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Targeted outdoor residual spraying, autodissemination devices and their combination against *Aedes* mosquitoes: field implementation in a Malaysian urban setting

Research Paper

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Abstract

Currently, dengue control relies largely on reactive vector control programmes. Proactive vector-control using a rational, well-balanced integrated vector management approach may prove more successful for dengue control. As part of the development of a cluster randomized controlled epidemiological trial, a study was conducted in Johor Bahru, Malaysia. The study included one control site (three buildings) and three intervention sites which were treated as follows: targeted outdoor residual spraying only (TORS site, two buildings); deployment of autodissemination devices only (ADD site, four buildings); and the previous two treatments combined (TORS + ADD site, three buildings). The primary entomological measurement was per cent of positive ovitraps—ovitrap index (OI). The effect of each intervention on OI was analyzed by a modified ordinary least squares regression model. Relative to the control site, the TORS and ADD sites showed a reduction in the *Aedes* OI (−6.5%, $P = 0.04$ and −8.3%, $P = 0.10$, respectively). Analysis by species showed that, relative to control, the *Ae. aegypti* OI was lower in ADD (−8.9%, $P = 0.03$) and in TORS (−10.4%, $P = 0.02$). No such effect was evident in the TORS + ADD site. The present study provides insights into the methods to be used for the main trial. The combination of multiple insecticides with different modes of action in one package is innovative, although we could not demonstrate the additive effect of TORS + ADD. Further work is required to strengthen our understanding of how these interventions impact dengue vector populations and dengue transmission.

Introduction

Aedes mosquitoes, primarily *Aedes aegypti* and to a lesser extent *Aedes albopictus*, are responsible for the transmission of several viruses which cause dengue fever and dengue haemorrhagic fever, yellow fever, Zika virus disease and chikungunya fever. Over 3.5 billion people are estimated to be at risk of dengue in more than 120 countries, with 390 million estimated infections per year. Of these infections, approximately 500,000 patients present with severe dengue requiring hospitalization, and of these, an estimated 2.5% result in fatality (Bhatt *et al*., 2013; Gyawali *et al*., 2016).

In south-east Asia, dengue has been estimated to cause each year, on average, about 2.9 million cases and 5906 deaths, with a total cost of approximately US$1 billion, almost half (US$451 million) being direct costs (Shepard *et al.*, 2013). Dengue is endemic in Malaysia, putting all 27.5 million inhabitants at permanent risk of infection. The annual incidence of dengue in Malaysia varied between 69.9 and 93.4 per 1000 population from 2001 to 2013 (Woon *et al.*, 2018). In 2009, the direct costs of dengue (medical costs and productivity loss) were over US$102 million. In addition, the Malaysian government spent US$73.5 million (0.03% of its GDP or 1.2% of its health care budget) on its national dengue vector control program. This amounts to US $1591 per reported dengue case. Such expenditure on dengue vector control is not unique. Surrounding countries spend similar amounts: as an example, the annual cost of dengue management in Singapore was US$50 million (0.02% GDP) (Carrasco *et al.*, 2011).

The efficacy of vector control in reducing the density of *Aedes* population is well established (Schliessmann and Calheiros, 1974; Kourí *et al.*, 1998; PAHO, 1997), but evidence of impact on *Aedes*-borne disease incidence is lacking (Bowman *et al.*, 2014; Andersson *et al.*, 2015).

Consequently, there is no consensus regarding the most cost-effective vector control tools (Achee *et al.*, 2015). The World Health Organization (WHO) recommends implementing sustainable and ecologically sound integrated vector management (IVM), adapted to the local situation and using local resources and existing systems (WHO, 2012, 2017).

In Malaysia, dengue control relies mainly on reactive vector control such as space spray (fogging), larviciding and source reduction. Proactive year-round vector-control using a rational, well-balanced IVM strategy could have a greater impact on dengue fever incidence and may prove more cost-effective than the currently used reactive approach.

We plan to set-up a cluster randomized controlled trial (cRCT) to evaluate the effectiveness of a proactive IVM strategy on the incidence of dengue in Malaysia. The IVM strategy will combine targeted outdoor residual spraying (TORS) by K-Othrine Polyzone, deployment of autodissemination devices (ADDs) and extensive public engagement activities.

