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RESEARCH

Regionality in vector control: effect of fluctuating temperature in the susceptibility of *Aedes aegypti* (Diptera: Culicidae) larvae to Pyriproxyfen

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Abstract

Using Pyriproxyfen in controlling *Aedes aegypti* shows great potential considering its high competence in low dosages. As an endocrine disruptor, temperature can interfere with its efficiency, related to a decrease in larval emergence inhibition in hotter environments. However, previous studies have been performed at constant temperatures in the laboratory, which may not precisely reflect the environmental conditions in the field. The aim of this study was to assess the effect of the fluctuating temperatures in Pyriproxyfen efficiency on controlling *Aedes aegypti* larvae. We selected maximum and minimum temperatures from the Brazilian Meteorological Institute database from September to April for cities grouped by five regions. Five fluctuating temperatures (17–26; 20–28.5; 23–32.5; 23–30.5; 19.5–31 °C) were applied to bioassays assessing Pyriproxyfen efficiency in preventing adult emergence in *Aedes aegypti* larvae in five concentrations. In the lowest temperatures, the most diluted Pyriproxyfen treatment (0.0025 mg/L) was efficient in preventing the emergence of almost thrice the larvae than in the hottest temperatures (61% and 21%, respectively, p value = 0.00015). The concentration that inhibits the emergence of 50% of the population was lower than that preconized by the World Health Organization (0.01 mg/L) in all treatments, except for the hottest temperatures, for which we estimated 0.010 mg/L. We concluded that fluctuating temperatures in laboratory bioassays can provide a more realistic result to integrate the strategies in vector surveillance. For a country with continental proportions such as Brazil, considering regionalities is crucial to the rational use of insecticides.

Keywords Fluctuating temperatures · Insect growth regulators · Thermal condition · Culicidae · Pyriproxyfen

Introduction

Arboviruses transmitted through the bite of infected *Aedes* (*Stegomyia*) *aegypti* (Linnaeus 1762) are still a huge public health concern, especially in tropical and subtropical regions. As a fast-growing mosquito-borne viral disease, dengue fever is one of the most frequent infections throughout the tropics and has been considered endemic in Brazil since 1986, when serotype 1 was introduced in the country (Mayer et al. 2017; Luna et al. 2020). Colón-González et al. (2021) estimated that the incidence of dengue fever alone increased 30-fold in the last 50 years.

The dynamics of mosquito-borne illnesses are climatic driven, and recent work suggests that increasing global temperatures will allow the expansion of *Aedes aegypti* into temperate regions and dramatically increase *Aedes*-borne virus transmission within the next century (Caldwell et al. 2021; Ryan et al. 2019, 2021). There are no medical treatments or specific medications for diseases transmitted by this mosquito, and the prevention through vaccination is accessible only for urban yellow fever (Rodhain 2022). Although there is a prospect of an effective and accessible dengue vaccine in the mid-term future, *Ae. aegypti* will continue to be a threat to public health due to the possibility of transmission of other arboviruses such as CHKV (Chikungunya virus) and ZKV (Zika virus) (Wilder-Smith 2022). Furthermore, Teixeira et al. (2021) described that *Ae. aegypti* mosquitoes can be simultaneously infected by both dengue and Zika virus. Therefore, the control

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of mosquito populations through mechanical removal of potential breeding sites associated with the application of insecticides as a supplementary measure are still important tools to prevent epidemics.

The conventional programs to control the populations of mosquito vectors mostly depend on a combination of measures such as detection of the targeted mosquito population, surveys on disease incidences, prediction of their dispersal, and populational control, for anticipating future outbreaks (Nayak et al. 2023). Additionally, there is a growing recognition that the solutions to control such arbovirus transmission surpass the health sector and rely on a diversity of structural actions, such as adequate sewage treatment, effective waste management programs, and water supply maintenance, along with community participation (Valle et al. 2019).

Given the many difficulties in guarantee the efficiency of an insecticide application, controlling the insect in its immature phases (egg, larva, and pupa) is more feasible, given that the development occurs in restricted and specific locations, unlike the adult phase, which can disperse throughout various environments and can escape from an insecticide dose (Campos et al. 2020). However, the continuous and intensive application of a compound can lead to the development of resistant mosquito populations, considering that the larvicide presents evolutive pressure in the environment for the individuals exposed. A sustainable and effective chemical control strategy must be based on detailed planning considering the mosquito populational distribution, the species susceptibility to compounds, and possible mechanisms involved in resistance selection, in order to decrease vector infestation and prevent epidemics (Roush 1989).

