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Review Article

A Review: Autodissemination of Pyriproxyfen as Novel Strategy to Control Dengue Outbreaks

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ABSTRACT

The new emergence and re-emergence of arbovirus infections transmitted by *Aedes* mosquitoes have been spreading across Southeast Asia, Central Africa, United States, tropical Oceania and has become a major of public health concern. These arbovirus diseases were found to have a similar vector, symptoms, and environments. The situation is complex due to no specific vaccine or treatments being available for the diseases. Therefore, vector control is currently the best defense against arbovirus diseases, but with its own challenges such as the difficulty in controlling scattered breeding sites and biological behavior. Herein, we present a literature review of studies on current techniques proposed to combat dengue transmission that can fill a crucial gap in vector control programs, which is the inability of conventional control methods to eliminate and destroy cryptic breeding sites. In particular, we focused on the concept of autodissemination, which is a self-delivery technique by manipulating the behavior of mosquitoes, carrying the

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insecticide and disseminating it to cryptic breeding sites. This technique has shown promising results in some countries and can be considered as an additional tool in a vector control program. Therefore, we conducted Boolean searches in several electronic databases including Google Scholar, PubMed, SciELO and ScienceDirect to identify relevant published data regarding dengue and autodissemination techniques.

Keywords: Aedes, autodissemination, dengue, pyriproxyfen, vector control

INTRODUCTION

To date, there are more than 300 known species of mosquitoes in the world but with only a small number of species responsible for vector-borne diseases (Caraballo & King, 2014). *Aedes aegypti* and *Aedes albopictus* are the most important vectors for the transmission of dengue, Zika, and chikungunya virus. According to the World Health Organization (WHO), mosquito infections affected more than one third of the world's population and caused about one million deaths annually (WHO, 2016).

Aedes aegypti is the most important disease vector worldwide. It is the principal vector of dengue, chikungunya, yellow fever and Zika viruses. *Ae. aegypti* is extremely anthropophilic, has frequent blood-feeding behavior, a long lifespan and is closely associated with humans, because of their ability to breed in human dwellings, and preferring to feed on humans even in the presence of other mammals (Faraji et al., 2014). The blood-feeding behavior becomes the primary concern because it is the major component of the dengue virus transmission where an infected patient gets bitten by a mosquito which then carries the virus to another person. Most mosquito species have their preferred distributions, with the *Ae. aegypti* being the primary vector of the dengue virus, but it is also an efficient vector for other viruses that cause human diseases such as the Zika virus and chikungunya virus.

Meanwhile, *Aedes albopictus* was found to be able to transmit over more than 20 arboviruses, increasing the risk of humans to mosquito-borne diseases (Wong et al., 2013) and was considered as a secondary vector in importance according to their zoophilic preferences (Delatte et al., 2010). In certain areas around the world, it has become one of the most invasive mosquito species. *Ae. albopictus* is considered a greater threat compared to *Ae. aegypti* due to the former's higher survival rate in larval densities (Camara et al., 2016), adaptation to extreme temperatures (Brady et al., 2013) and showing greater survivorship in food-limited competitions (Banerjee et al., 2017; Hopperstad & Reiskind, 2016).

SEARCH STRATEGY

We searched PubMed, ScienceDirect, SciELO and Google Scholar with the following keywords: dengue fever; dengue control; vector control; autodissemination; pyriproxyfen; pyriproxyfen autodissemination; horizontal transfer; autodissemination AND dengue or malaria; emergence inhibition; and pyriproxyfen (PPF) in several combinations using Boolean searches. Non-English language articles were also included if there was an available English translation. Due to the limited data published in scientific journals, we also explored the databases of leading organization, such as World Health Organization (WHO) and Ministry of Health Malaysia (MOH) and Centers for Disease Control and Prevention (CDC).

Dengue

Although dengue fever is among the most common mosquito-borne infections in the world, yet it has long been categorized as a "neglected tropical disease" (Faraji et al., 2014). The Chinese medical encyclopedia from the Jin Dynasty (265–420 AD) was probably the first record of which diseases were associated with flying insects. The first recognized dengue epidemics occurred almost simultaneously in Asia, Africa, and North America in the 1780s. The first confirmed case report of dengue hemorrhagic fever in Southeast Asia occurred in Manila in 1953 and during the second outbreaks in 1956. Today, dengue fever has become one of the major public health issues and is endemic in more than 125 countries globally such as in Malaysia (Othman et al., 2019), China (Xiang et al., 2017), Pakistan (Yousaf et al., 2018) and Sri Lanka (Sun et al., 2017).

