T. infestans* from the Chaco ecoregion would be associated with different pleiotropic effects of the genes that confer resistance. Moreover, environmental variables linked to temperature and precipitation would explain part of the distribution of resistant populations of *T. infestans* in some endemic areas of the Chaco ecoregion. Finally, the possible resistance management strategies for triatomines are discussed.

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1 Introduction

The development of resistance to insecticides has been demonstrated in most pest insect species exposed to chemical control (McKenzie 1996). Insecticide resistance is an evolutionary phenomenon through which insecticide use acts as a selective force that favors preexisting features conferring resistance to part of the insect population. This selection reduces the susceptibility to the applied insecticide that was previously effective for controlling individuals of this species. This is because resistant individuals survive after exposure to the insecticide and transmit their genetic background to their offspring (Fig. 1).

According to the Insecticide Resistance Action Committee (IRAC), resistance to insecticide is “a heritable change in the susceptibility of an insect population that is reflected in the repeated failure of the insecticide application to achieve the expected level of control when used according to the label recommendation for that species.”

The early detection of resistance in a population exposed to an insecticide is of considerable importance to avoid the development of high ratios of resistance (RR:

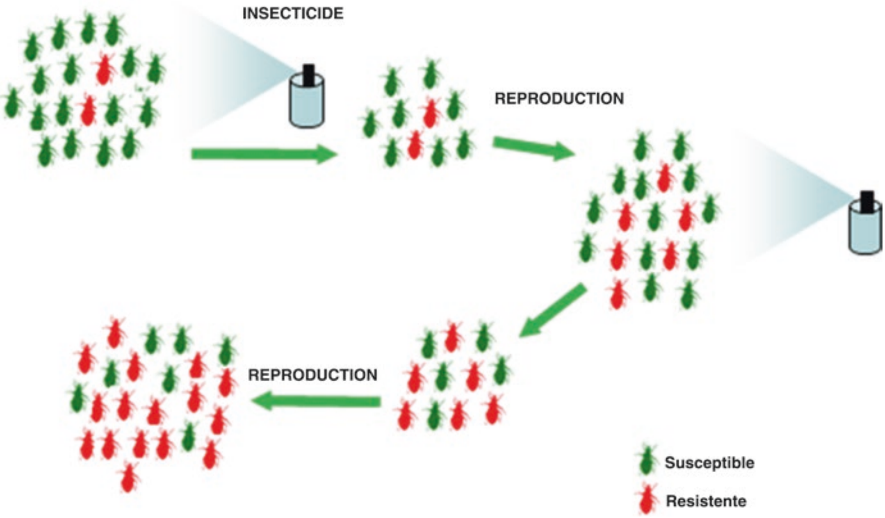

Fig. 1 Evolution of the resistance to an insecticide in an insect population
Insecticide application mainly eliminates susceptible individuals. The most resistant individuals survive and pass the resistant genetic character to the offspring. After several generations, the proportion of resistant individuals was increased, and the effectiveness of the insecticide in the population was reduced

LD_{50}-resistant population/LD_{50}-susceptible population) and to elaborate alternative control strategies adequate for that resistant population. The development of standardized tests fit to specific insect pests is of considerable importance for resistance detection activities. Additionally, resistance surveillance has been facilitated by incorporating the "discriminating dose" (DD) concept, namely, the use of a dose of an insecticide that is lethal to susceptible individuals, but allows the survival of resistant ones (ffrench-Constant and Roush 1990). The definition of such discriminating dose is based on a prior accurate determination of the dose-mortality curve and the estimation of the lethal dose for 99% (LD_{99}) of the exposed individuals of a susceptible population of the species.

The discriminating doses for *Triatoma infestans* (Klug) and *Rhodnius prolixus* (Stahl) were established as the lethal dose for 99% of the tested individuals according to the World Health Organization protocol. The protocol indicates that first instars (5–7 days old, mean weight 1,3 mg) starved since eclosion are treated by topical application on the dorsal abdomen with 0.2 microliter of the insecticide diluted in acetone. The mortality rates of control and treated insects are then recorded after 24 h according to their ability to reach the border of a 7 cm filter paper disc when released in its center, alone or after mechanical stimulation (WHO 1994). The use of this protocol allows comparing results obtained by different laboratories studying triatomine insecticide resistance. As an example, this protocol was used to assess the resistance to deltamethrin status of various Bolivian and Argentinian field populations of *T. infestans* (Lardeux et al. 2010; Germano et al. 2013). Two reviews on the resistance to insecticides in vectors of Chagas disease have been published in the last decade (Mougabure-Cueto and Picollo 2015; Pessoa et al. 2015).

