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Evaluation of density reduction of *Aedes aegypti* mosquitoes and biosecurity of the use of a paint containing propoxur in selected houses in Hermosillo, Sonora, Mexico

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Abstract: this study investigated the development of *Aedes aegypti* density in houses of the urban locality of Poblado Miguel Alemán Valdes, in the Sonora state of Mexico, after application of 1% propoxur paint as full wall coverage (IP) and targeted indoor painting (IP 1m) in comparison to IRS with propoxur 70% WP (full wall coverage). The 1% propoxur paint was applied by the homeowners by brushing and rolling at the recommended dose of 1L/8 m^2, equivalent to 1.5 g a.i./m^2, while IRS was conducted by professionals with Propoxur 70% WP at a dose of 1 g a.i./m^2. Adult mosquito surveys were conducted in a random sample of houses in each block one week before the interventions and at week 1, month 1 to 4, month 6, month 9 and month 12 post-interventions. All three propoxur based treatments provided similar reductions (43.7%, 44.9% and 41.3% for IP, IP 1m and IRS respectively) in the fraction of houses positive in female *Aedes aegypti* resting indoor and outdoor as one year average of 8 follow up surveys. Indoor resting density of *Aedes* females during the one-year evaluation was reduced by 77.5% through IP followed by IP 1m with 64.2% reduction and 30% reduction with IRS. *Culex* mosquitoes' interior density was affected as well by the insecticide treatments with similar average reductions for IP 1m (50.0%) and IRS (57.8%) in comparison with control. *Aedes* breeding was impacted by the insecticide paint in similar extent for both interventions, expressed by a substantial reduction of the House Index (20.1% IP, 31.2% IP 1m) and especially the Container Index (51.8% IP, 61.7% IP 1m) during the one-year surveys in comparison to control. In contrast, IRS treated block experienced an increase in both indexes. However, despite IP and IP 1m impacted in *Aedes* adult and immature indexes with noticeable reductions, the differences in all cases were not significative among the different insecticide treatments. The low sample size and mosquito population levels may have influenced the statistical outcomes. More than 80% of the interviewed residents were satisfied with the effectiveness of the paint and IRS treatments. The determination of the blood cholinesterase activity of tested individuals after the use of the carbamate paint and IRS in this study did not exceed acceptable inhibition limits. This study suggests that the application of propoxur paint by homeowners as full house coverage or as targeted indoor painting can be a safe and accepted intervention method for density reduction of *Aedes aegypti* populations in urban environments.

Key words: Propoxur, insecticide paint, *Aedes aegypti*, density reduction, Mexico

1. Introduction

Vector-borne diseases, in particular dengue, chikungunya and Zika are a major public health concern in the Region of the Americas. Increasing population densities in urban areas, inadequate urban infrastructures and improper water and waste management foster conditions for the reproduction and expansion of the virus-transmitting vector mosquitoes *Aedes aegypti* and *Aedes albopictus*. Overloaded public health systems with Covid 19 on top of the vector control activities[1] encourage insufficiencies in mosquito control programs[2]. The growing development of insecticide resistance in *Aedes* populations contribute additionally to the huge challenges for *Aedes* control in the region[3,4].

Dengue is the most widespread mosquito-borne arboviral disease today in the region of the Americas. The case numbers vary from year to year with dengue epidemics recurring in 3-to-5-year cycles. Brazil alone counted 3.7 million dengue cases with 1394 deaths in 2019 and 2020 together, accounting for 67.3% and 49.8% of total dengue cases and deaths in the Americas.[5] Mexico reported 0,27 million dengue cases and 371 fatalities in 2019, and again 0.12 million dengue cases including 79 deaths in 2020. This means that Mexico has the second highest dengue numbers in the region of Americas.[6]

In 2020, there were over 101,570 cases of chikungunya reported in the region of the Americas. 97% of all cases occurred in Brazil, followed by Bolivia with 1.5% and Colombia with less than 1% of the total cases. The cases of chikungunya in Mexico remained below 10 cases in 2019 and 2020.[7]

Zika virus spread in the past years in the regions of the Americas more widely. In 2020, 15 countries have reported a total of 21.785 mosquito transmitted Zika infections. Brazil reported the most cases (18.941 cases) followed by Paraguay, Bolivia, Guatemala with less than 1000 cases per country. The peak of reported Zika cases in Mexico dates to the years 2017 (3260 cases) and 2018 (8508 cases).[8]

The Pan-American Health Organization (PAHO) recommends for the control of arbovirus vectors in the Regions of America, the elimination of mosquito breeding sites in and around homes, the use of skin repellents against mosquito bites, and use of insecticide-treated materials as personal protection methods that individual homeowners can implement.[9]

For professional mosquito control larvicide application, space spraying and fogging and Indoor Residual Spraying (IRS) are methods for the control of adult *Aedes* mosquitoes that should be carried out by trained health professionals. For decades, control programs have applied larvicides and adulticides and have effectively killed *Aedes* populations.

However, the effectiveness of virus transmission reduction by these interventions is disputed.[10] It was the lack of scientific evidence of the effectiveness of existing intervention strategies in *Aedes* control against dengue, chikungunya, Zika that initiated the review of the control strategies, including the improvement of existing and the development of new tools/interventions against *Aedes aegypti* and *Aedes albopictus*.[11,12] A systematic literature review and meta-analysis of interventions in Latin America and the Caribbean for over 15 years confirmed that only few interventions in the region were supported by evidence on their effectiveness.[13]

Of the intervention toolbox, targeted indoor residual spraying (TIRS) seems to be promising methods to reduce the transmission of *Aedes*-borne arboviral infections.

It is evident that IRS is an effective adulticidal intervention against *Anopheles* mosquitoes in malaria control, however, only few studies demonstrated efficacy to control *Aedes* mosquitoes in dengue, chikungunya or Zika.[14]

With the introduction of the so called "targeted indoor residual spraying" (TIRS), instead of treating the entire inner surfaces of a house, only lower wall sections (<1.5m) and typical mosquito resting places are treated, and the spraying follows the resting behavior of *Aedes* indoors.[15]

In experimental houses in Merida (Mexico) conventional IRS and TIRS, both containing the carbamate bendiocarb, was compared for efficacy against pyrethroid-resistant *Aedes aegypti*. *Ae. aegypti* mortality did not differ among both interventions up to four months post-application. TIRS consumed much less insecticide compared to conventional IRS (38% reduction) and reduced application time on average by 31.3%.[16]

In a study conducted in Cairns (Australia) when TIRS was selectively applied on low walls (<1.5m) and potential resting sides such as under furniture, inside closets, and on any dark and moist surfaces, the calculated effectiveness of TIRS in preventing symptomatic dengue infections, compared to control houses, was greater than 86%.[17]