There are an estimated 120 million travelers to the subtropical and tropical regions with around two billion people living in developing countries (Banu et al., 2014), of which 40% are at risk of contracting the dengue virus annually, while the mortality rate is 2.5% with more cases of classical dengue with severe symptoms (Rasgon, 2011). There were an estimated 390 million cases of dengue infections in 128 countries, with approximately half a million with dengue fever needing hospitalization (WHO, 2020). In Malaysia, a total of 130,101 cases and 182 deaths were reported in 2019, compared to 80,615 cases and 147 deaths in 2018. Most of the cases were reported in the state of Selangor, with 72,543 cases which comprised 55.76% of the total cases reported in Malaysia (KKM, 2020). The escalation in the number of cases was attributed to poor environmental cleanliness, changes in serotypes and high population density in urban areas.

Control of Mosquitos

Currently, there are no curative treatments or vaccines available. Therefore, control of the dengue vector is crucial to reduce the transmission of dengue fever. A combination of multidisciplinary approach involving local authorities, mobilization of the community and integration of vector control must be done together to ensure the success of the strategy. However, there are many challenges in the response against dengue outbreaks that include unmanaged and rapid urbanization, poor sanitation systems and bad disposal management in the communities (Chang et al., 2011).

One of the most effective vector control methods is to control the level of vector populations (Ahmad-Azri et al., 2019; Mazrura et al., 2012). However, most of the vector control strategies nowadays are solely chemical-based, thus without careful monitoring, it will increase the insecticide resistance phenomenon (Besar et al., 2019). This situation has led the WHO and other agencies to demand for more sustainable and reliable strategies (Bourtzis et al., 2016). Thus, it is important to find novel surveillance and prevention strategies for dengue management (Huong et al., 2004). The occurrence of insecticide resistance may vary by geographical distribution due to high usage of pesticides by households and in agriculture. The development of resistance may also become faster and more severe than expected, thus it is essential to control *Aedes* mosquito populations by eliminating breeding sites through self-initiatives for source reduction in homes and the community (Mazrura et al., 2010).

There are several ways to control a vector population, which are through source reduction, biological control, genetic manipulation, and chemical control (Buhler et al., 2019; Evans et al., 2019; Arham et al., 2018; Awang et al., 2012; Sulaiman et al., 2007). However, the best vector control strategy is to combine source reduction methods, law enforcement and controlling the use of insecticides, which are crucial for the success of any vector control program (Boubidi et al., 2016; Schorkopf et al., 2016). The responsible agencies should prepare several strategies on mosquito management such as performing location assessment, insecticide treatment, educating the public, establishing the policies and regulations, conducting mosquito surveillance and utilizing new technologies (Zaini et al., 2019; Gerding et al., 2016).

The WHO has announced the concept of Integrated Vector Management (IVM) to optimize the use of resources in the management of vector programs that is a rational decision-making for the best management of vector control resources (Sukumaran et al., 2019). The IVM aims to more effectively prevent the transmission of vector-borne diseases such as dengue, chikungunya, malaria and Zika virus, while being more ecologically sound and sustainable (Niang et al., 2018). This strategy implies the collaboration between the public sectors, health sectors and the empowerment of communities by making insecticide application as the last resort. There are five key elements of IVM guidelines: (i) advocacy, social mobilisation and legislation which is enabling the embedding of IVM in policy-design across relevant organisations, (ii) collaboration within the health sector and other agencies, (iii) integrated approach by ensuring the rational use of available tools and resources, (iv) evidence-based decision-making based on local ecology, epidemiology and resources and, (v) capacity-building at national and local level (WHO, 2012). However, without a proper direction, the efficacy of the IVM would not be able to be fully utilized.

Insect Growth Regulators as an Alternative?

Insect Growth Regulators (IGR) are the third generation of insecticides that differ from earlier insecticides on their mechanism through influencing insect development, disrupting the activities of the insect endocrine system and metamorphosis (Palli, 2016). In comparison, the first generation of insecticides is characterized by chemicals known throughout human history that include oils and arsenic. The second generation of insecticides includes carbamates, organophosphates, and organochlorides that were synthesized after the discovery of dichlorodiphenyltrichloroethane DDT.