2 Populations Resistant to Insecticides

Triatomine control efforts have been mainly based on the application of insecticides. This has allowed achieving an important reduction in the domestic infestation and vectorial transmission of Chagas disease in Latin America. The first insecticides used to control triatomines were organochlorines such as hexachlorobenzene (HCB) and dieldrin (Zerba 1999). Later, the carbamates propoxur and bendiocarb were introduced in the 1960s mainly because of their proven efficacy and ovicidal properties. Subsequently, the organophosphorus malathion was recommended for the control of Chagas vectors in the 1970s. Finally, various pyrethroid insecticides were proven to be effective during the 1980s for controlling these vectors (Mougabure-Cueto and Picollo 2015).

Early studies evaluating field populations of *T. infestans* from Argentina that had been exposed to vector control campaigns detected growing percentages of deltamethrin-resistant populations (from 29% in 1997 to 40% in 2002, respectively, for Vassena et al. 2000 and González-Audino et al. 2004). These populations showed low levels of resistance (resistant ratios <10) that did not correlate with field control failures.

It was only with the advent of the new millennium that a decreased effectiveness was reported for the chemical control of triatomines in several areas of Argentina, Bolivia, and Colombia. High resistance to pyrethroid insecticides associated with ineffective field treatments was detected in 2002 for *T. infestans* in the San Martín department of Salta province in northern Argentina and Yacuiba, Sucre, and Mataral in southern and central Bolivia (Picollo et al. 2005). The resistance ratios for these pyrethroid-resistant populations of *T. infestans* ranged from 20 to 100.

High prevalence of infestation by *T. dimidiata* (Latreille) was reported in deltamethrin-sprayed dwellings from Colombia (Reyes et al. 2007). Besides, the presence of *R. prolixus* from sylvatic populations was reported for sprayed dwellings from an extensive geographic area of Colombia (Llanos Orientales) and Venezuela, where a high percentage of houses remained positive 1 year after spraying fenitrothion and deltamethrin (Sánchez and Jesús 2006; Angulo et al. 2006). Moreover, moderate (RR <100) and low (RR <10) levels of resistance to lambda-cyhalothrin and fenitrothion, respectively, were determined for a field population of *Panstrongylus geniculatus* (Latreille) collected in 2012 in the Chorreras, Capitanejo municipality, Santander department, Colombia (Torres et al. 2013).

Susceptibility to deltamethrin, malathion, and bendiocarb was characterized for 50 populations of *T. infestans* sampled in Bolivian human dwellings a decade ago (Lardeux et al. 2010). These populations were resistant to deltamethrin (RR: from 6 to 491), while none of them exhibited significant resistance to malathion or bendiocarb. Additionally, high resistance to deltamethrin (RR: from 25.6 to 54.7) was reported in domestic and sylvatic *T. infestans* collected in 2014 in four communities of the Municipality of Torotoro, Potosí department, Bolivia. Interestingly, different resistance values were estimated in insects from peridomiciliary structures of the same dwelling, indicating that this phenomenon is complex both at the community and microgeographical levels (Espinoza Echeverria et al. 2018).

All these investigations established that resistance to deltamethrin is high and widespread in Bolivia. In contrast, high deltamethrin resistance in Argentina seemed to be initially restricted to Salta province, in the northwestern area of the country (Germano et al. 2010a). Infestation by *T. infestans* after repeated spraying with pyrethroids was more recently reported in several rural areas of Chaco province in northern Argentina. High resistance to deltamethrin was assessed in the Güemes department of the Chaco province, in localities such as El Malá (Carvajal et al. 2012), La Esperanza (Germano et al. 2013, 2014), El Juramento (Sierra et al. 2016), Pampa Argentina, and El Asustado (Fronza et al. 2016). The levels of deltamethrin resistance assessed in these localities were the highest found so far (RR >1000). In Pampa del Indio, another area of the Chaco province located 103 km from the abovementioned ones, reinfestation due to the presence of resistant insects (RR: from 4.47 to 11.50) was reported after initial spraying with deltamethrin (Gurevitz et al. 2012) (Fig. 2).