The active ingredient of the TORS, K-Othrine Polyzone, has been prequalified by the WHO for vector control activities (WHO, 2018). K-Othrine Polyzone indoor residual spraying (IRS) application has been proven to reduce adult and immature *Aedes* populations (Paredes-Esquivel *et al.*, 2016). K-Othrine Polyzone kills host-seeking and adult mosquitoes landing on the treated substrate, thereby lowering the number of adult mosquitoes in the area (Dunford *et al.*, 2018). Its use in TORS can potentially reduce the frequency of current insecticide applications for *Aedes* control due to its longer residual effect (Hamid *et al.*, 2019).

ADDs (In2Care®) attract and kill *Aedes* mosquitoes via a combination of a slow killing adulticide, the entomopathogenic fungus *Beauveria bassiana* strain GHA, and the juvenile hormone analogue pyriproxyfen (PPF), a larvicide that can be autodisseminated to surrounding breeding sites (Buckner *et al.*, 2017). ADDs rely on mosquitoes behaviour to distribute the pesticide to cryptic, hard to find breeding sites and can potentially offer precision-targeted larval control and sustained breeding suppression of vector populations (Farenhorst *et al.*, 2009; Snetselaar *et al.*, 2014). Gravid female mosquitoes enter the device searching for a place to lay their eggs. When landing on the floater the females contact gauze contaminated with PPF and *B. bassiana* spores. The latter can take 7–14 days to develop and then kill exposed mosquitoes, providing the opportunity for them, in the meantime, to transfer PPF to other surrounding larval habitats (Snetselaar *et al.*, 2014).

The results of a field implementation study carried out to evaluate the feasibility, and guide the optimization of methods and procedures for the set-up and conduct of the cRCT, are presented here.

Methods

Setting

The study was carried out from February to June 2018 (3 weeks pre-treatment and 10 weeks intervention) in Johor Bahru, Malaysia. The study included one control site and three intervention sites to be treated with (a) targeted outdoor residual spraying only (TORS site), (b) deployment of autodissemination devices only (ADD site) and (c) combination of outdoor residual spraying and deployment of autodissemination devices (TORS + ADD site). The study sites were located within 10 Km radius with each other. TORS + ADD and ADD sites were 3 Km apart (fig. 1). The control site comprised three buildings of 17 floors each, and the TORS site two buildings of 14 floors each. The number of buildings for ADD and TORS + ADD sites were, respectively, four (nine floors per building) and three (four floors per building). This research was approved by the Malaysian Ministry of Health's medical research and ethics committee (17 October 2017).

Insecticide and treatments

Following the collection of pre-treatment data for a period of 3 weeks, outdoor space spraying was conducted (Ministry of Health Malaysia, 2009) in all study sites for a quick and short-term reduction of the *Aedes* population. TORS was applied in TORS and TORS + ADD sites at week 5, and consisted of spraying semi-indoor and outdoor perimeter concrete walls with K-Othrine Polyzone. The latter contains deltamethrin as its active ingredient (62.5 g l^{-1}). The insecticide dosage was 25 mg m^{-2} and was applied by using a compression sprayer.

ADDs were deployed in two sites (ADD and TORS + ADD). According to the manufacture's specification, one ADD is necessary for every 400 m^2. A logical distribution of ADDs would be to treat every floor. But, the key element of ADDs being the autodissemination effect, three strategies were evaluated in the intervention sites (ADD and ADD + TORS) to find a more economical distribution pattern: (A) two ADDs on each floor (strategy A, used in two buildings in the ADD site and one in the TORS + ADD site), (B) two ADDs every second floor excluding the top floor (strategy B, one building in each site), and (C) two ADDs on each of the first two floors, and two on the top floor (strategy C, one building in each site). Strategy C stemmed from the concept that most breeding sites are found at ground level, but high-rise buildings often have water reservoirs and potential breeding sites on the roof (Wan-Norafikah *et al.*, 2010; Lau *et al.*, 2013; Zainon *et al.*, 2016).

Monitoring of *Aedes* population

A total of 87 ovitraps were placed outdoors (near bushes and small plants) and another 136 semi-indoors (along the corridor, e.g. near shoe racks and flower pots) to monitor mosquitoes density. Semi-indoor was defined as not being completely enclosed by walls (e.g. corridors open on one side) but covered and protected

Figure 1. Locations of the study sites.

from sunlight and heavy rainfall. Entomological data were collected during the pre-treatment and for 10 weeks following the intervention.