Insect Growth Regulators (IGR) have a selective mechanism in their mode of action that specifically inhibit the development of insects into adults. The mechanisms of IGR delay the transformation and inhibit the cuticle formation in an insect's immature stage (Darabi et al., 2011). IGRs will be applied during the early life stage of the insects and kill the insect before they become adults, and thus unable to reproduce. IGR is a form of "birth control" and can be described as control of insects through the release of hormones/IGR into the populations. It is not necessary for the IGR to have high toxicity against the target sites but enough that it may lead to a change and abnormalities against insect survival. Two compounds are important in regulating the development of insects, namely: (i) ecdysone (also known as molting hormone, MH), and (ii) juvenile hormone (JH) which directly interfere with insect metamorphosis, embryogenesis, or reproduction.

Pyriproxyfen is a powerful JH agonist which affects the physiology of metamorphosis, embryogenesis, and reproductivity in insects with a unique mode of action. In general, pyriproxyfen is used in larvicidal activities to control mosquitoes, an example being the Sumilarv™ brand of IGR. Pyriproxyfen is useful in inhibiting the emergence of adult *Aedes* spp. and is used in the range of only 0.000048 ppm (Seccacini et al., 2008) to 0.33 ppm (Suman et al., 2017) and could inhibit the emergence of *Ae. albopictus* with a LC_{50} and LC_{90} of 0.0012 ppm and 0.021 ppm respectively (Lau et al., 2015), while the LC_{50} and LC_{90} for *Ae. aegypti* were 0.012 ppb and 0.61 ppb, respectively (Sihuincha et al., 2005). These studies proved that pyriproxyfen is one of the most effective larvicides against *Aedes* species in laboratory settings.

In addition to the larvicidal impact, pyriproxyfen has been reported to reduce the longevity, fertility, and fecundity in exposed mosquitoes. This is a novel strategy as the mosquitoes exposed to the pyriproxyfen are laying unviable eggs. Earlier studies on *Ae. aegypti* using sublethal pyriproxyfen doses demonstrated effects on mosquito fecundity and fertility (Harburguer et al., 2014). Due to its environmental persistence, specific activity against insect stages and being non-toxic to mammals, pyriproxyfen is considered as an attractive alternative to conventional insecticides. Furthermore, pyriproxyfen has been evaluated as a safe insecticide for application in drinking water with minimal impacts on non-target aquatic insects and the environment.

Pull and Push Concept: Autodissemination Potential Against *Aedes* Spp. Mosquitoes

Autodissemination is a novel technology to control mosquito populations by exploiting the ability of female mosquitoes to find suitable breeding sites, and on the skip-oviposition, the mosquito will lay their eggs in different containers during a single gonotrophic cycle. The contaminated mosquito is carrying a small particle of insecticide and will transfer it to other mosquitoes via mating, and oviposition in the hidden and cryptic breeding sites that humans may not be able to assess during inspections (Mains et al., 2015). The mechanism of autodissemination approaches is presented in Figure 1. Autodissemination can be considered as pull and push technologies with the attraction and dispersal concept which are beneficial and cost-effective to the vector control program (Unlu et al., 2017). For the autodissemination technique to be successful, specific prerequisites have to be met which are: 1) The ability of the autodissemination station to attract mosquitoes, 2) the autodissemination station is able to transfer the chemical to the mosquitoes and 3) the insecticide distribution from the exposed mosquitoes to the breeding sites (Caputo et al., 2012; Gaugler et al., 2012). In addition, another requirement is that the chemical used can work at a low concentration and persists in the environment for a long time (Mains et al., 2015).

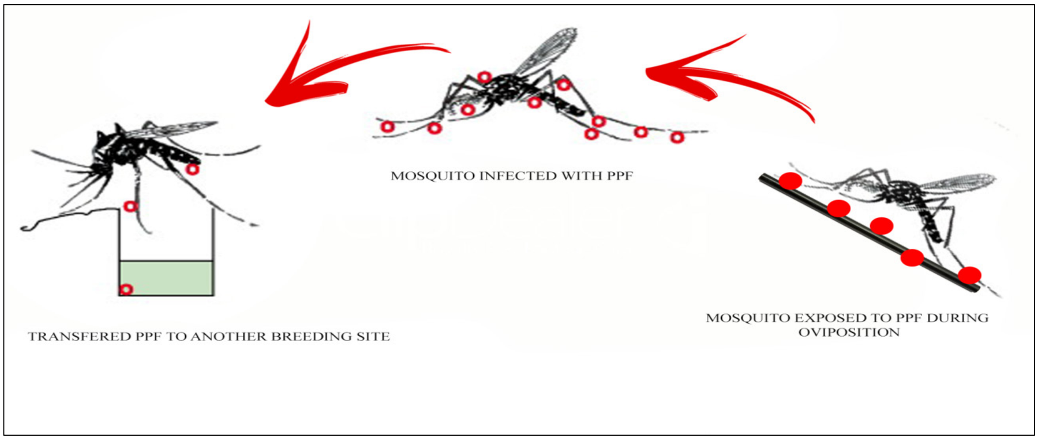

Figure 1. The mechanism of autodissemination of pyriproxyfen by female mosquitoes from exposure containers to other breeding sites.