The intradomicile application or TIRS is recommended by PAHO for dengue and other *Aedes*-borne diseases control. The selection of the insecticide for TIRS should be based on evidence of susceptibility of the local population of *Aedes* to the applied product.[18]

A nation-wide assessment of the insecticide susceptibility status in Mexican populations of *Aedes aegypti* was published in 2018. The study estimated the susceptibility to six pyrethroids, two carbamates and two organophosphates in 75 localities across 28 states. A widespread resistance to pyrethroids types I (bifenthrin, δ-phenothrin, permethrin) and II (α-cypermethrin, deltamethrin, λ-cyhalothrin) was confirmed, however, the levels of insecticide susceptibility varied among (and within) states. High levels of variance among states and within states were detected as well for resistance to the two tested organophosphates (chlorpyrifos, malathion). All evaluated *Aedes* populations across the 28 states showed susceptibility to the two carbamates (bendiocarb, propoxur). As the carbamates remained highly effective, they are considered as an optional strategy in mosquito population control by the Mexican Ministry of Health.[19]

Propoxur 70% Wettable Powder and Bendiocarb 80% Wettable Powder were the only carbamate formulations registered in Mexico for IRS vector control. With the registered new propoxur containing paint, an alternative product concept appeared that may not only help to manage insecticide resistance but may provide advantages compared to conventional IRS.[20] The paint may be implemented as TIRS with the benefit that the residents can treat without the need for a specialized team as is the case with IRS. The painting by brush or roller may also have advantages over spraying in terms of safety, convenience, and acceptability. When paint lasts longer than spray formulations, the frequency of retreatment could be reduced.

The Organization for Economic Co-operation and Development (OECD), with Mexico, Brazil and the ILSI Research Foundation published in 2018 a consensus document on biology of mosquito *Aedes aegypti*, in which they considered paints an alternative for the prevention of mosquito bites.[21] Insecticide paints for *Aedes* control was also recognized by the WHO in 2020 as one intervention method for the treatment of specific areas where *Aedes* vectors frequently rest indoors.[22] The Innovative Vector Control Consortium (IVCC) consider insecticide paint an innovative product which would be of great help in reducing vector burden inside the houses and can be safer and an aesthetic alternative for indoor residual sprays.[23]

Insecticide paints with other active ingredients than propoxur have been used in the past for *Aedes* control in field programs in Ecuador, Colombia, and Costa Rica with *Aedes* mosquito population reduction for 6-12 months. This long-lasting effect is aligned with other evaluations of insecticide paints addressed to *Culex*[24] and *Anopheles*[25] mosquitoes, triatomine bugs[26] and sandflies.[27]

Previous laboratory studies (unpublished) showed that the propoxur based paint achieved mortalities higher than 95% during one year against field collected *Aedes aegypti* mosquitoes of Hermosillo city, Mexico. In another study Chagas bugs (*Triatoma mazzotti*) in the health region 04 "Costa" Pochutla, Oaxaca were exposed to propoxur paint in comparison to deltamethrin paint. While the efficacy diminished to 30% after 6 months with the deltamethrin, the propoxur paint provided 80-100% mortality 6 months post-application (unpublished).

Efficacy results of laboratory trials with propoxur paint conducted for a 6-month period with adult females of field collected *Anopheles gambiae* in Nigeria (University of Nasarawa) demonstrated complete mortality of mosquitoes within 24 hours post exposure during the 6 months trial period (unpublished).

The potential of propoxur paints as a durable insecticidal treatment for the netting screens used to mosquito-proof windows across the tropics was assessed in Ifakara, rural southern Tanzania. Pyrethroid susceptible *Anopheles gambiae* were exposed to the treated screens. When surveyed during, 18 months post treatment, the propoxur paint killed essentially all mosquitoes within 72 hours after they contacted the treated screen (unpublished).

The goal of this study was to investigate the development of *Aedes aegypti* density in houses of the urban locality of Poblado Miguel Aleman Valdes, in the Sonora state of Mexico, after application of propoxur paint (full house coverage and targeted indoor painting) versus IRS with propoxur WP (full house coverage).

We anticipate first indications about the development of mosquito density of propoxur painted houses, relative to the IRS application. As the painting is conducted by the homeowners, we expect information about the convenience and acceptability of paint application. A health check will provide data related to the health risk and safety during and after application.

2. Materials and methods

Study site

The study was conducted in the urban locality of Poblado Miguel Alemán Valdes (PMA), in the Sonora state of Mexico. This small city community is in the Northeast and near the border with the United States of America. The estimated population is 39.474 inhabitants[28] mainly dedicated to agriculture, with an intense migration of farmer workers coming from the south of Mexico. Historically, high levels of social deprivation are well known in this area.[29] The city is 60 meters above sea level with a very dry climate and a rainy season during summer.[30]

Dengue is usually endemic in PMA with nearly 300 cases reported yearly. Transmission season occurs mainly during July through October due to the greater abundance of *Aedes* mosquitoes favored by the rainy periods.

A cluster of houses were selected for the trial (coordinate's Lat 28.8471294, Lon -111.5010849) and aligned in four blocks (Figure 1). Houses are mainly constructed with sun dried

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bricks, mud, waste materials and in some cases plastered with cement. Walls and ceilings were painted in a few houses. Tin sheets were the dominant type of roofing.

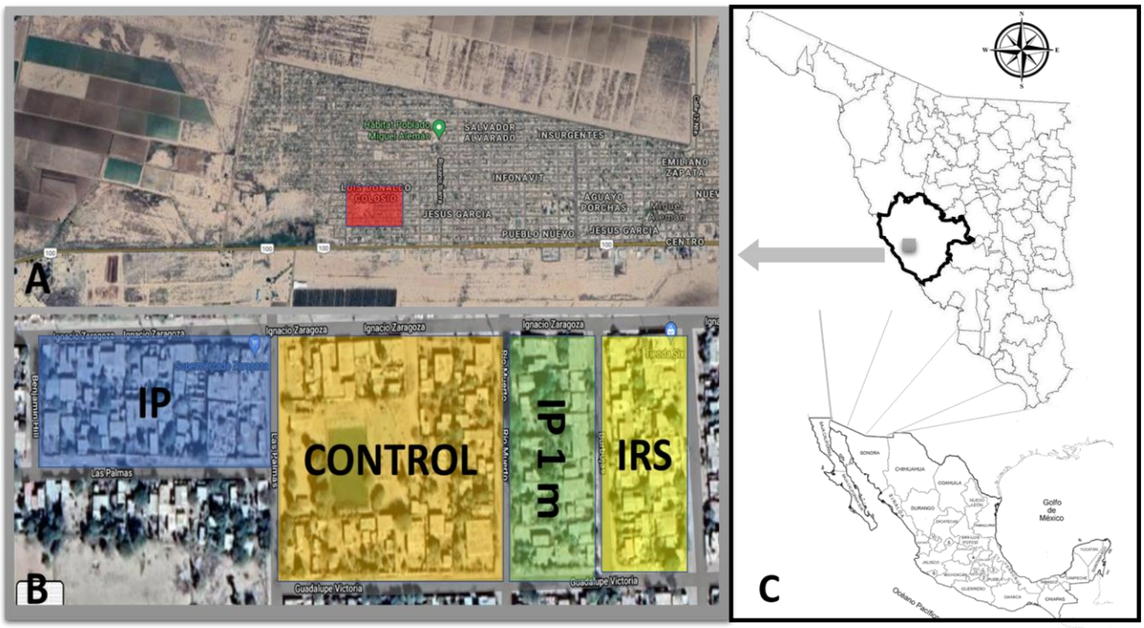

Figure 1. Satellite view of the general location of the trial site (A) and specific view of the treatment and control arms (B). Area of intervention in Sonora, Mexico (C)