In summary, resistance to insecticides was demonstrated for different triatomine species in several areas of their geographical distribution in the last 20 years. This

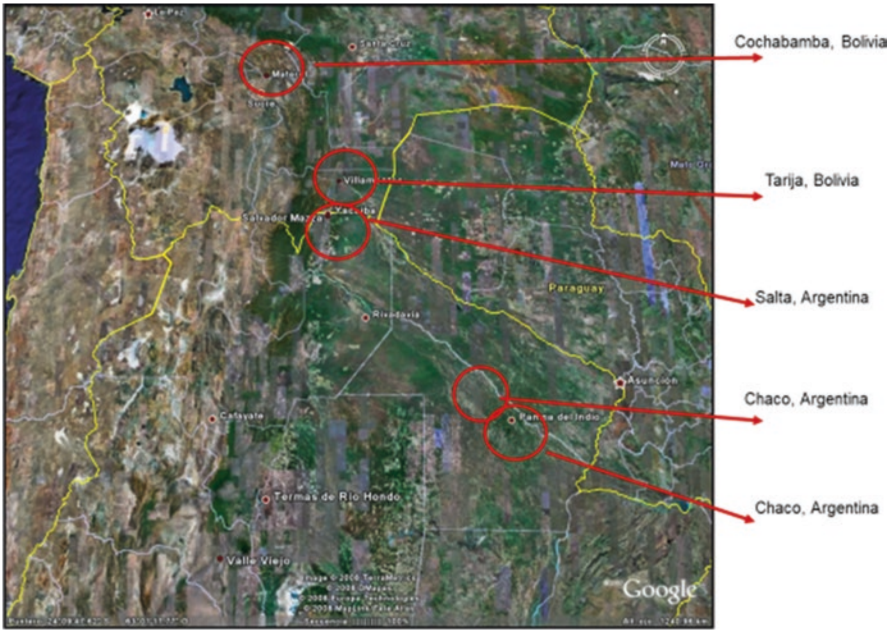

Fig. 2 Geographical distribution of high deltamethrin-resistant populations of *T. infestans* from Bolivia and Argentina
Areas where high resistance to pyrethroid insecticides was associated with ineffective field chemical treatment for *T. infestans* from Bolivia (Cochabamba and Tarija departments) and northern Argentina (Salta and Chaco provinces)

canceled the former prevailing assumption that there was a low probability of occurrence of insecticide resistance in triatomines due to an apparently low genetic variability in domiciliated species. At present, it is known that triatomine species showed rich genetic variability through its distribution range, and it has been demonstrated that this phenomenon is more widespread than was previously assumed.

3 Resistance Profiles

Several studies demonstrated that pyrethroid-resistant populations exhibit different toxicological profiles when exposed to the same chemical class. Deltamethrin-resistant *T infestans* populations from the Salta province, Argentina (Salvador Mazza, La Toma, El Chorro, and El Sauzal), were shown to be resistant to other pyrethroids (beta-cypermethrin, beta-cyfluthrin, and lambda-cyhalothrin), but not to fenitrothion (organophosphorus insecticide), bendiocarb (carbamate), or fipronil (phenylpyrazolez insecticide) (Toloza et al. 2008; Santo-Orihuela et al. 2008). Germano et al. (2012) defined three resistant profiles according to the toxicological and biochemical characteristics of resistant populations from Acambuco (Argentina) and Entre Ríos and Mataral (Bolivia). The Acambuco profile exhibited moderate deltamethrin resistance in nymphs and eggs (RR: 32.5 and 28.6, respectively) and increased detoxifying metabolism as a resistance mechanism through enhanced pyrethroid-esterase activity. The Entre Ríos profile exhibited high deltamethrin resistance (RR: 173.8) in nymphs and moderate in eggs (RR: 39.1), low resistance to fipronil (RR: 12.4), and increased pyrethroid-esterase activity. Finally, the Mataral profile exhibited low deltamethrin resistance in nymphs and eggs (RRs: 17.4 and 8.4, respectively), increased pyrethroid-esterase activity, and moderate level of resistance to fipronil. Obviously, the characterization of these three profiles does not permit the generalization of three resistance forms. Besides, different levels of susceptibility to deltamethrin and fipronil were reported for sylvatic *T. infestans* that had never been exposed to chemical control. This suggests that populations from different geographic areas have naturally different toxicological responses to insecticides (Roca-Acevedo et al. 2011; Gomez et al. 2014).

The differences in resistance profile and susceptibility to insecticides reported for field populations of *T. infestans* suggest independent evolutionary processes based on insecticide pressures, genetic variation of natural populations, and local environmental factors. It is possible to propose that insecticide pressure was not the main cause generating these profiles because vector control campaigns in the studied areas had been sparse, and fipronil was never used as triatomicide. This hypothesis was later evaluated by analyzing the effects of environmental and spraying factors on the distribution of *T. infestans*-resistant populations (Gomez et al. 2014; Fronza et al. 2019) (see Sect. 7 in this chapter).