Each ovitrap consisted of a 300 ml black plastic container, of diameter 6.5 cm and height 9.0 cm. Fresh water was added to a level of 5.5 cm and a hardboard oviposition paddle ($10 \times 2.5 \times 0.3\ \text{cm}^3$) was placed in the water with the rough surface upwards. The ovitraps were collected and taken back to the laboratory every 7 days. All the larvae were counted and identified under a compound microscope (Nikon Eclipse E100, Japan). Evaluation of the adult *Aedes* population was based on the analysis of ovitraps (Lee, 1992) recommended by the Malaysian Ministry of Health.

Population-based survey and community engagement

We conducted a survey in which 10% of the study population (head of households or any available adult) were interviewed, to evaluate their socio-economic status and identify the most suitable communication strategy for the main trial. Income categories were based on reported household income and basic amenities as follows: top 20% (T20: >US$1440/month), middle 40% (M40: US $720–1440/month) and bottom 40% (B40: <US$720/month) (Department of statistics Malaysia, 2017).

Community engagement was conducted by meeting with the head of localities and COMBI volunteers prior to the start of the study to explain the purpose of the study and to secure their cooperation and goodwill.

Statistical analyses

The primary entomological outcome was the weekly ovitrap index (OI), which is the percentage of positive ovitraps (i.e. those with larvae in the trap). This was calculated as the number of positive ovitraps divided by the total number of recovered ovitraps in each site at the end of each week. We also calculated the number of larvae per ovitrap (the larvae index, or LI) expressed as the total number of *Aedes* sp. larvae in each recovered ovitrap at the end of each week. To quantify the effect of each intervention on OI in comparison to control, a modified ordinary least squares regression model using a robust standard error estimator was used (Cheung, 2007). The mean LI during the pre-treatment (baseline) period of each site and the ovitrap location (semi-outdoor vs. outdoor) were included in the regression model, as well as the intervention applied.

The same analysis strategy was applied to quantify the intervention effect on LI using a negative binomial regression model. For this model, the response variable was the number of larvae in each ovitrap. A logarithmic link function was used, so the results can be interpreted as ratios of means, or expressed as per cent changes in means.

Knowing the slow killing effect of ADDs due to targeting the next generation of mosquitoes, we also evaluated the effect of the interventions over time by dividing the intervention period in two: weeks 1–5 and weeks 6–10. The analysis of each outcome (OI and LI) included an interaction between the intervention periods and the treatment (intervention site).

Identification of the most suitable strategy for the deployment of ADDs was based on the above-mentioned regression models. All analyses were carried out with SAS® software using the procedures proc surveyreg for the OI analysis and proc genmod for the LI analysis (version 9.4, SAS® Institute Inc., Cary, NC, USA). The regression coefficients were tested using the Wald test. Statistical significance (two-sided) was set at $P \leq 0.05$.

Results

During the surveys, between 80 and 100% of the semi-indoor and outdoor ovitraps were recovered after 7 days. Of the total of