Interventions

The four blocks were assigned the following treatments: full coverage of insecticide paint (IP) on interior walls, IP on interior walls applied up to 1 m height from the floor (IP 1 m), full coverage of indoor residual spraying (IRS) on interior walls and untreated control. All houses of each block received the treatment with total number of 16, 10 and 16 houses for IP, IP 1 m and IRS respectively. Control block contained 19 houses.

Carbapaint 10 (microencapsulated propoxur 1.0%, manufacturer Inesfly Corporation S.L., Valencia, Spain) was used as IP. This formulation is registered in Mexico under the tradename SAFECOLOR/CONTROLCOLOR PROPOXUR and distributed by CODEQUIM S.A. de C.V. (Mexico D.F., Mexico). The insecticide paint was applied at the recommended dose (1L/8 m^2, equivalent to 1.5 g a.i./m^2) by homeowners by brushing and rolling. A water-based sealant was applied as a first layer to reduce paint absorption in high absorbent wall materials like bricks. Residents were informed and trained in safety measurements and paint application by the research team.

IRS was conducted by professional staff of the Sonora's Health Department with Propoxur 70% WP with an application dose of 1 g a.i./m^2 by means of a Hudson® sprayer portable machine with Teejet 8002 nozzle and calibrated to 760±4ml/min, at 55 psi.

Entomological surveys

Adult and immature mosquito surveys were conducted in a random sample of houses in each block one week before the interventions and at week 1, month 1 to 4, month 6, month 9 and month 12 post-interventions. Larval and pupal survey at week 1 was omitted due to the non- expected impact of the treatments at such short time post application.

Adult collections in resting sites were performed by trained technicians with a CDC backpack aspirator. Technicians spent 15 min during the inspection of the interior and exterior parts of the house in accordance with the method described in published studies.[31] Collected mosquitoes were recorded and classified per species and sex. Adult house index was calculated as the percentage of houses with presence of any female mosquito.[32] Adult density was calculated as the number of females collected per positive house.

Larval survey consisted in the recording of positive breeding sites (larvae and pupae) for *Aedes aegypti* in water holding containers or objects following WHO-TDR guidelines[33]. Percentage of water holding containers, House Index (HI) and Container Index (CI) were obtained for each block and follow up time in accordance with WHO definitions[34].

Human exposure to insecticides survey

Carbamate insecticides act at the nervous system of insects and mammals inactivating acetylcholinesterase enzyme in a reversible way. Exposure of propoxur to residents was assessed through the measurement of cholinesterase levels in blood samples taken from adult volunteers from both sex and a wide range of age prior intervention and one week plus one month after application of insecticides.

Blood extractions, transportation and analysis were performed according to operational guides issued by Mexico Health Secretary.[35,36] The cholinesterase study was performed by the *Quantitative determination of cholinesterase* (CHE) IVD method using the Spinreact kit®, and it was carried out in a certified private laboratory of Santa Fe, Mexico.

Resident's perceptions of insecticide interventions

The acceptability, perceived efficacy, and side effects of the three interventions was assessed by interviewing a household adult at month 3 after treatments using a defined questionnaire. Researchers recorded the answers from a selected sample of households of each treatment arm.

Ethical considerations

The testing protocol was reviewed and approved by the Research Bioethics Committee from the University of Sonora (UNISON) (DMCS D 109/2018).

Study participants were informed about the research project and the family representant signed a consent form. Paint and painting tools were provided by free. Empty buckets and used brushes and rollers were recovered and disposed according to environmental requirements of Sonora State. Medical assistance was offered to participants for treating any side effects derived from the interventions. Confidentiality of the personal and medical data was ensured through internal protocols of the University of Sonora.

Data analysis

Adult monitoring: a chi-square analysis was used to estimate the differences in the proportion of positive/negative infested houses between control and treated houses. To compare the proportion of *Ae. aegypti* and *Culex* spp., at interiors and exteriors, a chi-square analysis was also used. Values of adult density among treatments (C, IP, IP1m, and IRS) and specie, at interiors and exteriors, were analyzed using a factorial general linear model ANOVA.

Larva monitoring: a nonparametric Kruskal–Wallis test was used to test the significance of the differences in the number of larvae among treatments (Control, IP, IP1m, and IRS). A chi-square analysis was used to estimate the differences in the type of containers used as breeding sites between control and treated houses.

Cholinesterase levels: levels were obtained by subtracting the baseline level (one week before intervention) and the cholinesterase levels at a week and one month after intervention. Differences among intervention groups (Control, IP, IP1m, and IRS) in cholinesterase blood levels (one week and one month after intervention) were analyzed using mixed effects generalized linear models with a log link function, with groups and sex as categorical factors and age as continuous predictor.

For all analyses, significance threshold was set at 0.05. Data were analyzed using IBM SPSS (Statistics Version 21, IBM Corporation, USA), JMP (SAS Institute, USA) and STATISTICA 13.0 (Tibco Software Inc., USA).

3. Results

3.1 Entomological surveys

3.1.1 Adult monitoring

Inspections of randomly selected houses (IP 33.6%, IP 1 m 57.5%, IRS 41.4%, Control 19.7%) in the control and treatment blocks at different times after interventions showed a reduction in the fraction of positive houses in *Ae. aegypti* females collected in interior and exterior resting sites (Table 1). The one-year average reduction was 43.7%, 44.9% and 41.3% for IP, IP 1m and IRS respectively to control (Table 1). Differences in the proportion of positive/negative infested houses between control and treated houses were observed (χ^2=14.128, P=0.0027).