In Brazil, insecticide resistance in *Ae. aegypti* populations was detected for different compounds applied to temephos (organophosphate) and deltamethrin (pyrethroid) (Valle et al. 2019). The intense application of temephos between 2003 and 2014 is worth noting, showing the relation between long time exposition and resistance development in *Ae. aegypti* mosquito populations (Rahman et al. 2021). Currently, temephos resistance is so widespread in Brazil that this compound is no longer considered as the first choice larvicide for use against *Ae. aegypti*, and it has been replaced by other, non-neurotoxic products (Valle et al. 2019).

To strategically avoid the development of resistance to insecticides, the Brazilian Ministry of Health (MoH) adopted a larvicide rotation approach, changing the compound applied every 4 years (SVS 2012). Between 2014 and 2018, MoH deliberated the application of Pyriproxyfen to control *Ae. aegypti* larvae. Pyriproxyfen is a non-neurotoxic compound, classified within the insect growth regulator (IGR) class of insecticides. Pyriproxyfen is a juvenile hormone analog that acts inside the organism preventing the molting into the adult stage, causing death as a consequence of this endocrine disruption.

As a larvicide, Pyriproxyfen shows great efficiency in laboratory and semi-field settings demonstrating high emergence inhibition for larvae exposed to low concentrations (Vythilingam et al. 2005; De resende and Gama 2006; Lau et al. 2015; Samuel et al. 2017; Marina et al. 2018; Campos et al. 2020; Hustedt et al. 2020; Fansiri et al. 2022; Asgarian et al. 2023; Campos et al. 2023; Moura et al. 2023). However, environmental factors known to interfere with the developmental aspects of the larvae (e.g., temperature, organic matter loads, pH) can also affect the larvicide efficiency, considering its mode of action as a non-neurotoxic compound (Carrington et al. 2013a, 2013b; Ohashi 2017; Durant and Donini 2018; Talaga et al. 2020; De nadai et al. 2021; Huzortey et al. 2022). Considering the impacts of temperature, insect responses to fluctuating temperatures contrast with responses to constant temperature at multiple levels of organization, from physiology and stress tolerance to life history traits and fitness (Colinet et al. 2015). Previous research testing insecticide susceptibility in field populations of mosquitoes has demonstrated that there is seasonal variability in sensitivity, suggesting that environmental interference is important to mosquito control programs (Hernandez et al. 2022). Considering this, few previous studies have addressed the impact of fluctuating temperature in response to insecticides (Salinas et al. 2021). Given that the mode of action of Pyriproxyfen is directly related to the development during immature stages, the fluctuating temperatures could interfere with its efficiency. On an indirect way, the temperatures directly influence the development rate of the larvae and so, consequently, reflect into the time of exposure. On the other hand, a direct effect could be related to detoxification through heat shock proteins expression to survive a Pyriproxyfen exposure (Ware-Gilmore et al. 2023). However, none of these possible effects has been tested yet, and given a climate changing world, it is crucial to understand all effects that different temperatures could pose to this important vector.

Given the continental proportions of Brazilian territory, with an area comprising 8.516.000 km^2, fluctuations of temperature follow distinct patterns in different regions. This, in turn, produces different temperature fluctuations in daily cycles, as a response to climatic factors (e.g., latitude, vegetation, and continentality). We hypothesized that different patterns of temperature fluctuation grouped by Brazilian regions produce differences in Pyriproxyfen susceptibility to *Ae. aegypti*. In this study, we report the differences in susceptibility of *Ae. aegypti* larvae exposed to Pyriproxyfen under simulated daily temperature ranges.

Materials and methods

Regional temperatures

We tested the effect of temperature on *Ae. aegypti* susceptibility to Pyriproxyfen combining five concentrations of the larvicide and two different temperatures, one designed for the day cycle and the other for the night cycle to simulate natural conditions of daily temperature regimes. The temperatures were based on registers from automatic meteorological stations provided by the Brazilian Meteorological Institute database (INMET - National Institute of Meteorology 2020). We selected the capital city of each state plus three cities through simple random sampling. Afterwards, we chose the records of maximum and minimum temperatures from 1988 and 2018 of all the cities. After the sampling, we selected the time horizon from September to March for the calculations, comprising the spring and summer months in Brazil. The location of the cities sampled for the calculations can be seen in Online Resource 1. We calculated the mean value of both maximum and minimum temperatures grouped by region. The mean maximum and minimum temperatures for each region were programmed for light and dark cycles of the experiments, respectively (Table 1).