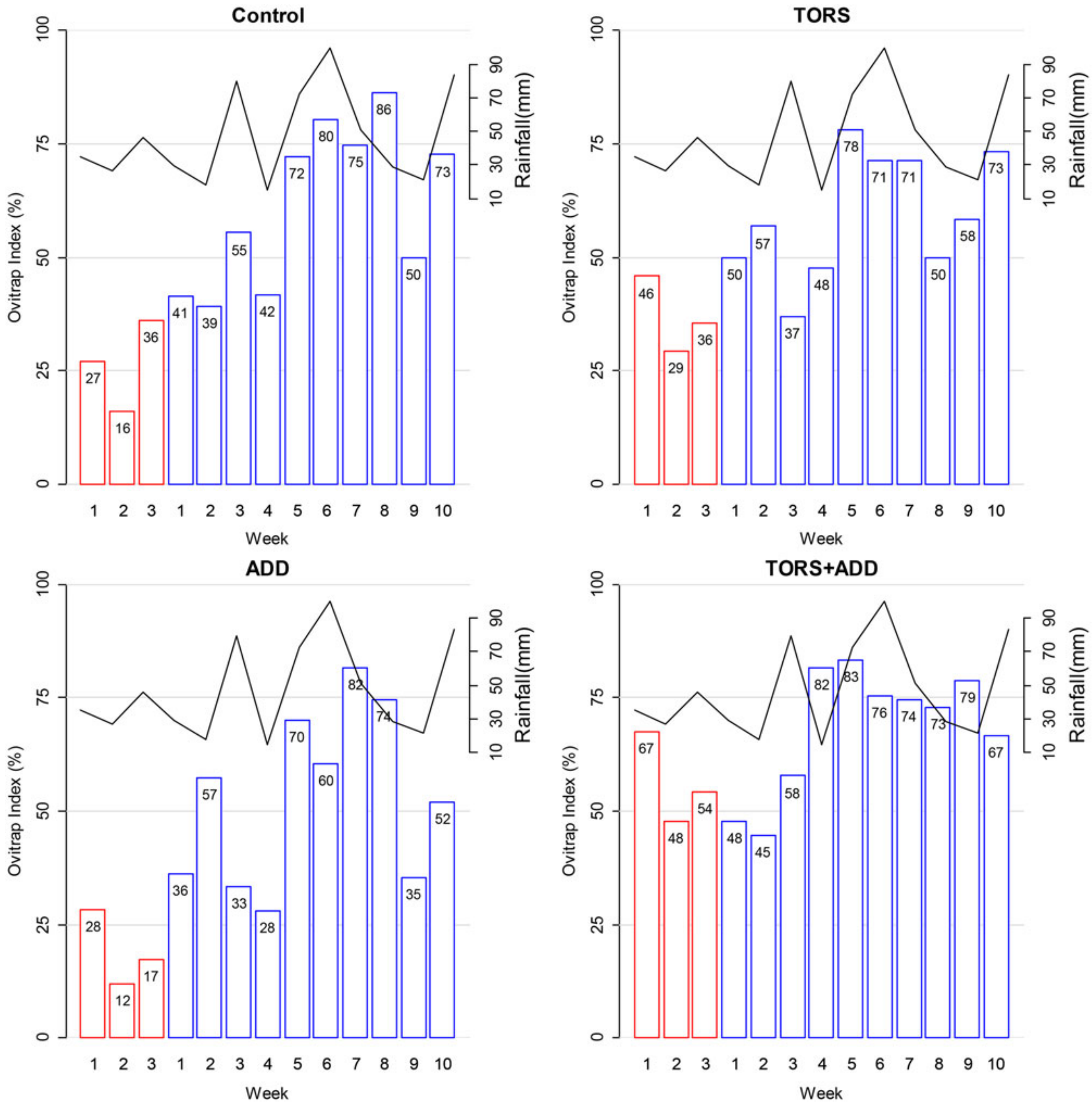

Figure 2. Ovitrap index (%) and rainfall (mm) per week during the baseline (red) and the intervention period (blue) in study sites.

65,118 larvae examined, 39,070 (60.0%) were *Ae. aegypti* and 25,982 (39.9%) were *Ae. albopictus*. During the pre-treatment period, the highest mean OI (56.5%) were found in TORS + ADD site while the lowest values were observed in the ADD site (mean 19.0%, fig. 2). Following the intervention, we observed an increase in the overall OI in all study sites, although there was weekly variation in both control and intervention areas. The overall OI and LI (larvae index) were in general higher in outdoor as compared to semi-indoor areas (Supplementary table S1). Analysis by species showed higher OI and LI for *Ae. aegypti* in semi-indoor areas (Supplementary table S1). As for OI, the mean LI overall was higher in all study sites during the intervention period as compared to the pre-treatment period (Supplementary fig. S1).

The results of the effect of the intervention on OI are summarized in table 1. As compared to the control site, the overall outdoor and semi-indoor OI was lower in the intervention sites ADD (−8.3%, $P = 0.04$) and TORS (−6.5%, $P = 0.10$) and slightly higher in TORS + ADD (+1.8, $P = 0.63$). The difference reached statistical significance only in the ADD site. Relative to the control site, the outdoor and semi-indoor OI for *Ae. aegypti* was lower in ADD (−8.9%, $P = 0.03$) and TORS (−10.4%, $P = 0.02$) and slightly higher in TORS + ADD (+4.9%, $P = 0.29$). Regarding *Ae. albopictus*, relative to the control site, outdoor and semi-indoor OI was slightly lower in ADD (−4.2%, $P = 0.19$) and TORS + ADD (−3.4%, $P = 0.34$) and slightly higher in TORS (+4.5%, $P = 0.18$) but none reached statistical significance.