Table 1. Adult *Ae. aegypti* house index (%) (number of houses inspected)

TAT	IP	IP 1 m	IRS	CONTROL
Pre-intervention	0 (4)	75 (4)	55,6 (9)	80 (5)
Week 1	0 (4)	25 (4)	25 (4)	100 (4)
Month 1	25 (4)	25 (4)	75 (4)	75 (4)
Month 2	50 (2)	33,3 (6)	75 (4)	ND
Month 3	33,3 (6)	16,7 (6)	0 (6)	ND
Month 4	16,7 (6)	33,3 (6)	45,5 (11)	100 (6)
Month 6	100 (6)	100 (5)	100 (7)	100 (6)
Month 9	33,3 (6)	50 (8)	30 (10)	50 (6)
Month 12	88,9 (9)	85,7 (7)	71,4 (7)	100 (4)
AVR	48,8	47,8	50,9	86,7
CI 95%	19,8-77,9	22,2-73,5	23,2-78,7	64,7-108,6

TAT = time after treatment; ND= no data; AVR = average; CI 95% = Confidence Interval at 95%

Species identification in adult collections revealed that *Culex* spp. females were more abundant indoors and outdoors than *Aedes aegypti* (χ^2=60.16, P<0.0001) (Table 2). The dominance of *Culex* spp. in all the three intervention sites was greater for IP and IP 1 m, while in a lesser extent for IRS in comparison to control. Among groups, in interiors *Culex* spp. proportion was higher than *Ae. aegypti* (χ^2=83.46, P<0.0001; Figure 3), particularly for the IP group. No differences between *Culex* spp. and *Ae. aegypti* proportions in exteriors were observed ($\chi2$=5.995, P=0.111).

Table 2. Mosquito species distribution in interior and exterior collections

		IP		IP 1m		IRS		CONTROL	
		N	**FRAC (%) (CI 95%)**	**N**	**FRAC (%) (CI 95%)**	**N**	**FRAC (%) (CI 95%)**	**N**	**FRAC (%) (CI 95%)**
INT	*Ae. aegypti*	12	6,2 (-9,7-22,2)	20	32,8 (3,3-62,2)	48	52,2 (1,8-1026)	66	40 (-4,7-94,7)
	Cx. spp.	181	93,8 (77,8-109,7)	41	67,2 (37,8-96,7)	44	47,8 (-2,6-98,2)	99	60 (5,3-114,7)
EXT	*Ae. aegypti*	21	28 (-81,5-144,9)	27	21,1 (-53,8-96,0)	61	31,0 (-22,1-84,1)	21	36,8 (-29,5-107,6)
	Cx. spp.	54	72 (-37,5-188.8)	101	78,9 (4,0-153,8)	136	69,0 (15,9-122)	36	63,2 (-3,2 (134,0)
TOT	*Ae. aegypti*	33	12,3 (-21,7-46,3)	47	24,9 (-6,1-55,8)	109	37,7 (-7,2-82,6)	87	39,2 (-10,5-88,9)
	Cx. spp.	235	87,7 (53,7-121,7)	142	75,1 (44,2-106,1)	180	62,3 (17,4-107,2)	135	60,8 (11,2-110,5)

INT= interior; EXT= exterior; TOT= total; N= total number of collected female mosquitoes during the one year follow up; FRAC= fraction of mosquito species in percentage; CI 95% = Confidence Interval at 95%

Aedes mosquito density defined as number of resting females collected per positive house in *Ae. aegypti* recorded one-year average reductions of 77.5%, 64.2% and 30.0% in interiors for IP, IP 1 m and IRS respectively when compared to control arm. However, no significative differences among treatment groups were detected in interior densities (Wald $\chi2$=0.24, P=0.97) and neither difference between species total densities (Wald $\chi2$=0.08, P=0.77). Despite *Ae. aegypti* showed lower densities than *Culex* spp. in all groups (Figure 2), no differences for the interaction Groups*Species were detected (Wald $\chi2$=1.00, P=0.80). In exteriors no differences among groups (Wald $\chi2$=1.52, P=0.67), specie (Wald $\chi2$=0.76, P=0.38) and interaction Groups*Species (Wald $\chi2$=0.44, P=0.93) were observed.

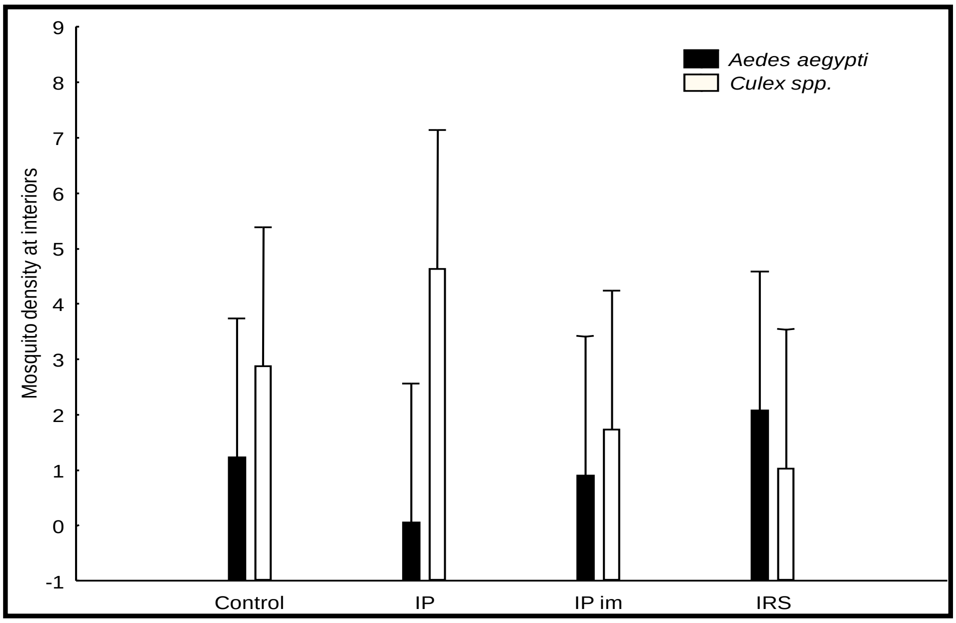

Figure 2. *Aedes aegypti* and *Culex* spp. densities per groups at interiors

A noticeable variability occurred in the time series and study arms with absence of *Aedes* females in all blocks at month 1 (April) and few individuals at month 3 (July) and 9 (January) (Table 3). Comparison of *Aedes* and *Culex* total density (Table 3) confirmed the greater abundance of *Culex* spp. and the null impact of any of the insecticide interventions to this specie in contrast with the average reductions to control observed for *Aedes aegypti* in the IP (51.5%) and IP 1m (36.4%). *Culex* spp. populations appeared to be very seasonal and peaked importantly on month 12 (April) inspection with a total female number of 469 among 592 recorded during the complete (8) follow up collections.