The experiments were conducted inside incubator chambers (Eletrolab®, Model EL212/4LED) with a light/dark cycle of 14/10 h.

Larval rearing

To investigate the efficiency of the compound under the fluctuating temperatures and prevent the interactions with the susceptibility status of local mosquito populations, we conducted the experiments with a susceptible reference strain of *Ae. aegypti.* We used a Rockefeller strain from a laboratory population established since 1996 (ASR – Analytical and Scientific Research Laboratory®) provided by eggs attached to porous paper. We stored the mosquito eggs inside plastic boxes at room temperature (26 °C ± 2) and a relative humidity of 70% (± 5). To stimulate egg hatching, we immersed 1 cm^2 of the paper containing the eggs in 1 L of tap water and 1 g of *Saccharomyces cerevisiae* (MP Biomedicals, France). After 24 h, we separated batches of 20 I instar larvae to avoid effects of intraspecific competition (Steinwascher 2020). We placed the larvae into new plastic vessels containing 250 mL of tap water with 64 mg of *S. cerevisiae* added as a nutritional source (Souza et al. 2019). The batches of larvae were maintained inside an incubator chamber (Eletrolab®, Model EL212/4LED) until they reached late III instar under the temperature regimes of the experimentation interest, considering the region to be simulated (photoperiod 14:10 light:dark, considering a high temperature for the light cycle and a low temperature for the dark cycle). We have chosen the light:dark cycle of 14:10 to simulate the higher sunlight exposition that is typical of the spring and summer in tropical areas (Costanzo et al. 2015). Every 2 days, we added a new nutritional source (64 mg of *S. cerevisiae*) until larvae reached III instar. The larvae were kept at the chosen temperature regimes from first to last instar, to avoid thermal stress which could interfere with the results.

Table 1 Information about the temperatures used in the larval bioassay

Region	Temperature (°C)	
	Minimum	Maximum
Central-West	19.5	31
Northeast	23	30.5
North	23	32.5
Southeast	20	28.5
South	17	26

Insecticide formulation

We utilized Sumilarv 0.5G® (CAS #95737–68-1), gently donated by the Epidemiological Surveillance of Araraquara (São Paulo, Brazil), for the experiments. Sumilarv 0.5G® is synthesized by Sumitomo Chemical (Tokyo, Japan) containing 0.5% active ingredient (weight:weight) in a granular formulation. Sumilarv 0.5G® has a slow-release formulation due to its constitution with pumice and sand as main solutes (Sumitomo Chemical 2012).

Larval bioassay experiments

We prepared a stock solution with Sumilarv 0.5G® following the methodology

described by Sihuincha et al. (2005) and Moura et al. (2021). The final concentrations derived from the stock solution were 0.0025, 0.005, 0.01, 0.02, and 0.04 mg/L, comprising lower and higher concentrations based on the WHO recommendation for *Ae. aegypti* control programs (0.01 mg/L) (WHO 2005, 2016).

For each concentration, we prepared five replicates containing 250 mL into 500 mL beakers and 20 III instar larvae, based on the WHO protocol (WHO 2016). We provided 64 mg of *S. cerevisiae* for each beaker. Simultaneously, five replicates of beakers with 250 mL of tap water and the same amount of yeast containing 20 larvae each were used as the control experiment. The control experiment beakers were kept under the same conditions of the experiments, under fluctuating temperatures accordingly with the Brazilian region. All beakers were covered with netting to prevent

emerged adults from escaping. We repeated the experiments five times on different days, using new stock solutions and new batches of larvae each day. We monitored the survival by counting and removing dead larvae and pupae daily until complete emergence of the adults in the control experiment beakers. During the daily monitoring, we changed the position of the beakers inside the incubator chamber to reduce the likelihood of a position effect (Gutiérrez et al. 2020).

Data analysis

After the larval bioassay experiments, we treated the data concerning the number of individuals that did not reached adult stage as the main response variable. The number of dead larvae and pupae, registered daily for each replicate, was considered to calculate the percentage of emergence inhibition in each treatment. The experiments were considered valid when the larval mortality in control experiments was below 10% (WHO 2016). We then calculated the descriptive statistics of the emergence inhibition for each thermal condition and the mean time of exposure, using the software Origin (Origin (Pro), Version 2022. 2017).