The analysis of the interaction with the period showed a greater effect of the intervention on OI during weeks 6–10 as compared to weeks 0–5 in TORS (−13.1% vs. −0.66%, $P = 0.02$) and ADD (−12.3% vs. 4.7%, $P = 0.03$) but the interaction did

Table 1. Outdoor and semi-indoor Ovitrap Index (overall and per species) in study sites during the pre-treatment and intervention periods, and estimated differences in Ovitrap Index, relative to the control site (modified ordinary least squares regression)

	Pre-treatment		Intervention			
Study area	*N*	OI (%)	N	OI (%)	Difference in OI relative to control* (95% CI)	*P*-value
Overall (all *Aedes*)						
Control	179	26.3	598	61.0	–	–
TORS	141	36.9	471	59.7	−6.5% (−14.4, + 1.4)	0.10
ADD	142	19.0	484	52.9	−8.3% (−16.2, −0.3)	0.04
TORS + ADD	138	56.5	469	68.7	1.8% (−5.7, + 9.4)	0.63
Ae. Aegypti						
Control	179	18.4	598	47.2	–	–
TORS	141	12.1	471	31.0	−10.4% (−18.8, −2.0)	0.03
ADD	142	11.3	484	37.4	−8.9% (−16.9, −0.9)	0.01
TORS + ADD	138	26.8	469	47.3	4.9% (−4.2, + 14.1)	0.29
Ae. Albopictus						
Control	179	10.1	598	24.1	–	–
TORS	141	29.1	471	41.4	4.5% (−2.1, + 11.1)	0.18
ADD	142	10.6	484	20.2	−4.2% (−10.5, + 2.2)	0.19
TORS + ADD	138	41.3	469	34.9	−3.4% (−10.5, + 3.6)	0.34

N, Total number of ovitraps recovered; OI, Ovitrap index; 95% CI, 95% confidence interval.
*Adjusted for baseline and for ovitrap location.
The number of oviposition sites was the same during the pre-treatment and intervention periods, but the positivity of the ovitraps was measured every week for 10 weeks during the intervention as compared to 3 weeks for the pre-treatment period.

not reach statistical significance in TORS + ADD (−4.8% vs. + 7.9%, $P = 0.11$; Supplementary table S2).

The relative difference in mean number of larvae per ovitrap in ADD, TORS and TORS + ADD in comparison to the control site was estimated to be −35.4% (95% confidence interval (CI): −48.7, −18.7; $P = 0.004$), −31.3% (95% CI: −46.8, −11.4; 0.0002) and +3.6% (95% CI: −22.9, + 39.3; $P = 0.81$), respectively (table 2). Similar trends were observed for *Ae. aegypti* but the difference reached statistical significance only in ADD (−37.6%; $P = 0.002$). Regarding *Ae. albopictus*, as compared to the control site, the mean number of larvae per ovitrap was lower in all intervention sites but none reached statistical significance. As for OI, the LI showed a greater effect of the intervention during weeks 6–10 compared to weeks 0–5 in TORS ($P < 0.0001$) and ADD ($P < 0.0001$) (Supplementary table S3).

Distribution of ADDs deployment strategies

Regarding the best strategy for the deployment of ADDs, the OI was significantly higher for strategy A (ADDs on all floors) (+10.9%; 95% CI: + 0.02, + 21.8, $P = 0.05$) and strategy B (ADDs on every other floor excluding the top floor) (+18.2%; 95% CI: + 7.4, + 29.0, $P = 0.001$) as compared to strategy C (ADDs on the first two floors and on the top floor) (Supplementary table S4).

Population-based survey and community engagement

Baseline characteristics of the 732 individuals that completed the survey are presented in Supplementary material (Supplementary table S5). The highest percentage of individuals with primary school education and low income was observed in the TORS + ADT site. This site had also the highest rate of unemployed individuals. Television and radio were identified as the preferred source of information about dengue (71.5%), followed by internet (31%) and relatives (28.2%). COMBI volunteers were available in all study sites but did not participate in the study in the TORS + ADT site. Lower education level in this site might explain this lack of participation.

Discussion

As part of the development of a cRCT, the present study provided insights on the methods to be used and some preliminary results on the effect of different vector control approaches on *Aedes* mosquitoes density in Johor Bahru, Malaysia.

As in other surveillance studies in Malaysia (Wan Norafikah *et al.*, 2009; Lim *et al.*, 2010; Norzahira *et al.*, 2011), both *Aedes* vector species were present, though *Ae. aegypti* was the dominant species, representing 60.0% of the mosquito population.