Table 3. *Aedes aegypti* and *Culex* spp. females' total density per positive house

TAT	Ae. IP	Ae. IP 1m	Ae. IRS	Ae. Control	Cx. IP	Cx. IP 1m	Cx. IRS	Cx. Control
Pre-intervention	0,0	3,3	8,4	0,0	0,0	0,0	0,0	0,0
Week 1	0,0	0,0	2,0	0,5	0,0	0,0	0,0	0,0
Month 1	0,0	0,0	0,0	0,0	1,0	7,0	4,3	1,3
Month 2	3,0	2,0	2,0	0,0	0,0	0,5	0,0	0,0
Month 3	2,0	4,0	0,0	0,0	2,0	2,0		0,0
Month 4	1,0	2,0	5,8	10,0	17,0	1,0	0,6	3,0
Month 6	3,3	4,6	10,0	4,2	4,3	4,4	5,9	1,2
Month 9	0,5	0,3	0,0	0,0	4,0	3,5	5,7	5,3
Month 12	0,5	1,8	0,4	0,0	22,4	15,7	21,2	22,5
AVR	1,6	2,1	4,0	3,3	11,2	6,5	6,7	5,2
CI 95%	0.3-2.8	0.5-3.8	0.7-7.4	0-6.7	4.6-17.7	1.7-11.2	-0.2-13.6	-0.7-11.1

TAT= time after treatment; Ae. = *Aedes aegypti* females; Cx. = *Culex* spp.; AVR= average;
CI 95% = Confidence Interval at 95%

3.1.2 Larval monitoring

A total of 268 houses (54.9%) were randomly inspected during the seven surveys conducted after the interventions (May 2018 to April 2019) where 1132 (15.2%) containers were found filled with water among the 7462 potential ones that were recorded, and 69 showed presence of *Aedes aegypti* larvae. One-year average House Index was 20.1% and 31.2% reduced due to the complete painting and the 1-meter painting respectively. Reduction was also noticed for the Container Index in IP (51.8%) and IP 1m (61.7%) study arms. IP and IP 1m showed the lowest HI (Table 4) but no differences among groups were detected ($H_{(3,33)}$=2.51, P=0.47). Higher indexes were obtained in the sprayed houses in comparison with control in all cases.

Table 4. House Index and Container Index for *Aedes aegypti* larvae

TREATMENT	NH	HI (%)	IC 95%	NC	CI (%)	IC 95%
IP	48	12.7	-6.2-31.6	321	3.3	-0.5-7.0
IP 1m	46	11.0	-3.1-25.1	199	2.6	-0.4-5.7
IRS	51	24.4	4.1-44.8	292	8.8	3.6-14.0
CONTROL	58	16.0	4.9-27.1	320	6.8	1.4-12.3

NH= number of houses inspected; HI = House Index; NC= number of water holding containers; CI= Container Index; CI 95% = Confidence Interval at 95%

Time evolution of the House and Container indexes in Figure 3 and 4 showed peaks at month 2 (June) and month 6 (October) for most of the study blocks. Breeding sites for IP 1 m remained absent for *Aedes* up to month 4 while IRS treated houses had the greatest larval indexes in most of the surveys.