In the search of alternatives to control deltamethrin-resistant *T. infestans*, several insecticides with different modes of action were evaluated on a highly resistant population from Chaco, Argentina (see Sect. 8 for details). As an outcome, fenitrothion and imidacloprid were found effective against both susceptible and resistant populations, becoming control alternatives (Carvajal et al. 2012). Fenitrothion formulated as wettable powder showed high effectiveness for vector field control (Zaidemberg 2012). For imidacloprid, only a spot-on formulation applied to pigeons in a laboratory bioassay was shown effective against pyrethroid-resistant *T. infestans* that fed on treated pigeons (Carvajal et al. 2014).

4 Resistance Mechanisms

Several biochemical/physiological processes modify the individual susceptibility determining the resistant phenotype; these are called resistance mechanisms. Furthermore, resistant insects can exhibit more than one of these mechanisms at same time (McKenzie 1996). These mechanisms are alterations of the toxicokinetic and toxicodynamic steps occurring during the insect- insecticide interaction which determine the degree to which the toxicant can damage the organism (i.e., the toxicity) or, what is the same, the degree to which the organism is damaged by the toxicant (i.e., the susceptibility) (ffrench-Constant 2013). Toxicokinetics describes what happens to the toxicant when it makes contact with the insect and once inside it and involves the absorption, distribution, metabolism, and excretion processes. Toxicodynamics describe the molecular interaction between the toxicant and the molecular target, also known as the site of action, which will trigger the toxic response (Hodgson and Levi 1997). The main mechanisms altering insecticide toxicity are enhanced enzymatic detoxification, altered target sites, and reduced cuticular penetration. The three mechanisms have been described for triatomine pyrethroid-resistant populations (Mougabure-Cueto and Picollo 2015).

Enhanced Detoxification Insects have evolved various detoxification mechanisms to survive to natural toxins. These mechanisms can allow them to overcome insecticides by a rapid enzymatic detoxification. Pyrethroids are mainly cleaved by monooxygenase activity and esterase-mediated hydrolysis. Monooxygenase or P450 enzyme activity leading generally to a detoxification of the molecule can be involved in the metabolism of virtually all insecticides. Esterases deserve main attention because they can hydrolyze ester bonds present in chemicals that are extensively used by vector control programs (Roush and Tabashnik 1990; McKenzie 1996). For some insects, detoxification is so active that the insecticide does not reach its molecular target before being metabolized and degraded by the enzymes.

Increased monooxygenase and pyrethroid-esterase activity was assessed in pyrethroid-resistant *T. infestans* populations from the Salta and La Rioja provinces of Argentina and in the Yacuiba department of Bolivia (Santo-Orihuela et al. 2008). This increased enzymatic activity allows insects a faster breakdown of the insecticide to nontoxic compounds. Enhanced insecticide metabolization was also demonstrated for late developing embryos of these resistant populations. The most significant increase in enzymatic activity was observed for pyrethroid esterase, which grew steadily throughout the embryonic development of both susceptible and resistant populations, even though being always higher in resistant embryos (Roca-Acevedo et al. 2013, 2015). Recently, Grosso et al. (2016), Traverso et al. (2017), and Dulbecco et al. (2018) showed overexpression of P450 genes belonging to the CYP4 clade in deltamethrin-resistant *T. infestans* from Argentina. However, it is worth to mention that both inhibiting the detoxifying enzymes and RNAi-mediated gene silencing of CYP4s led to slight increases or did not affect the susceptibility to deltamethrin of resistant insects, suggesting a secondary role for these enzymes in mediating resistance (Picollo et al. 2005; Dulbecco et al. 2018).

Target-Site Modifications Altered target site is another mechanism conferring pyrethroid resistance in triatomines. Pyrethroids exert their insecticidal action on the insect nervous system by modifying the normal function of voltage-gated sodium channels in the membranes of neurons. In resistant insects, these effects on the nervous system are reduced due to the presence of point mutations in the sodium channel gene. Most resistance-conferring mutations affecting voltage-gated sodium channels are located in domain II of this protein, particularly the region between transmembrane segments IV and VI (IIS4-IIS6 region) (Soderlund and Knipple 2003).

Fabro et al. (2012) cloned and sequenced the domain II of the *T. infestans* sodium channel based on the sequence of this domain in the *Rhodnius prolixus* para sodium channel. Thus, the presence of a resistance-conferring mutation (L1014F) was identified in a deltamethrin-resistant population (RR: 35.7) of Madrejones, a small locality of Salta province of Argentina. Later, a different new pyrethroid resistance-conferring mutation (L925I) was identified in a deltamethrin-resistant population of Mala, a small locality of the Chaco province of Argentina (RR: 1031). Interestingly, and unlike the L1014F mutation described for many insect species belonging to different orders, the L925I mutation seems to be exclusive of hemipterans (Capriotti et al. 2014). Recent studies demonstrated that both mutations were associated with two geographically differentiated foci of *T. infestans*-resistant populations: those on the Argentina-Bolivia border carrying L1014 mutation and those from the Argentinian Chaco province carrying L925I mutation (Sierra et al. 2016).