To test the normality of data, we applied the Shapiro-Wilk test (considering $\alpha = 0.05$). A two-way analysis of variance (ANOVA) was used to test whether Pyriproxyfen has reduced efficiency in warmer and more stable thermal variations using Statistica software (TIBCO 2023). In this analysis, we also tested whether longer times of exposure of larvae in Pyriproxyfen are significantly related to an increase in the larvicide efficiency. In addition, we used the Tukey post hoc test to proceed with multiple comparisons between the concentrations in each thermal simulation. All statistical tests were used considering a 95% confidence interval. The concentration that inhibits the emergence of 50% of the larvae population (EI_{50}) for each thermally simulated region was estimated by fitting log-logistic models to the data. After a model fitting procedure based on the maximum likelihood method, the three-parameter log-logistic model was applied to emergence inhibition dose-response data. The EI_{50} was estimated for each thermal condition with the "estimate_EC50()" function from the package "ec50estimator" with the R software (Alves 2022; R Core Team 2021).

Results

Development time variations of *Aedes aegypti* in different thermally simulated regions

In general, in lower temperature conditions, the larvae took longer to develop into an adult stage in the control experiments, and therefore the time of exposure in treatments with Pyriproxyfen was also longer (Table 2). The colder condition, corresponding to the South region of Brazil, presented the longer time of exposure of 10.5 days on average. On the other hand, the thermal simulation for the Northeast region of Brazil presented the shortest duration for the experiments, with 5 days of larval exposure to Pyriproxyfen.

Table 2 Quantification of larvae exposed and the duration of the bioassays in each experimental condition

Region simulated	Number of larvae exposed	Experimental days (mean)	Standard deviation
Central-West (19.5–31 °C)	400	7	1.6
Northeast (23–30.5 °C)	400	5	0.95
North (23–32.5 °C)	300	8.2	0.8
Southeast (20–28.5 °C)	300	8	1.3
South (17–26 °C)	300	10.5	2.19

Table 3 Analysis of variance (two-way ANOVA) test results for both temperatures (regions) and duration of the experiment ($\alpha = 0.05$)

Effect	SS	Degrees of freedom	MS	*F*	*p* value
Intercept	110.6	1	110.6	1807.25	0.000
Region	3.28	4	0.82	13.43	0.000
Duration of the experiment (days)	1.62	7	0.23	3.80	0.0005
Error	27.35	447	0.06		

Pyriproxyfen regional efficiency

Among the combinations of temperature applied in the bioassays, we found that the efficiency of the larvicide increased significantly with the exposure time. We also found that there was a significant difference in Pyriproxyfen efficiency between the regions thermally simulated (Table 3).

For the South region that was simulated thermally, the larval sensitivity to Pyriproxyfen was high even in lower concentrations, for which we found an emergence inhibition of 60% of the population tested. In the experiments simulating the Southeast region, the emergence inhibition was significantly higher in a dose-dependent model, but there was no evidence that the emergence inhibition was different for exposure to 0.01 and 0.02 mg/L ($p = 0.9013$). In addition, the emergence inhibition in 0.01 and 0.02 mg/L was higher than 80% of the population of larvae exposed which represents an increase in efficiency of 37% from the emergence inhibition to a concentration two times lower. Regarding the simulation for the Central-West region of Brazil, the larval sensitivity was lower in all concentrations,

except for the highest (0.04 mg/L). Given the simulation in the North region, the emergence inhibition of the larvae exposed to 0.02 mg/L is significantly higher than in 0.005 mg/L ($p = 0.012403$). The same relation was observed in the Northeast thermal simulations, shown in Fig. 1.

Analyzing the multiple comparisons with Tukey's post hoc test, we found that the conditions simulated for the South region exhibited the highest sensitivity to 0.0025 mg/L of Pyriproxyfen than in other conditions ($p < 0.01$ in all comparisons). On the other hand, larvae exposed in the Central-West thermal conditions showed significant reduced sensitivity to 0.0025 mg/L of the compound (21% of emergence inhibition, $p < 0.01$). We observed the same pattern for the 0.005 mg/L exposition, showing evidence of significantly higher emergence inhibition for the larvae in South thermal conditions than in the Central-West ($p < 0.01$). For the concentration recommended by the WHO (2016), we observed that at least 50% of the population had its emergence inhibited by Pyriproxyfen exposition in all the conditions tested (Fig. 2). However, we found evidence that emergence inhibition in the Southeast conditions was significantly higher than Central-West and Northeast ($p = 0.001$ and 0.04, respectively). In the two highest concentrations (0.02 and 0.04 mg/L), all conditions showed emergence inhibition rates equal or above 80% of the population of larvae, except for the Northeast region. In the highest concentration, there was evidence that the Northeast region exhibited a lower emergence inhibition proportion when compared with the South and Southeast conditions ($p = 0.0001$ and 0.002, respectively). All probability values calculated with Tukey's post hoc test can be seen in the tables in Online Resource 2.