History of Autodissemination Methods

The concept of autodissemination devices has been tested on other weeds and pests (Pell et al., 1993; Vega et al., 2000). One example is an automatic device using a fungus as biocontrol agents (BCAs) working as a lure. Once the insect is attracted and enters the device, it becomes contaminated and transfers the BCA into populations after leaving the device. The use of BCA dissemination by honey bees was significantly more efficient than conventional sprayers to spread the inoculums against a pest-infested flower (Gross et al., 1994). To enhance the impact of BCAs, the "push-pull" strategy was devised by stimulating the insects out from the population ("push") with feeding the deterrents and extracted ("pull") into the trap. The deterrent lures must be more favorable and attractive than the crop to encourage the insect to enter the traps. In several studies, autodissemination has shown promising results within the pest population when using an attractant device as the initial source of infection (Moslim et al., 2011; Scholte et al., 2004).

Autodissemination has widely been used against diamondback moth (DBM), *Plutella xylostella* using *Zoophthora radican* and rhinoceros beetle, *Oryctes rhinoceros* using *Metarhizium anisopliae.* The manipulation of DBM behavior using semiochemicals such as pheromones has been used to attract and developed epizootic populations before the critical level was achieved (Pell et al., 1993). Other studies in Klang and Selangor, Malaysia found that the mortality rate of *Oryctes rhinoceros* was 75% to 90% when infected by *Metarhizium anisoliae* with the percentage of trapped adults leaving the traps ranging from 85% to 95% (Moslim et al., 2011).

Autodissemination of Pyriproxyfen on Mosquitoes

Although there is still a lack of autodissemination field trials, more studies are being carried out on the effectiveness of pyriproxyfen, with some researchers making favourable general conclusions. Most of these studies found that autodissemination did occur and successfully killed the larvae and reduced *Aedes* spp. populations. Table 1 summarizes the autodissemination studies conducted under semi-field and field settings. The first trial was done in a laboratory (Itoh et al., 1994), and then the concept was furthered by others (Chism & Apperson, 2003). These studies operated under the assumption that mosquitoes were better at carrying insecticides to their preferred breeding sites compared to human operators. The key to the success of the technique is to use pyriproxyfen in small particles to contaminate mosquitoes which can affect control to the whole area (Gaugler et al., 2012)

A novel method was developed based on the skip oviposition behavior of mosquitoes where female mosquitoes transfer small particles of insecticides to their cryptic breeding sites, thus interrupting the development of the larvae and subsequently killing and reducing the mosquito population in target areas. In 2009, a significant trial for an autodissemination concept with pyriproxyfen was conducted in Iquitos, Peru. The placement of the autodissemination was 5% from the available resting areas, which achieved a 42-98% reduction in adult mosquito emergence with a maximum mortality rate of 98% (Devine et al., 2009). Commercially prepared pyriproxyfen in an emulsifiable concentrate (EC) form was shown to be transferred as far as 200 m from the treated areas.

Table 1

Overview of autodissemination trials conducted under semi-field and open field trials