We observed an increase in mosquito density, measured by OI and total larvae (LI), following the intervention. It is reasonable to assume that the observed overall increase could be due to heavy rainfall. In a study carried out in Malaysia, the amount of rainfall was positively associated with OI after a 1-month lag time, which corresponds to the time between the hatching of eggs and first oviposition (Wee *et al.*, 2013).

Relative to the control site, and even though hampered by sudden major rains, both interventions sites TORS and ADD showed a trend toward reduction in the *Aedes* populations, although the magnitude of these effects could not be expected to substantially reduce transmission. These preliminary results showed that

Table 2. Outdoor and semi-indoor mean larval index (overall and per species) in study sites during the pre-treatment and intervention periods, and estimated differences in larvae index, relative to the control site (negative binomial regression model)

Larvae index						
	Pre-treatment		Intervention			
Study area	*N*	Mean (SD)	*N*	Mean (SD)	Relative difference* (95% CI)	*P*-value
Overall						
Control	179	5.8 (16.1)	598	25.6 (36.4)	–	–
TORS	141	6.4 (14.7)	471	23.7 (37.7)	−31.3% (−46.8, −11.4)	0.0002
ADD	142	2.0 (7.0)	484	16.1 (27.8)	−35.4% (−48.7, −18.7)	0.004
TORS + ADD	138	15.3 (25.4)	469	30.2 (44.6)	3.63% (−22.9, + 39.3)	0.81
Ae. Aegypti						
Control	179	4.3 (14.4)	598	16.9 (30.8)	–	–
TORS	141	1.1 (5.1)	471	9.8 (26.6)	−24.9% (−51.8, + 16.8)	0.20
ADD	142	0.9 (4.6)	484	10.4 (21.8)	−37.6% (−53.6, −15.9)	0.002
TORS + ADD	138	3.7 (11.1)	469	20.7 (41.3)	35.6% (−8.2, + 100.4)	0.13
Ae. albopictus						
Control	179	1.5 (7.1)	598	8.6 (25.4)		
TORS	141	5.3 (13.9)	471	13.9 (26.9)	−26.39% (−48.9, + 5.9)	0.09
ADD	142	1.1 (5.1)	484	5.7 (19.9)	−20.8% (−51.8, + 30.2)	0.36
TORS + ADD	138	11.6 (22.6)	469	9.5 (21.9)	−12.5% (−44.4, + 37.5)	0.56

N, Total number of ovitraps recovered; SD, standard deviation; 95% CI, 95% confidence interval.
*Adjusted for baseline and for ovitrap location.

outdoor vector control strategies could be used for *Aedes* control in densely populated urban districts.

As reported in other investigations (Lee *et al.*, 2015; Hamid *et al.*, 2019) and in agreement with our results, TORS or ADDs effectively reduced the mosquito population. It can, therefore, be expected that co-application of these techniques together with public cooperation would further enhance the vector control efficacy. The lack of an observed additive effect of the combined TORS + ADD on the mosquito population may be related to differences between the TORS + ADD site and the other intervention sites in terms of socio-economic, waste management and architectural characteristics. The frequent presence of objects such as pet cages, fish aquaria, furniture and edible plants in the semi-indoor areas in this site led to TORS coverage of 50% as compared to 100% in the TORS-only site. An average coverage of 70% of walls is requested for an effective action of TORS. More discarded waste, often plastic, was also observed in the TORS + ADD site, and this could slow down the autodissemination effect of the ADDs. As plastic waste forms breeding sites, fewer females choose the ADD as a primary breeding site. In addition, for those females that did choose the ADD first, the more breeding sites are available on leaving the ADD, the smaller is the initial effect. Some larger breeding sites need more than one mosquitoes visit to reach the appropriate threshold for killing over 80% of the pupae, thus having a multitude of breeding sites can lead to longer periods before the threshold is reached. Finally, 26% of ADDs were subject to vandalism in this site as compared to only 3% in the site with ADDs alone. The lower education level of the population and the lack of COMBI activities in TORS + ADT site could have contributed to higher vandalism. The more frequent presence of bird cages and aquaria at the time of TORS spraying could also have tended to negate any effect. Moreover, the architecture of the buildings in TORS + ADD site made the semi-indoor walls more subject to rainfall and hence, plausibly, quicker wash-off of K-Othrine Polyzone during the heavy rainfall that occurred after the introduction of the intervention.