Reduced Cuticle Penetration The integument covers the insect externally. It is formed by the cuticle and the epidermis, playing essential protection roles to avoid desiccation, mechanical injury, and toxins. Indeed, the cuticle is the first and major barrier that insecticides should penetrate to reach target sites.

Penetration resistance refers to cuticular alterations that reduce the entry rate of toxic compounds within the insect body. This can be effected through either modifying the composition of the cuticle or increasing its thickness. These mechanisms prevent or delay reaching toxic levels of insecticide molecules at the target site in the nervous system. Moreover, the reduced rate of penetration allows detoxification enzymes more time to act multiplying their effectiveness in the degradation of the toxic compound (Roush and Tabashnik 1990).

Two mechanisms have been described to explain penetration resistance in triatomines, cuticular thickening and altered cuticular composition (Pedrini et al. 2009). In fact, the cuticle of *T. infestans* fourth-instar nymphs of deltamethrin-resistant populations from Salta and Chaco provinces (Argentina) was significantly thicker. The cuticle width revealed by scanning electron micrographs (SEM) of transversal sections of the second abdominal tergite was 32.1+/−5.9 micrometers and 17.8+/−5.4 micrometers for pyrethroid-resistant and pyrethroid-susceptible insects, respectively. Moreover, these resistant populations had an impressive increase in the amount of cuticular hydrocarbons (CHCs), 50% more CHCs, revealed by capillary gas chromatography coupled to mass spectrometry analyses. Since HC-free cuticles were more susceptible to insecticide penetration, it was proposed that CHC enrichment would delay the uptake of pyrethroids through the cuticle.

Although most of the detoxification metabolism of insects is considered to occur in the fat body, new members of the cytochrome P450 gene family (*CYP*) that belong to the highly genome-wide expanded *CYP3093A* and *CYP4EM* subfamilies were recently described in the integument of *R. prolixus* and *T. infestans.* A suite of CYP4-clan genes was overexpressed (1.7–3.8-fold) in the integument of deltamethrin-resistant *T. infestans* nymphs (*CYP3093A11* and *CYP4EM10*), as was evidenced by the biochemical determination of increased activity of the ethoxycoumarin-O-deethylase. These studies suggested a cytochrome P450-based detoxification role of the integument in the deltamethrin-resistant insects (Dulbecco et al. 2018).

In summary, after more than two decades of studies, resistance to insecticides in triatomines is known to occur by a multiplicity of physiological-biochemical mechanisms that can act in an overlapping manner (i.e., enhanced metabolism, modified site of action, and reduced penetration).

5 Inheritance and Genetic Basis of Insecticide Resistance

The individual susceptibility is the expression of multiple biochemical and physiological processes that occur during the toxicokinetic and toxicodynamic phases of the insect-insecticide interaction, each one determined by genetic and environmental factors (Mougabure-Cueto and Sfara 2016). Due to variation in these factors, individual susceptibility is randomly distributed among the individuals of a population. This distribution is expressed as a symmetric sigmoid curve when the proportion of responding individuals (dead) is plotted against insecticide dose, i.e., the cumulative normal distribution of susceptibility (Hewlett and Plackett 1978). It is on the genetic variation that underlies the distribution of susceptibility where the insecticide selection pressure operates. The consequence is a shift of the dose-response curve toward higher doses. If the active dose of insecticide falls within this distribution, a polygenic-based resistance is expected because the selected individuals are part of a distribution partially determined by many genes (i.e., the most likely scenario in laboratory selection). On the other hand, if the dose of insecticide is higher than the maximum dose of the susceptibility distribution, the resistance is expected to be determined by one or a few genes because the selected individuals probably carry rare mutations that places them outside the original distribution (i.e., the most likely scenario in field selection) (McKenzie 1996; ffrench-Constant 2013).

Cardozo et al. (2010) showed that the resistance of insects from Salvador Mazza (Argentina) would be controlled by more than one gene and, presumably, at least three. This is consistent with the studies described above (see Sect. 4 in this chapter) that showed that different resistance mechanisms (i.e., two families of detoxifying enzymes, two mutations in the sodium channel, and alterations in the cuticle) were present in *T. infestans* even within the same population, which shows that resistance to deltamethrin is determined by more than one gene. Moreover, Cardozo et al. (2010) and Germano et al. (2010b) showed that deltamethrin resistance in *T. infestans* is an autosomal and incomplete dominant character. Finally, Bustamante Gomez et al. (2015) showed that the resistance ratio increased more than 20 times in 2 generations after selection with deltamethrin and estimated a realized heritability (h^2) equal to 0.37, suggesting that resistance is an additive and cumulative factor.