Settings	Target species	Methods	Result	Conclusion	References
SF	*Ae. aegypti*	A dissemination of pyriproxyfen was conducted in a house (6 x 10 m) in Bangkok, Thailand. Four resting cups (source of pyriproxyfen) were placed in the house against ten oviposition cups. The study was maintained for 16 days and all oviposition cups were monitored every four days. All oviposition cups were brought to the laboratory for larva bioassays and monitoring of their development	Most of the samples collected from oviposition cups showed a high emergence inhibition, comfirming the autodissemination of pyriproxyfen had occurred. The male mosquitoes may also play an important role as a transportation of the pyriproxyfen.	This small study was the first to demonstrate autodissemination activity from the resting place to the oviposition sites	Itoh (1993)
OF	*Ae. albopictus*	Field evaluations of autodissemination were conducted in two isolated sites in Rome with a high density of *Aedes* sp. Two sites were selected: i) oldest cemetery (22 x 2 m) and, ii) enclosed garden (1 ha) Ten DS and ten SS were deployed in both sites placed 90 cm to two meters from each other. Two replicates were conducted using 0.5% and 5% pyriproxyfen formulation in Site I; while 5% formulation was used in Site II. Samples collected from all DS and SS together with *Ae. aegypti* larvae were monitored for seven to 12 days.	Two sets of trials showed a significant increase in mortality ranging from 20.8 to 71.2% compared to control. However, a higher concentration of pyriproxyfen (5%) showed better dissemination with higher mortalities in sentinel sites.	The application using 5% pyriproxyfen showed > 50% larvae mortality. This suggested that the higher concentration of pyriproxyfen was able to improved the efficacy of the autodissemination approaches.	Caputo et al. (2012)

Note: SF, semi-field; OF, open field; PPF, Pyriproxyfen; EI, emergence inhibitions; d, days; w, weeks; m, months; DS, Dissemination Station; SS, Sentinel sites

Table 1 *(Continued)*

Settings	Target species	Methods	Result	Conclusion	References
SF	*Ae. albopictus*	Six bed nets (height, 227 cm; width, 270 cm; length, 270 cm) were used in a large greenhouse (16 m x 10 m) at Nagasaki, Japan. Each bed net was provided with artificial and natural resting sites, sugar water, ten ovitraps (3 mg of 1:1 mixture of mouse pellet and yeast as food larvae and 0.2 g hay infusion). A total of 100 pairs of *Aedes albopictus* were released into each bed net and were monitored for 20 (Exp I) to 44 (Exp II) days. Different concentrations of pyriproxyfen were used in Exp I (1 %) and Exp II (0.1 %) Number of eggs laid, hatching rate and females on rats were monitored. The activity of autodissemination were then assessed via larva bioassays obtained from the water samples collected from each ovitrap.	All monitored parameters (number of eggs laid, pupae and egg hatch) showed a significant reduction after pyriproxyfen treatment compared to the control. Moreover, larva bioassays showed significantly increased larva mortality. The pyriproxyfen-treated bed net could be transferred on mosquitoes and subsequently suppressed the mosquito density.	*Aedes albopictus* were exposed to pyriproxyfen by direct contact with the bed nets. Significant reductions (fecundity and egg hatchability) in mosquito population were observed during the trials	Ohba et al. (2013)
SF	*An. arabiensis*	The semi-field trial was conducted in a semi-field system (SFS) (9.6 m x 9.6 m, 3.9 m high) in rural Southern Tanzania. A small hut was provided for tethered cow bait and posible resting sites for mosquitoes. Four identical chambers were used to assess the autodissemination activity. Unfed mosquitoes were released into the SFS and the experiment was conducted for 25 days. All pupae were removed from clay pots and the emergence rates were recorded. The impact of pyriproxyfen were compared between treatment and control sites.	The mean number of adult emergence rates was significantly higher in treatment compared to the control. A higher number of autodissemination clay pots point (8 autodissemination devices) have shown a better reduction in pupae collection and adult emergence rather than using one clay pot.	The first study conducted against the malaria vector in Africa. The application of autodissemination approaches can be considered as one of the additional tools in the malaria program.	Lwetoijera et al. (2014)

Note: SF, semi-field; OF, open field; PPF, Pyriproxyfen; EI, emergence inhibitions; d, days; w, weeks; m, months