Pyriproxyfen concentrations that inhibit the emergence of 50% of the population in different thermally simulated regions

Among the five thermally simulated Brazilian regions, the EI_{50} did not surpass that recommended by the WHO (0.01 mg/L) even in the hottest treatments (North and Northeast), which can be seen in Fig. 3. We found higher sensitivity in the individuals in the South conditions, where the EI_{50} was three times lower ($\bar{x} = 0.004$; $\sigma = 0.14$) than the concentration preconized by the WHO (2016) followed by the Southeast treatments, which was two times lower ($\bar{x} = 0.005$; $\sigma = 0.013$). For individuals exposed in Central-West temperatures, the EI_{50} was 1.5 times lower than the concentration recommended by the WHO ($\bar{x} = 0.007$; $\sigma = 0.015$). The simulations for the temperature conditions for the North and Northeast both showed EI_{50} close to the concentration preconized by the WHO ($\bar{x} = 0.01$; $\sigma = 0.017$ and $\bar{x} = 0.008$; $\sigma = 0.0012$, respectively).

Discussion

In the larval bioassay, juvenile hormone analogs, such as Pyriproxyfen, offer an excellent potential for controlling *Ae. aegypti* larvae by preventing their successful development into viable adults (Fansiri et al. 2022). In addition, Pyriproxyfen is considered as a non-toxic pesticide to vertebrate animals, with no genotoxic or carcinogenic effects (Suman et al. 2014). Taking this into consideration, Pyriproxyfen is recommended to be used in drinking water at a concentration of 0.01 mg/L (WHO 2016). However, considering that Pyriproxyfen is an endocrine disruptor, environmental factors that affect the development of *Ae. aegypti* can interfere with the emergence inhibition.

Temperature is one of the factors that directly affects the responses to insect growth regulators, because it alters the life-history traits and the sensitivity of the target-organisms to Pyriproxyfen (Alomar et al. 2021). Higher temperatures were associated with the decrease in emergence inhibition in *Ae. aegypti* treated with Pyriproxyfen in laboratory conditions (Moura et al. 2021). However, experiments with constant temperatures fail to represent what happens in field conditions when compared with bioassays that apply different temperatures according to the photoperiod phase. Higher temperatures during the daylight phase of the photoperiod and lower temperature in the dark phase are more likely to mimic what happens in natural conditions, with the natural temperature fluctuation between day and night. Temperature fluctuation between day and night can interfere with the regulation of heat shock proteins and, consequently, with the thermal tolerance which can influence the metabolic resistance involved with detoxification mechanisms and, consequently, with sensitivity to insecticides (Colinet et al. 2015).

Salinas, Feria-Arroyo and Vitek (2021) showed that *Ae. aegypti* susceptibility to deltamethrin and permethrin decreased significantly in higher thermal regimes (ranging between 36 °C in the light phase and 24.6 °C in the dark phase) when compared to treatments with lower temperature regimes. Despite the different mode of action, the results found by our study with Pyriproxyfen are very similar, whereby *Ae. aegypti* individuals showed lower sensitivity in scenarios with higher temperatures in the light and dark phases, such as those simulated for North and Northeast conditions.

It is important to highlight the relation between larval susceptibility with exposure time in the different thermal regimes. Given that all individuals were from the same strain and, therefore, had the same susceptibility status, it is worth mentioning that the longer the larval were exposed to Pyriproxyfen, the less opportunity they had to emerge successfully as adult mosquitoes. As observed