The observed greater effect of the intervention on the mosquitoes population overtime in the ADD site fit well with the slow killing effect of this device. ADD is designed to attract mosquitoes and then contaminate the adults which then carry pyriproxyfen to other sites before dying from the exposure to the *Beauveria* within approximately 10 days. The PPF targets the next generations; it prevents the pupae from transforming to the adult stage and tarsal contact with pyriproxyfen has been shown to suppress egg production and hatchability in adult females (Ohba *et al.*, 2013). Thus, we did not expect to see much effect of PPF within the first 2 weeks. The increased effectiveness of the ADDs over time is consistent with the accumulation of PPF occurred in surrounding breeding sites. Depending on the size of the breeding site, a single contaminated mosquito might not be enough to kill the larvae in these breeding sites. Multiple visits might be necessary to reach this threshold, which again will delay the effect. A trend towards a lower proportion of positive ovitraps in the TORS + ADD area was observed although it was not statistically significant. We do not have a specific explanation for the observed greater effect of TORS during weeks 6–10. An efficacy lag of 1 month on 24 h mortality rates of *Anopheles gambiae* on wood panels treated with K-Othrine Polyzone was also reported by Dunford and collaborators (Dunford *et al.*, 2018).

The attempt to evaluate three ADD deployment strategies, including potentially suboptimal one, may have led to the effect of ADD being underestimated. However, the main objective of this study was to obtain information on the optimization of the intervention procedures for the cRCT, rather than obtaining a precise estimate of the intervention effect. Despite the reduced power resulting from multiple ADD deployment strategies across limited numbers of buildings, the results did give some insight as to optimal deployment. We found that strategy C (ADDs on the first two floors and on the top floor) seems to be a valid alternative to reduce the number of ADD needed while keeping the quality of the expected results. Strategy A with ADDs in every floor did not perform better than strategy C. Factors such as different overall population levels between buildings within a site or different distributions over the floors have been reported in the past (Lau *et al*., 2013) and could explain the observed results. The better result of strategy C compared to strategy B (two ADDs every second floor excluding the top floor), even though more ADDs were deployed under strategy B, could be due to better/smarter distribution, as strategy B did not include the second and the top floor. These floors have been reported as sometimes having a higher infestation than other floors (Wan-Norafikah *et al*., 2010; Zainon *et al*., 2016). If we were to conclude from these results, it would be that, in buildings up to nine floors, reducing the ADD coverage from every floor to the first two and top floors seems to be possible without necessarily lowering the impact.

The data extracted from the national dengue surveillance system (eDengue) reported 11 dengue cases in the control area as compared to one, three and zero dengue cases in the TORS, ADD and TORS + ADD sites, respectively, during the study period. However, the study was not designed to test the impact of the interventions on dengue incidence.

Conclusions and lessons learned

The combination of multiple insecticides with different modes of action in one package is innovative, although we could not demonstrate the additive effect of TORS + ADD.

Higher education level in TORS and ADT sites suggests better health literacy and could explain tangible results in these sites. Health education of the public will be the first step in community engagement for the planned cRCT epidemiological trial. Active public engagement will start before the intervention and will be maintained throughout the study period. Banners, posters and announcement brochures will be distributed to explain the objectives of the study. Random allocation of eligible sites for the planned cRCT will be stratified on socio-economic status. The use of indoor ovitraps was not initially planned due to the reluctance of the study population. However, regular contact between the study population and the field workers during the collection of baseline data created the public trust and some flat owners accepted the ovitraps to be deployed in their homes (results not shown). For the cRCT, it is planned to place indoor ovitraps in volunteers' flats.

Offering a better understanding of a proactive IVM approach on *Aedes*-related diseases by conducting large-scale randomized controlled trial is key to further reduce their incidence and improve global health. Successful implementation of such large-scale studies requires the existence of appropriate infrastructure (expertise in vector control management, strong social mobilization capacities, existence of surveillance systems) and high dengue endemicity. Furthermore, the Ministry of Health has an epidemiological and entomological surveillance system specifically for the *Aedes*-borne diseases: dengue, Zika and chikungunya. This system also records post-outbreak vector control activities and dengue virus serotypes. These are the main reasons for carrying out the planned trial in Malaysia. We believe that the planned cRCT will allow us to further expand upon and validate the entomological evidence generated here, to evaluate the impact of the proposed IVM approach on dengue incidence and to help shift the conception of policies to handle *Aedes*-borne diseases from treatment to prevention, thus saving public funding.

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