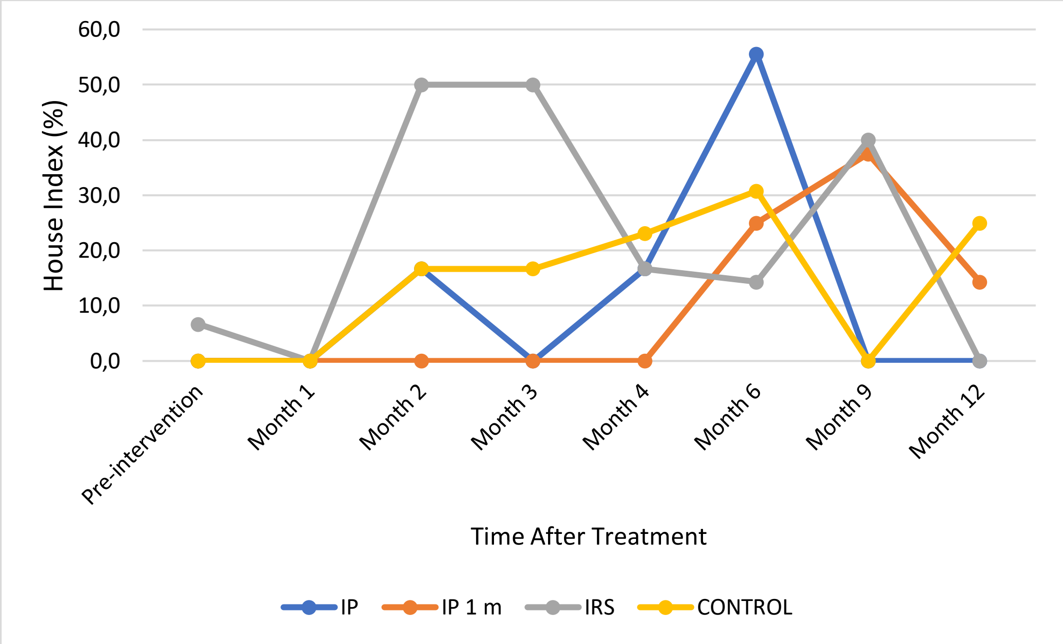

Figure 3. Evolution of the House Index

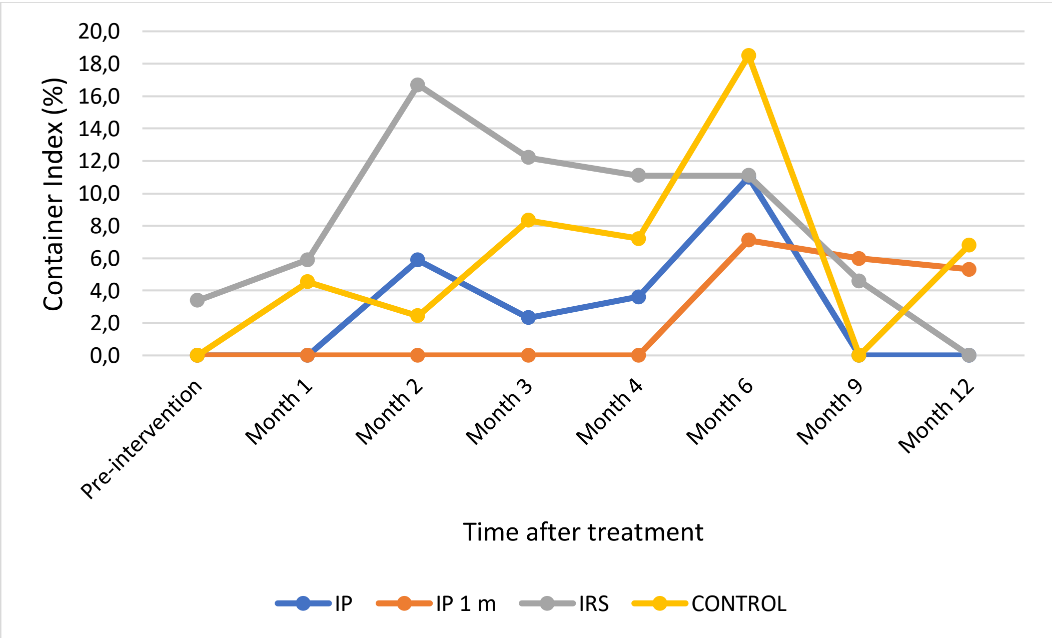

Figure 4. Evolution of the Container Index

Inspection of the typical water holding containers during all the study led to identify the preferred breeding sites of *Aedes aegypti* (Figure 4). Null presence of immature *Aedes* stages was observed in sinks, jars, big jars, wells, and toilets despite recording these objects holding water in the inspected houses. Other small containers (26.1%), tanks (17.4 %), tires (10.1%) and buckets (10.1%) account for the 63.7% of the found breeding sites in the total sum of the study arms. Slight variations of the distribution of the major breeding containers were observed among the insecticide treatments and control but no differences were detected (χ^2=43.21, *P*=0.11).

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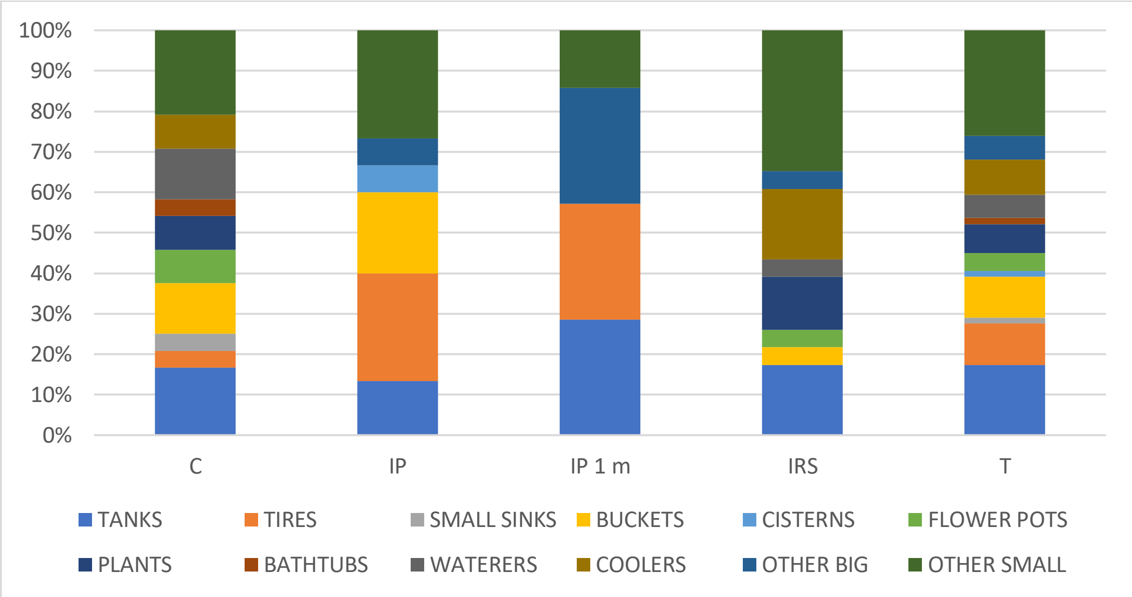

Figure 5. Percentage distribution of *Aedes aegypti* immature stages presence in water holding containers

3.2 Measurement of acetylcholinesterase in exposed residents

A total number of 119 adults from all ages participated in the study (38.7% males and 61.3% females) that provided 280 blood samples during the survey at 1week prior intervention (104), one week (104) and one month (72) after interventions.

Cholinesterase becomes a biomarker for exposure to organophosphate and carbamate insecticides. Individual reductions of this blood parameter after exposure to propoxur in IRS or paint form in comparison with baseline level and control arm were considered for this analysis. Individual inhibition of cholinesterase levels was observed for seven and three residents at week 1 and month 1 after intervention respectively (Table 5) with a maximum reduction of 18.9% recorded for IRS at 1 week. Levels were found to grow on average for all the study arms after insecticide interventions so negative inhibitions were obtained (Table 6).

Table 5. Cases detected with cholinesterase levels inhibition at different times post insecticide interventions

	1 Week		1 Month	
TREATMENT	Cases (%)	C.L. INH (%)	Number (%)	C.L. INH (%)
IP	1 (9,1)	8,4	1 (5,9)	2,9
IP 1m	2 (11,1)	2,2	0	0,0
IRS	3 (18,9)	10,3	1 (6,3)	3,7
CONTROL	1 (5,3)	4,0	1 (6,3)	11,0

C.L. INH = individual cholinesterase level inhibition average

A deeper statistical analysis showed that individual cholinesterase levels at one week did not differ significantly among intervention groups (P=0.402) or gender (P=0.999) nor interaction (P=0.242) (Table 7). However, an age effect was found (P=0.00). Similar results were found at one month after intervention where individual differences with baseline cholinesterase levels did not differ significantly among intervention groups (P=0.501), age (P=0.192), gender

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(P=0.0.644) nor interaction (P=0.327). Interestingly, older people tend to show higher levels of cholinesterase (Figure 5).

Table 6. Average inhibition of individual cholinesterase levels

	1 Week			1 Month		
TREATMENT	N	C.L. INH (%)	IC 95%	N	C.L. INH (%)	IC 95%
IP	11	-30,6	-38,5 -24,8	17	-33,8	-37,9 - 29,7
IP 1m	18	-31,2	-37,8 - 24,7	12	-26,6	-35,5 - 17,7
IRS	19	-32,5	-39,9 - 25,1	16	-30,1	-38,8 - 21,5
CONTROL	16	-31,7	-38,1 - 25,3	16	-32,0	-40,7 - 23,2

N = number of individuals; C.L. INH = individual cholinesterase level inhibition average

Table 7. Mixed effects generalized linear model ANOVA testing for the effect of groups and sex and age (continuous predicto) at one week and one month.