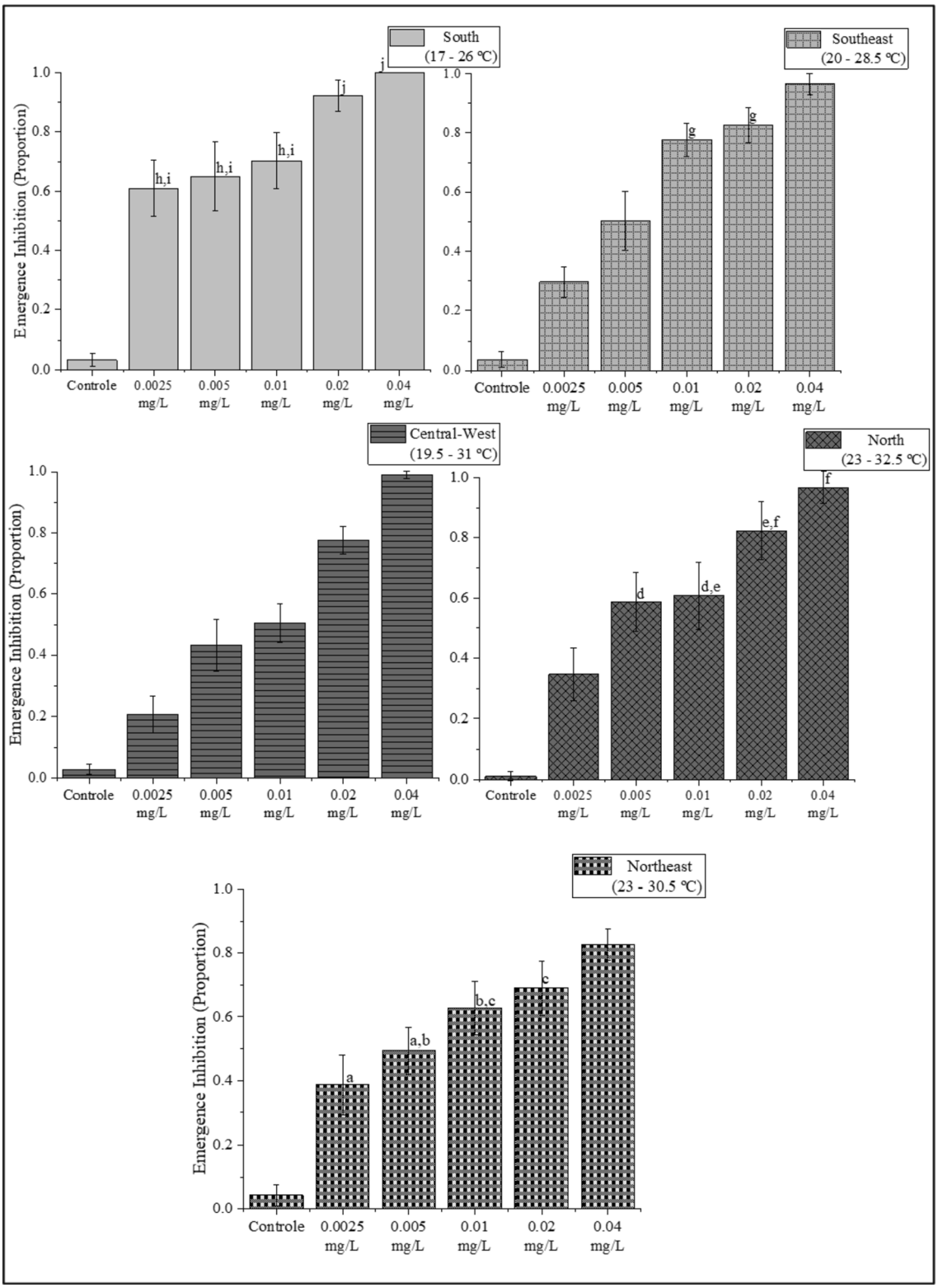

Fig 1 Proportion of emergence inhibition of *Aedes aegypti* to Pyriproxyfen in different thermal conditions for five Brazilian regions simulated in the laboratory. N.B.: Bars with the same letter are not significantly different from each other