6 Pleiotropic Effects of the Insecticide Resistance

The genetic alterations that generate the individual resistance to an insecticide can have pleiotropic effects on different physiological processes (other than the toxicological processes involved as resistance mechanisms) with possible consequences at ecological and evolutionary levels (McKenzie 1996; Kliot and Ghanim 2012). In addition, in vector insects, these effects can have direct consequences on disease transmission by modifying the vectorial capacity of the insect (Rivero et al. 2010). Pleiotropic effects can occur due to a detrimental modification of physiological processes involving genes that carry resistant mutations or genes linked to them or by the maintenance of the resistant phenotype that reduces the energy available for other processes (Rivero et al. 2010; Kliot and Ghanim 2012). The pleiotropic effects may be selectively neutral or may have positive or negative consequences with respect to the adaptation of the resistant insects to the natural environment (i.e., without the toxicant) (Mougabure-Cueto and Picollo 2015). The negative consequences are those that are more likely to be represented in a resistant population and are referred to as biological or adaptive costs of resistance, while positive consequences are involved in the evolution of tolerant populations as adaptations (Lobbia et al. 2018). In addition to the evolutionary implications, this comparison in adaptive terms has a practical importance for vector control and resistance management strategies. In the case of adaptive costs, the proportion of resistant insects is expected to decrease when chemical control is discontinued. Alternatively, it is not expected to decrease when pleiotropic effects are adaptively positive (Mougabure-Cueto and Picollo 2015).

The few studies comparing the performance of different biological processes between susceptible and resistant triatomine phenotypes were carried out on pyrethroid-resistant *T. infestans* from Argentina. Germano and Picollo (2015) investigated possible modifications in the ontogenetic development and reproductive potential of resistant insects from Aguaray village (Salta province, Argentina). The study demonstrated reproductive costs, expressed as a lower fecundity, and developmental alterations, expressed as shorter second and third nymph stages and a larger fifth stage. The authors also suggested a maternal effect since these alterations were observed in resistant females and their progeny regardless of the toxicological phenotype of the male. Lobbia et al. (2018) studied the alterations in the excretion/defecation pattern in resistant *T. infestans* from La Rinconada and El Asustado villages located in the high resistance focus of the Chaco province (Argentina). The resistant insects began to defecate later, defecated less, and showed a lower proportion of defecating individuals compared with susceptible insects during the first hour after feeding. The authors suggested that the alterations could generate an adaptive cost in the natural environment and that the resistant insects would have a lower vector competence than susceptible ones. Lobbia et al. (2019a) studied the effect of resistance on the reproductive efficiency after dispersal in *T. infestans* from El Asustado village (Chaco province, Argentina). In non-dispersed control insects, the resistant females showed lower reproductive efficiency than susceptible females.

However, the dispersed resistant females showed a higher reproductive efficiency compared to the dispersed susceptible females and compared to the non-dispersed resistant females. The authors suggested that the resistant insects probably carry an adaptive cost when both toxicological phenotypes do not disperse but, if both phenotypes disperse, the resistant insects would have an adaptive advantage over the susceptible ones. Finally, Lobbia et al. (2019b) investigated the effect of resistance on the dispersal capacity of *T. infestans* from El Asustado village (Chaco province, Argentina). The resistant insects showed a lower number of dispersal events, a lower proportion of dispersed individuals, and less exit and entry events from/to experimental shelters. This lower dispersal capacity associated with the resistance could reduce the colonization and reinfestation capabilities and possibly the relevance of the resistant insects as vectors.

The insects studied in the latter reports came from the Argentine Chaco ecoregion. Therefore, the evolution of resistance in this region might be associated with a complex expression of pleiotropic effects of genes that confer resistance or genes linked to them (Lobbia et al. 2019b). This scenario could be explained in part by the multiple resistance mechanisms detected in the different resistant foci (Germano et al. 2012; Mougabure-Cueto and Picollo 2015; Sierra et al. 2016).