Table 1 *(Continued)*

Settings	Target species	Methods	Result	Conclusion	References
OF	*Ae. albopictus*	Two types of experiments were conducted in NJ, USA. Point source application This study was conducted using a tire pile that was treated with pyriproxyfen. Oviposition containers were placed in four opposite compass directions up to 200 m (2010) and 400 m (2011). Larva bioassays were conducted against water samples collected from each oviposition container for six weeks after treatment Areawide treatment In 2010, approximately 25% were treated in scattered checkboard pattern using backpack sprayers to treat the foliage-covered areas. While in 2011, truck-mounted ULV was sprayed around 24.8% of the areas. BG traps were used to monitor adult mosquitoes and pyriproxyfen autodissemination was assessed via larva bioassays	A direct treatment using point source treatment showed a high number of larval mortalities in 2010 compared to 2011. The mosquitoes were found able to disseminate pyriproxyfen up to 200 meters. However, the area-wide treatment was unable to reduce mosquito populations and rainfall may be playing an important role in reducing the effectiveness of pyriproxyfen in the field.	This proved that autodissemination activities had occur from the direct treatment. The implementation under area wide assessment showed no signifcant impact against the control site.	Suman et al. (2014)
OF	*Ae. aegypti* *Ae. albopictus*	A total of 100 dissemination stations were deployed in 7 ha of sub-areas in Amazonas, Brazil for four months coinciding with the wet season. The pre-treatment took 10 months, intervention (4 months) and post treatment (6 months). The oviposition were collected after six days before further investigation in the laboratory. The percentage of larvae mortality, and contamination of oviposition were assessed seperately.	The coverage of pyriproxyfen contamination was > 85% with sentinel ovitrap distances up to 397 m. Larval bioassay showed 75.1% (after treatment) compared to 4.2% (before treatment) in all ovitraps against all species collected. The mortality decreased over the distance between oviposition sites and dissemination stations.	This study found that high numbers of *Aedes* sp. and mosquitoes would facilitate the efficacy of the autodissemination technique	Abad-Franch et al. (2015)

Note: SF, semi-field; OF, open field; PPF, Pyriproxyfen; EI, emergence inhibitions; d, days; w, weeks; m, months

Table 1 *(Continued)*

Settings	Target species	Methods	Result	Conclusion	References
OF	*Ae. aegypti* *Ae. albopictus*	The study was conducted in two sites in Lexington, USA. Field study 1 – mosquito populations were monitored using BG Sentinel traps in both treatment and control areas. About 4500 males treated with pyriproxyfen were released for 20 weeks from the release point. Oviposition sites were placed around 150 m from the release point. Larva bioassays were conducted against water sampled from oviposition sites to assess emergence inhibition of mosquitoes.	A significant contamination result was observed in larval mortality ranging from 40% to 70% up to 150 m from the release station points. Bioassays demonstrated a significant reduction in mosquito survival compared with control. This evidence showed that the released mosquitoes can transfer the pyriproxyfen to other breeding sites	This study revealed the feasibility of male mosquitoes for autodissemination approaches	Mains et al. (2015)
OF	*Ae. aegypti*	Field evaluation was conducted in a public cemetery, Iquitos Peru. Two treatment sites (Site A: 53 x 4 m; Site B: 52 x 3 m) were treated with 10 dissemination stations and 40 oviposition sites in each site. Oviposition sites consisted of 25 uncontaminted laboratory larvae and 200 ml of water. All oviposition and dessimination stations were located between 1.05 m to 37.5 m from each other.	The use of 3 -5 % breeding site treated with pyriproxyfen caused > 95% contamination in sentinel sites. The overall number of mosquito reduction (EI) was 42 – 98% during the trials.	This is the first study reported in an open field setting with 49 – 84% larval mortality in sentinel sites. However, the locations were close to the dissemination station and oviposition station, which would be unreasonable for an operational program.	Devine et al. (2009)

Note: SF, semi-field; OF, open field; PPF, Pyriproxyfen; EI, emergence inhibitions; d, days; w, weeks; m, months

Table 1 *(Continued)*

Settings	Target species	Methods	Result	Conclusion	References
OF	*Ae. aegypti*	The treatment was conducted in two villages in Rayong Province, Thailand. Dissemination stations were deployed around a 150 m radius circle. Each house was given four dessimination stations. Oviposition sites were deployed to monitor mosquito populations. The autodissemination activity was assessed using bioassays on water samples collected from oviposition sites.	A significant difference was recorded against eggs laid ($p < 0.05$) and larva mortalities ($p < 0.01$). However, there is no evidence of pyriproxyfen transferred between treated devices to water-holding containers.	Even though the BG Trap data showed a reduction in *Aedes* sp. population, there was no clear evidence of autodissemination activity having occurred in the study sites.	Ponlawat et al. (2013)
SF	*Ae. albopictus*	Two different studies were conducted in NJ, USA under semi-field and open field settings. SF – mosquito proof tunnel cage (50 m x 2 m x 3 m) with open and cryptic breeding sites were introduced with gravid females. The number collected from each ovipostion site was used to assess the prefences of oviposition OP-	SF: most of the mosquitoes demonstrated a strong preference for cryptic breeding sites even after exposure to pyriproxyfen.	The exposure of pyriproxyfen during oviposition does not effect the preferences of female mosquitoes to lay their eggs in the cryptic sites. A higher preference for cryptic sites was observed during the study periods.	Chandel et al. (2016)
OF	*Ae. aegypti* *Ae. albopictus*	Three oviposition cups consisting of 100 ml of water and 3rd instar larvae were deployed around the treatment sites. One of the oviposition cup was covered in mesh to prevent any contamination from other mosquitoes and served as control site. All oviposition were deployed for four to five days and were brought back to the laboratory to assess larva mortality and development.	A significant larvae mortality (45%) was observed in the treatment cup (Site 1), however, no significant difference was detected in Site 2. The abundance of ovisites, climatic conditions, and population dynamics may affect the efficacy of ADS.	Local mosquito was found to transfer the pyriproxyfen particles. However, the resultsvaried and were not significant in study 2.	Kartzinel et al. (2016)