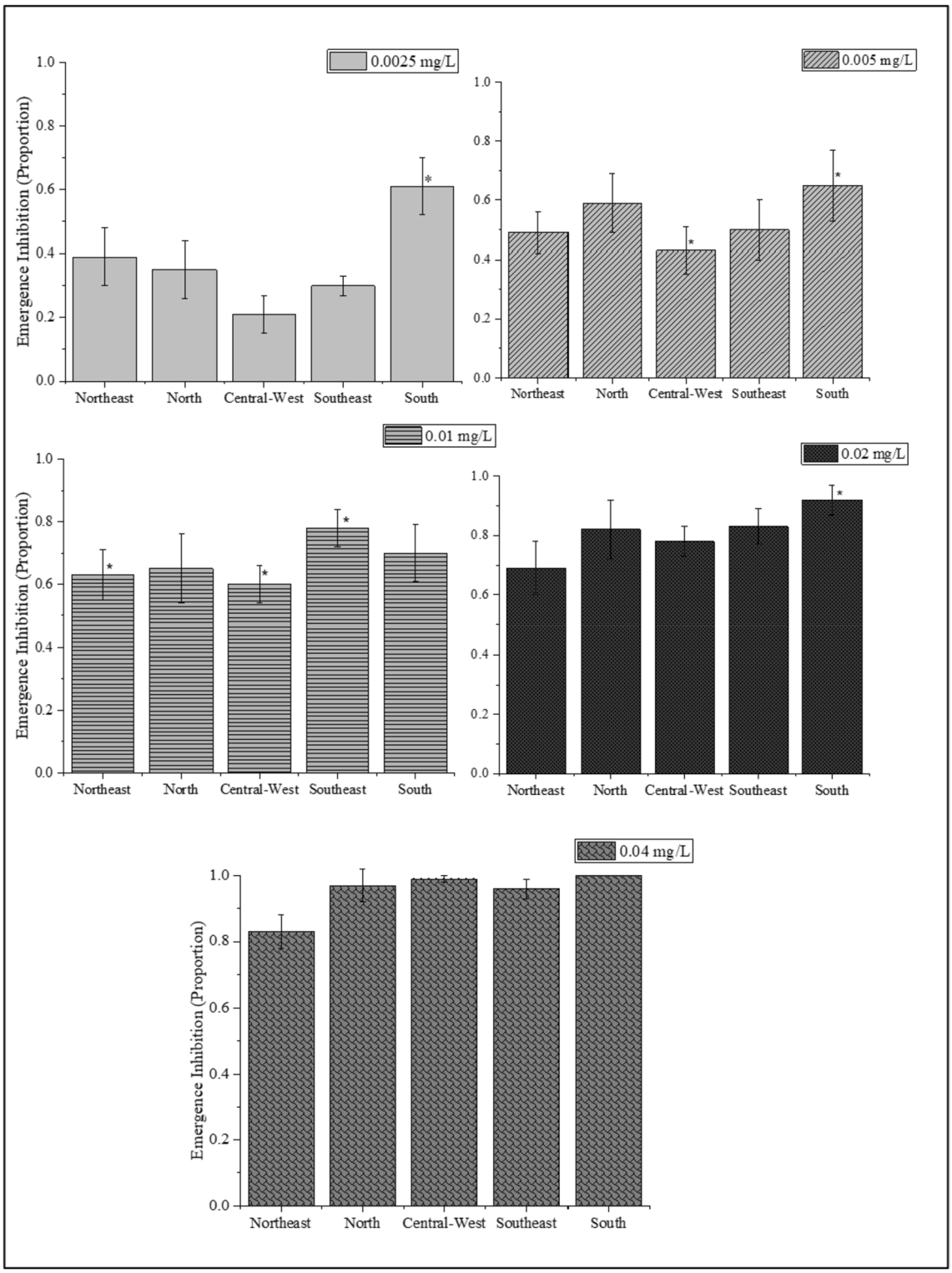

Fig 2 Multiple comparison results of different Pyriproxyfen concentrations in emergence inhibition of *Aedes aegypti* among thermal simulations of five Brazilian regions. N.B.: Asterisk denotes treatments that differ significantly from each other

by Alomar et al. (2021), lower temperatures were correlated to longer larval development in *Ae. aegypti* exposed to Pyriproxyfen. This corroborates with the results found in our study. Moreover, longer exposition to the larvicide in the colder treatment (South thermal simulation) implies more chance of Pyriproxyfen intake. As a result,