7 Environmental Factors Associated with Insecticide Resistance

As emerges from the definition, insecticide resistance evolves as a consequence of the continued use of insecticides. The insecticide is the main determinant, acting as a selection agent. However, environmental variables, both from the natural environment and associated with anthropic activities, may influence the evolution of resistance. Variables that affect the effectivity of the insecticide will determine the position of the dose used in the dose-response curve (i.e., the proportion of individuals of the population that is affected by the insecticide). Thus, this will determine the intensity of selection pressure. This context frames the possible role of the peridomestic structures of the rural dwellings in the evolution of insecticide resistance in triatomines. The intricate construction and diverse materials used for these structures hinder the uniform application of the insecticide, exposing insects to variable doses. Besides, due to their presence in open air, the surfaces of these structures expose insecticide molecules to degradation by light and heat (Cecere et al. 2004; Gürtler et al. 2004). In this way, the effective dose of an insecticide decays rapidly, allowing the survival of less susceptible individuals and the evolution of resistance (see Sect. 5). This scenario is different from what happens in the intradomicile. There, the insecticide lasts longer in its optimal dose (i.e., lethal for 100% of the susceptible individuals) and would only select the individuals located outside the natural distribution of susceptibilities of the population, if they were present (Mougabure-Cueto and Picollo 2015; Fronza et al. 2019). Thus, it is possible that toxicological heterogeneity exists between both environments of a dwelling. The only study that compared *T. infestans* from domestic and peridomestic areas found no statistical association between toxicological status (resistant vs. susceptible) and original location of the insects (Germano et al. 2013).

In addition to their effect on the insecticide selection regime, environmental variables might be directly involved in a process related to the evolution of resistance: the evolution of tolerance to insecticides. Some environmental variables could select individuals carrying certain phenotypic attributes not involved with the interaction with the insecticide but determined by genes that simultaneously confer individual resistance or that are linked to resistant genes. In this situation, the frequency of resistant insects would increase in the natural environment without insecticide resulting in a population with low natural susceptibility, i.e., a tolerant population. The low susceptibilities to pyrethroids and the phenylpyrazole fipronil shown by sylvatic populations of *T. infestans* from Bolivia (Roca-Acevedo et al. 2011; Depickère et al. 2012; Gomez et al. 2014) have been interpreted as an indication of the existence of naturally tolerant populations (Roca-Acevedo et al. 2011; Mougabure-Cueto and Picollo 2015).

The evaluation of relative roles for environmental factors and variables linked to spraying with insecticides (e.g., frequency, coverage, etc.), as well as their possible interaction, has received little attention in studies about the evolution and distribution of resistance in triatomines. Bustamante Gomez et al. (2016) and Fronza et al. (2019) have studied whether environmental variables show an association with the distribution of pyrethroid-resistant *T. infestans* populations. Bustamante Gomez et al. (2016) carried out a bibliographic review of studies reporting pyrethroid resistance in the latter species and showed that resistance is a localized event associated with a combination of variables linked to temperature and precipitation in the area of the border between Argentina and Bolivia. The model developed by the authors allowed to describe the potential distribution of highly resistant populations, but did not detect 5 out of 13 populations in the department of Güemes from Chaco province (Argentina), the area where the highest resistance levels were reported for *T. infestans* (Carvajal et al. 2012; Sierra et al. 2016, Fronza et al. 2016). Alternatively, Fronza et al. (2019) focused their study on this area of very high resistance and high toxicological heterogeneity. These authors included bioclimatic statistics and information on chemical control actions as explanatory variables and showed that three indicators of temperature and precipitation are good descriptors for insecticide resistance. Furthermore, their models increased their explanatory power when village-size variables were added. The spraying variables did not contribute to explain toxicological heterogeneity, possibly due to the fact that the pressure with insecticides in the area had been homogeneous and executed with low frequency. The authors proposed that the environmental variables explain part of the resistance distribution because they modulate the selection pressure exerted by the insecticide (e.g., the temperature modifying the toxicity of pyrethroids and the precipitation affecting the availability of insecticide).

8 Management of Insecticide Resistance

The evolution of insecticide resistance leads to the failure of previously successful chemical control strategies. Therefore, resistance management strategies must be implemented. The main goal of these strategies is to initially detect resistance at the lowest level possible and interrupt the ongoing selection process. A complete resistance management strategy should monitor the toxicological profile of populations under chemical control, identify resistance mechanisms, develop alternative control strategies (i.e., alternative insecticides, biological control, etc.), and study the biological process underlying the evolution of resistance (i.e., population structure, dispersal capacity, costs of resistance, etc.) (Mougabure-Cueto and Picollo 2015). Before resistance reaches a level leading to field failures, and even before knowing the existence of resistance, the so-called resistance prevention tactics can be implemented (e.g., rotation of insecticides, use of refuges for susceptible individuals, etc.) (McKenzie 1996). However, such strategies only work if resistance genes are present in the population; if there are no resistance genes, their implementation is meaningless. These tactics are, in fact, methods that interrupt or delay the selection process, avoiding increases of the resistance level of the population.