One week	d.f.	Log-likelihood Type 3	Chi-square	P
Age	1	-134.673	15.99446	0.000064
Groups	3	-128.141	2.932	0.402229
Sex	1	-126.675	0	0.999544
Treatment*Sex	3	-128.765	4.17982	0.24269
One month				
Age	1	-96.2914	1.697259	0.192647
Groups	3	-96.6213	2.357106	0.501669
Sex	1	-95.5489	0.212445	0.644858
Treatment*Sex	3	-97.1667	3.447902	0.327582

d.f. = degrees of freedom

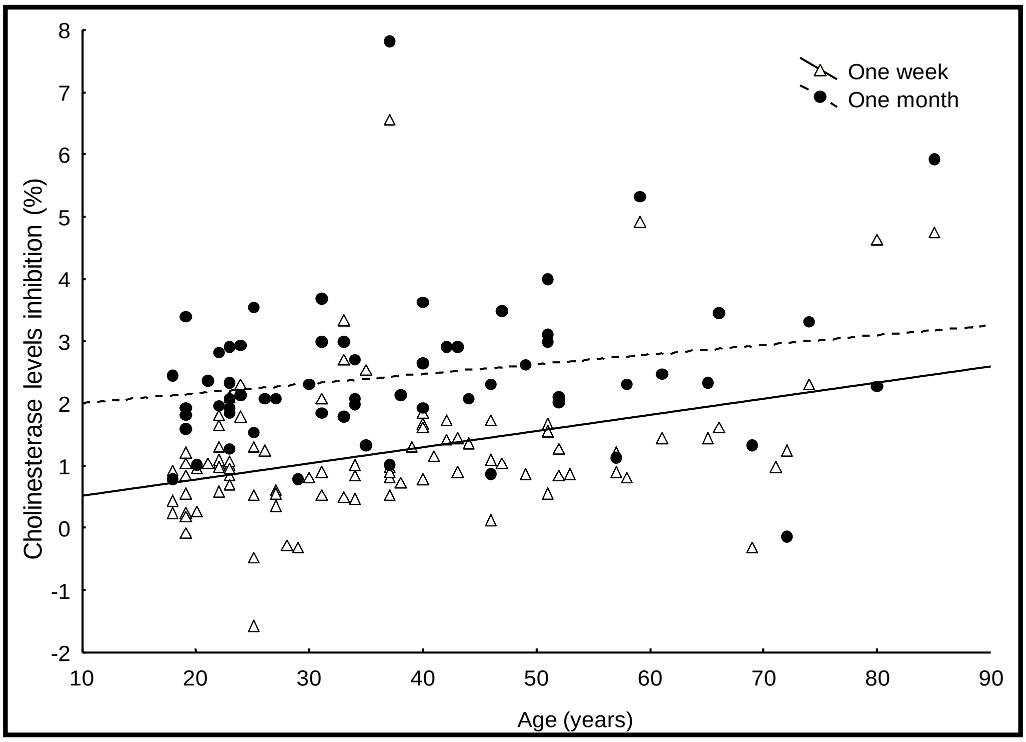

Figure 5. Age association of cholinesterase levels inhibition (%) in the studied population.

3.3 Resident's perceptions of insecticide interventions

Interviews of adult residents at month 3 after interventions lead to a total number of 24 surveys from 42 houses included in the treatments (IP 10, IP 1 m 6, IRS 6).

Insecticide paint and IRS were considered as effective for insect control and would be recommended to others with slight better scores for IRS than PIM and PIM 1 m (Table 8). Despite paint was not found difficult to apply by any surveyed adult, irritation was declared by 1 person and unpleasant smell by 30% and 16.7% of paint users that applied full and partial paint coverage on walls respectively.

Table 8. Questionnaire results of resident's perceptions of the insecticide interventions

Question	IP Affirmative (%)	IP 1 m Affirmative (%)	IRS Affirmative (%)
Paint/Spraying helped to control insects that affects human health	90	83,3	100
Paint was difficult to apply	0	0,0	NA
Paint/Spraying provoked irritation or discomfort	10	0,0	0
Paint/Spraying had unpleasant aroma	30	16,7	0
Recommendation of paint/spraying application to others	100	83,3	100
Paint/Spraying helped to improve the house	100	83,3	100
Died insects observed after painting/Spraying	100	83,3	100

NA = not applicable

4. Discussion

Recently, dengue vector control interventions have been focused to source reduction through larvicides and removing of breeding sites by means of community mobilization. Space spraying of insecticides become a routinary activity for dengue outbreaks targeting adult population. Finally, personal protection with repellents is a consumer driven option for bite prevention. Despite the massive and sustained deployment of these interventions there is a scientific community consensus about the lack of strong evidence of its effectiveness[37].

In a wider approach WHO promotes the strategy known as Integrated Vector Management (IVM) to control mosquito vectors, including those of dengue[38] where other tools are gathered. In 2019 PAHO issued a guideline for indoor residual spraying specifically for *Aedes* control in urban areas[39] due to the growing evidence of the efficacy of this technique[40].

IRS was included by WHO in the intervention type residual insecticide surface treatment where paint was considered as an application method to deliver the insecticides to the surfaces[41].

Our study aims to evaluate the residual efficacy of an insecticide paint applied in interior walls under field conditions and compared with IRS as a positive control. Previous laboratory studies (unpublished) showed that this propoxur based paint achieved mortalities higher than 95% during 18 months against field collected *Aedes aegypti* mosquitoes of Hermosillo city, Mexico. This long-lasting effect is aligned with other evaluations of insecticide paints containing other active ingredients addressed to *Culex*[42] and *Anopheles*[43] mosquitoes, triatomine bugs[44] and sandflies.[45]

Interior and exterior resting density was selected as primary entomological indicators for adult impact assessment of these insecticide-based interventions. All three propoxur based treatments provided similar reductions (41.3% - 44.9%) in the fraction of houses positive in female *Aedes aegypti* resting indoor and outdoor as one year average of 8 follow up surveys.

Indoor resting density of *Aedes* females was closely related with the formulation and its surface extension. Insecticide paint applied in all the wall surface led to the greatest reduction (77.5%) followed by the insecticide paint applied on a band of 1 meter height from the floor (64.2%) and finally a propoxur WP formulation sprayed on walls reached 30.0% of reduction during the one-year evaluation. Baseline densities were noticeable for IP and IRS so reinforcing the impact of the treatments. *Culex* mosquitoes' interior density was affected as well by the insecticide treatments with similar average reductions for IP 1m (50.0%) and IRS (57.8%) in comparison with control.

Very few field studies related with IRS and *Aedes* mosquitoes have been published yet with entomological and epidemiological outcomes. Among them, a deltamethrin based IRS intervention in Peru achieved a significant drop in adult *Aedes* (male and female) positive houses percentage from 18.5% at baseline to 3.1% at four weeks after treatment[46]. However, the control houses experimented a similar decrease as well during the 16 weeks study period.

In addition to the endophylic and endophagic behavior of *Aedes aegypti*, outdoor presence has been also recorded[47] with 20% catches in a study conducted in Brazil. Any of the tested insecticide treatments in our study had impact on the average exterior density.