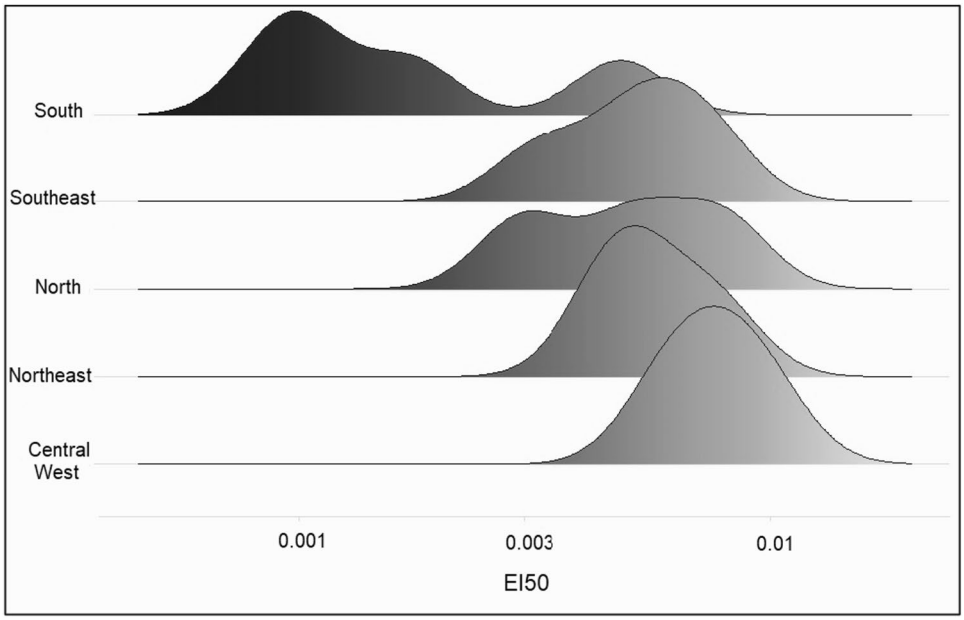

Fig. 3 Distribution of the Pyriproxyfen concentration that inhibits the emergence of 50% of the population of *Aedes aegypti* larvae in each region simulated in the laboratory

the concentration for IE_{50} in this condition (South—17 to 26 °C) is lower than hotter treatments.

The application of lower concentrations of larvicide in the thermal scenarios where the susceptibility was higher can present a potential strategy to epidemiological surveillance to reduce the threat to non-target species. Moreover, low concentrations of Pyriproxyfen can be associated with the application of other compounds with a different mode of action, such as spinosad. A recent study has shown that the association of apinosad (0.0125 mg/L) with Pyriproxyfen (0.00063 mg/L) resulted in a high efficiency of *Ae. aegypti* larval control (Santos et al. 2020). Santos et al. (2020) also reported that the effective concentrations did not impair reproductive parameters or increase *Daphnia magna* mortality.

As environmental parameters, such as fluctuating temperature, are important for larvicide efficiency, so are the characteristics of local mosquito populations. Sylvatic strains are under constant evolutive pressures that can be particular of a given environment and from a particular mosquito population that can present different susceptibility statuses to the compound. As far as we are aware, this is the first report of toxicological bioassays that demonstrated the influence of fluctuating temperatures in Pyriproxyfen efficiency to control *Ae. aegypti* larvae from a susceptible reference strain. This result can serve as a reference to compare with local populations response to both larvicide and fluctuating temperatures. Therefore, it is important that future studies investigate the wild mosquito populations responses to Pyriproxyfen under the local fluctuating temperatures.

Although there are no previous studies that tested the effects of temperature fluctuation on the emergence inhibition of *Ae. aegypti* treated with Pyriproxyfen, this compound is known to present high efficiency in larval control in semi-field conditions with low concentrations (Gómez et al. 2011; Devillers 2020; Hustedt et al. 2020). Recently, Campos et al. (2020) demonstrated that 126 of 132 *Ae. aegypti* populations in different Brazilian regions are susceptible to Pyriproxyfen in low dosages. Only six populations from Northeast cities demonstrated moderate resistance to the compound (Campos et al. 2020). Maintaining the efficiency of the compound in a sustainable way is crucial to enhance *Ae. aegypti* control.

Although more studies are important to assess the regional and local population susceptibilities in response to the compound under fluctuating temperatures, a regional approach instead of a countrywide one must be taking into consideration to future vector control programs in Brazil. Given that the dynamics of vector-borne transmissions are multifactorial, understand the influence of temperature is crucial to improve our knowledge on preventing epidemics. Dutra et al. (2023) highlighted that there are still several gaps in our current knowledge that limit any attempt to forecast the effects of global change on vector competence and, as a result, vector-borne disease transmission. Thus, in a climate-changing world, taking into account the fluctuating temperatures when assessing the susceptibility of mosquitoes of medical importance to other compounds is crucial to a more rational use of these resources against the vectors.

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Author contributions LM: conceptualization, methodology, investigation, formal analysis, data visualization, writing—original draft. JJC: validation, resources, data curation, writing—review and editing, supervision, project administration, funding acquisition. Both authors read and approved the final manuscript.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate Not applicable

Consent for publication Not applicable

Competing interests The authors declare no competing interests.

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