Note: SF, semi-field; OF, open field; PPF, Pyriproxyfen; EI, emergence inhibitions; d, days; w, weeks; m, months

Table 1 *(Continued)*

Settings	Target species	Methods	Result	Conclusion	References
OF	*Culex quinquefasciatus*	The study was conducted in CA, USA using a treated catch basin. The inhibition emergence was assessed up to eight weeks by comparing the result from treatment and control catch basin.	A high number of emergence inhibition (100%) was recorded against *Culex quinquefasciatus* for the first 3 weeks. However, the efficacy of the insecticide was reduced to 69% (pyriproxyfen) and 68% (methoprene) at 4 weeks. The result was also obstructed by the high mortality in control sites.	A high mortality in control catch basin. Although the study was not specifically designed for autodissemination approach, there is some evidence showing that autodissemination occurred during the trials	Mian et al. (2017)
OF	*Ae. albopictus*	This study was conducted in NJ, USA. Six hotspots were selected and 26 to 28 autodissemination stations were deployed in the treatment plot. All treatments and control sites were assessed using BG Sentinel, oviposition cups and SBS. Larva bioassays were conducted from water samples collected in each SBS. The trials were conducted for nine weeks following the installation of autodissemination stations.	A significant difference was reported in pupa mortality which was 12.4% compared to control (0.5%) The mean number of egg/ovicup and mean number of larvae in ovitraps were also reduced and were significantly different compared to control sites.	This study demonstrated a clear finding regarding the egg population reduction and larvae mortality obtained from the SBS.	Unlu et al. (2017)
SF	*Ae. aegypti/ Ae. albopictus*	The evaluation was conducted in semi-field settings using 4.6 x 4.6 x 4.6 m adjoining screening rooms. The larvicidal activity was assessed by comparing the mortality of larvae between treatment and control stations. The activity of autodissemination was assessed based on emergence inhibition.	A significant inhibition of emergence was observed i) direct trap (100%), ii) in ovitrap (81% - 94%). The exposure against in2Care for 48 h significantly reduced the longevity of adult mosquitoes.	This commercial device was found to effectively transfer pyriproxyfen to other breeding sites and showed higher mortality rate in every stage of larvae growth.	Buckner et al. (2017)

Note: SF, semi-field; OF, open field; PPF, Pyriproxyfen; EI, emergence inhibitions; d, days; w, weeks; m, months

Table 1 *(Continued)*

Settings	Target species	Methods	Result	Conclusion	References
OF	*Ae. aegypti*	Evaluation of BGST as an autodissemination station was conducted in Madeira, Portugal. The BGST capture bag was treated with pyriproxyfen. Seven adapted BGST and 37 artificial breeding sites (ABS) were distributed randomly throughout the study areas. Each ABS contains 250 ml de-chlorinated water, cat food and 20 third instar larvae. The activity of autodissemination was assessed using larval bioassays.	The autodissemination approach consistently showed an impact against the number of mosquitoes. The effectiveness of the autodissemination strategy was also dependent on the distance, local density of adult mosquitoes and time of the implementations.	BGST was found to be effective as an autodissemination station.	Seixas et al. (2019)
SF	*An. arabiensis*	This study was conducted using the semi-field system (SFS) in Southern Tanzania. Four clay pots served as pyriproxyfen sources and 20 aquatic habitats were introduced into the treatment chambers. Self-propagating populations were established inside the SPS. The emergence larvae were fed on tethered cattle. The activity of autodissemination were assessed by larval bioassays and mortality were compared between control and treatment chambers.	A significant reduction in *An. arabiensis* population compared to the control chamber was observed. Before treatment, the emergence of mosquito was similar between control and treament chambers. Three months after treatment, the mean number of emergence was 5.22 ± 0.42 (control) and 0.14 ± 0.04 (treatment) with > 97% suppression was reported in treatment chambers.	This study demonstrated the abilities of a malaria vector to disseminate pyriproxyfen and subsequently reduced the populations.	Lwetoijera et al. (2019)