The management of insecticide resistance in triatomines is determined and conditioned by their role as disease vectors and by the biological, social, cultural, and operational characteristics associated with Chagas disease and its control. The use of strategies that maintain susceptible individuals in the population is hampered because triatomines transmit a pathogen causing a human disease. The shortage of insecticides and formulations for the control of Chagas disease vectors does not allow the implementation of strategies such as molecule rotation or the use of mixtures of insecticides that belong to unrelated chemical classes. On the other hand, effective alternatives to the spraying of dwellings with residual insecticides have not yet been developed and implemented on a large scale. However, four main tools could be effective in controlling pyrethroid-resistant insects: (1) insecticide treatment of domestic animals acting as food sources for triatomines (Reithinger et al. 2005, 2006; Gürtler et al. 2009; Amelotti et al. 2009a, b, 2012; Juan et al. 2013; Carvajal et al. 2014; Dadé et al. 2014, 2017); (2) use of insecticidal paints based on microencapsulated formulations containing organophosphates or pyrethroids, together with an insect growth regulator (Dias and Jemmio 2008; Amelotti et al. 2009b; Alarico et al. 2010; Maloney et al. 2013); (3) entomopathogenic fungi, like *Beauveria bassiana*, as biological control agents (Luz et al. 1999, 2004; Pedrini et al. 2009; Forlani et al. 2011; Zumaquero-Rios et al. 2014); and (4) traps that combine structures that allow insects to enter but hinder their exit with physical or chemical stimuli that attract insects to such structures (Guerenstein et al. 1995; Guidobaldi and Guerenstein 2013; Mota et al. 2014). In turn, these baited traps can be combined with adhesive surfaces, insecticides, or some natural enemy so that they exert a control action (Pedrini et al. 2009). Future research is needed to assess the effectiveness of these alternatives on a large scale, as well as their safety to humans and the domestic and natural environment.

The organophosphates fenitrothion and malathion, and the carbamate bendiocarb (acetylcholinesterase inhibitors), are the current effective alternatives for the control of resistant foci of *T. infestans* in the context of traditional chemical control. In particular, resistant foci in Argentina have been controlled with fenitrothion or malathion (Zaidemberg 2012; Gurevitz et al. 2012; Germano et al. 2014), while bendiocarb was mainly used in Bolivia (Programa Nacional de Chagas 2009). However, the toxicological risk of these insecticides (greater than that of pyrethroids) and the quality and receptivity of their formulations by residents are the main reasons that promote the search for alternative insecticides. Several non-pyrethroid insecticides from different chemical groups have been evaluated on susceptible and deltamethrin-resistant *T. infestans* in laboratory assays. Amitraz (octopamine receptor agonist), flubendiamide (ryanodine receptor modulator), ivermectin (chloride channel activator), indoxacarb (voltage-dependent sodium channel blocker), and spinosad (nicotinic acetylcholine receptor allosteric activator) showed no lethal activity on either susceptible or resistant populations at the doses tested (Carvajal et al. 2012). Fipronil (GABA-gated chloride channel blocker) showed high activity against resistant populations from Argentina but was not effective against resistant populations from Bolivia (Toloza et al. 2008; Germano et al. 2010b). Finally, imidacloprid (nicotinic acetylcholine receptor agonist) showed high toxic potency against susceptible and resistant *T. infestans* (Carvajal et al. 2012). The latter results promote the development of an adequate formulation for Chagas vectors and its evaluation under field conditions.

In summary, current triatomine control is based on spraying pyrethroid insecticides (e.g., deltamethrin), mainly formulated as suspension concentrates, as long as no resistant foci are detected. As soon as a systematic pyrethroid application is implemented in an area, the toxicological (i.e., tracking the evolution of resistance) and genetic (i.e., determining the field frequency of resistant alleles) monitoring of bug populations are necessary actions that allow the detection of resistance in early stages of evolution and change the scenario in time. When resistant insects are detected, fenitrothion (as wettable powder), malathion (as emulsifiable concentrate), and bendiocarb (as wettable powder) are, at the moment, the available options for *T. infestans*. Finally, it is always necessary to emphasize that house improvement and environmental management, including that of domestic animals and their shelters, are extremely relevant and needed. The great positive impact of these practices on the life standards of rural populations greatly exceeds the control of Chagas vectors. In the context of the control of triatomines, the integrated implementation of these actions with the rest of the tools available (e.g., chemical control), respecting the diversity of cultural practices of the American continent, will improve the outcomes of control programs as well as reduce the environmental impact of insecticides.

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