Total *Aedes* collections were lower than *Culex* spp. in accordance with the observations of natural population densities of *Aedes* in comparison to most other mosquito species[48], and specifically *Cx. quinquefasciatus*.[49] The distribution of both species was impacted by the treatments meaning that *Aedes* were killed or displaced from the treated houses in a greater extent than *Culex* mosquitoes. This fact was observed in decreasing trend from IP (12.3% *Aedes*) to IP 1 m (24.9%) while IRS (37.7%) had similar *Aedes* fraction than control (39.2%). Differences were bigger for IP in the interior collected mosquitoes with *Aedes* proportions of 6.2% and 40.0% at control houses due to the interior treatment of walls. This finding is in accordance with the known different tolerance to insecticides of mosquitoes' species. In our case, it is known that some topical repellents provide larger protection periods for *Culex* than for *Aedes*[50] while the opposite occurs when insecticides are applied topically to mosquitoes. LD_{90} (mg/mg mosquito) obtained for Cx. *quinquefasciatus* were 57.5, 11.7 and 12.4-fold than for *Ae. aegypti* exposed to permethrin, carbaryl and diazinon respectively.[51]

Control houses had a mean and maximum interior density of 2.5 and 7.2 *Aedes* females per positive house respectively, while the figures per total inspected house were 2.2 and 7.2. These data are comparable to an extensive indoor aspiration sampling performed in Iquitos, Peru where similar catching method revealed an interior density minor than 10 adults per house in the dengue season.[52] Despite the average number of mosquito density, collections had a noticeable variability during the one year follow up, recording zero *Aedes* individuals in 2, 2, 3 and 5 time series surveys for IP, IP 1 m, IRS, and control arms respectively. These limited figures may hinder reliable interpretations of the results. The seasonal pattern has previously been observed in Mexico (Monterrey[53], Yucatan[54]) for adult populations by trapping but not equivalent records were found for interior resting density through aspiration devices.

Indoor resting density measurements through timed adult aspiration methods is considered a reliable entomological indicator for mosquito population.[55] However, this sampling method is dependent on the aspiration effort (minutes of the activity)[56] and it can be influenced as well by collector variability and housing characteristics with marked bias for low mosquito density situations. Enhanced technique called sequential removal sampling using the same Prokopack aspirators led to a 5-fold increase in adult collections from the 10 minutes standard practice.[57]

Aedes breeding was impacted by the insecticide paint in similar extent for both interventions in terms of substantial reduction of HI (20.1% IP, 31.2% IP 1m) and especially CI (51.8% IP, 61.7% IP 1m) during the one-year surveys in comparison to control. In contrast, IRS treated block experienced an increase in both indexes. Yearly average HI in the whole study arms belonged to the high infestation level defined by PAHO[58] (HI >5%), but the association to dengue outbreak risk remains still uncertain despite several studies.[59] It is probable that these variations were provided by a limited number of treated houses in each block (≤70%) and hence incomplete coverage of the interventions.

In the abovementioned evaluation in Peru, a noticeable reduction of all immature index was observed after IRS intervention with deltamethrin despite no significant differences from baseline. A similar trend was recorded in Taiwan where areas with Breteau Index higher than 35% were sprayed with Alpha-cypermethrin in their interior walls and the undersurface of furniture. This larval index dropped to 1% after three years of this IRS intervention.[60] Another adult addressed residual intervention like Long Lasting Insecticide Screens installed on doors and windows did not show significant differences in HI and CI at 5 months post-intervention between treated and untreated houses. However, this Alpha-cypermethrin impregnated nets achieved a significant impact at 12 months post-intervention only for the pupae-based indicators in a large study conducted in Mexico.[61]

Aedes mosquitoes are known to disperse their eggs in several breeding sites and our study revealed that small containers, tanks, tires, and buckets were the preferred ones accounting for 63.7% of the water holding ones with larval or pupal presence. These sites were also found to be prevalent in Mozambique for *aegypti* and *albopictus.*[62] Discarded tires and water tanks were identified as preferred sites for *Aedes* in Tanzania.[63] Despite all these known productive breeding sites, elimination or chemical control remains difficult for individuals, community, and authorities.

Despite IP and IP 1m impacted in *Aedes* adult and immature indexes with noticeable reductions, the differences in all cases were not significative among the different insecticide treatments. Again, the low sample size and population levels may influence the statistical differences.

Resident's acceptance and satisfaction with insecticide treatments for vector control become a key aspect for a sustained and effective public health intervention. IRS campaigns are generally well accepted in malaria endemic areas with low refusals rates. A study with 834 household interviews in South Iran showed an acceptance rate of 94% respectively. Satisfaction of interviewed people were between 69% and 60.9% in two villages of Malawi.[64] Minimal adverse effects of the chemicals after spraying and killing of other insects apart from mosquitoes were declared as main positive factors. IRS for leishmaniasis prevention in Bangladesh was also largely accepted by residents (85.3%).[65]

Insecticide paints lack of abundance of acceptability and satisfaction studies because of its novelty and limited spread as a massive vector control tool. An evaluation conducted in Nepal related with sandfly control revealed that 94% of interviewees perceived a reduction of sandflies after the application of an insecticide paint and 5.9% declared side effects (headache and itching).

In this study, more than 80% of the interviewed residents were satisfied with the effectiveness of the paint and IRS treatments and found the paint easy to apply. They would recommend painting as intervention method but 30% and 16.7% of paint users that applied full and partial paint coverage on walls respectivley complained about an unpleasant smell. One case of irritation/discomfort was recorded.

The determination of the blood cholinesterase activity tested individuals is generally taken as a biosecurity indicator for the exposure of applicators and residents during and after organophosphate or carbamate applications. A study in Brazil detected 4.6% of small-scale agricultural workers with inhibition levels higher than 30% in respect to average control population.[66] Monitoring of blood cholinesterase activity on residents living in houses sprayed with malathion and fenitrothion as part of the Haiti's national malaria program revealed that all individuals did not suffer inhibitions higher than 25% of baseline levels at 1 day and 7 days after spraying.[67] Similar results were observed in South Iran in a sample of 925 residents exposed to fenitrothion IRS treatment, where no significant individual changes were recorded for cholinesterase levels before and after spraying.[68] Propoxur exposure to humans was assessed in Nigeria through blood cholinesterase measurements among 10 and 16 residents in sprayed houses. The analysis found reductions of 5.8% and 0% at 1 and 6 days after treatment respectively.[69]

After the use of the carbamate paints and IRS in this study the blood acetylcholinesterase levels of the tested volunteers did not exceed the inhibition limit established by the Mexican Authorities (30%)[4] and did not significantly differ from the control arm. This fact was aligned with several evaluations conducted for other organophosphate and carbamate insecticides in previous studies.

Our field study suggests that the application of the propoxur paint by homeowners as a complete covering of house walls or as a targeted indoor painting can be a highly safe and accepted intervention method for effective density reduction of *Aedes aegypti* populations in urban environments.

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