Note: SF, semi-field; OF, open field; PPF, Pyriproxyfen; EI, emergence inhibitions; d, days; w, weeks; m, months

Table 1 *(Continued)*

Setting	Target Species	Methods	Result	Conclusion	Result
OF	*Ae. aegypti*/ *Ae. albopictus*	A total of 80 autodissemination stations with 120 conventional ovitraps were deployed throughout the study areas. the autodissemination stations and conventional ovitraps were placed less than five meters from each other. Pre-intervention study was conducted for two weeks, intervention (3 months) and post intervention study (four weeks).	There was a significant reduction in egg collection after 3 months of intervention by using autodissemination stations ($p < 0.05$). All eggs directly collected from the autodissemination station showed a significant emergence inhibition compared to the conventional ovitrap.	The autodissemination station (Aedestech Mosquito HomeSystem) was found to effectively control *Aedes* sp. population	Yazan et al. (2020)
OF	*Ae. albopictus*	A three years study of autodissemination tehnique was conducted in NJ, USA from 2014 to 2016. A total of 26-28 autodissemination stations, five oviposition cups and ten sentinel cups were deployed in each city block. Both oviposition cups and sentinel cups were sampled and re-deployed at weekly or biweekly intervals. All water samples collected from ovitraps or sentinel cups were then filtered to remove any debris or dead insects. Autodissemination activity in the field were assessed using larval bioassays. Pupal and larval mortality were recorded for statistical analysis.	The larva and pupal mortalities ranged from 12-19% in the treatment areas. Even though the number of eggs was significantly reduced in 2014, there was no significant difference observed in 2015 and 2016. The impact of autodissemination against mosquito populations was lower compared to previous trials. Several problems and limitations were observed due to the reduction in autodissemination effectiveness such as logistical and technical problems (blockage and exit size of ADS) and limited access to individual properties	The autodissemination station successfully transferred pyriproxyfen to other breeding sites. However, the impact of pyriproxyfen against mosquito populations was low in 2015 - 2016 and it remains unclear and need further investigations.	Unlu et al. (2020)

Note: SF, semi-field; OF, open field; PPF, Pyriproxyfen; EI, emergence inhibitions; d, days; w, weeks; m, months

More recently, the effectiveness of autodissemination methods using pyriproxyfen has been studied in Trenton, New Jersey, which was reported to have a high *Ae. albopictus* population (Unlu et al., 2017). The study showed a reduction in the number of dengue cases, fewer numbers of eggs and residual effects of pyriproxyfen within the treatment areas. Autodissemination has also been studied under different conditions in small-scale field trials against *Ae. albopictus* and *Ae. aegypti* (Buckner et al., 2017; Caputo et al., 2012). Moreover, in 2014, the first study against *Anopheles arabiensis* was conducted in Tanzania, Africa, which observed a 82% inhibition of adult mosquitoes by using pyriproxyfen autodissemination and similar results were observed against *Culex quinquefasciatus* and *Anopheles gambiae* (Mbare et al., 2014). This strategy has shown promising results and can be considered as an alternative vector control against malaria in the future (Lwetoijera et al., 2014). However, a large-scale application of the autodissemination approach needs further investigation.

Recent Advances in Autodissemination on Mosquitoes

A recent advance in autodissemination is the boosted sterile insect technique (SIT) which is a combination of two methods: releasing sterile mosquitoes and contaminating them with pyriproxyfen. Despite the failure of mating, the percentage of pyriproxyfen contamination between the populations is high. During the mating, male mosquitoes will contaminate females and at the same time can contaminate the breeding sites too. Currently, ongoing research has been conducted to explore the effects of pyriproxyfen against mosquito competitiveness, the amount of pyriproxyfen needed from males to females and then, from females to breeding sites and the design of the smart machines to release the mosquitoes in a large scale (Bouyer & Lefrancois, 2014).

One study enhanced the persistence of the insecticide and attraction using a dual treatment system involving an EC formulation and granule formulation for the autodissemination stations and showed that the mosquito can carry the insecticide up to 200 m along the residential areas in the study as detected by residue analysis (Suman et al., 2017). Other studies using a combination of *Beauveria bassina* (entomopathogenic fungus) and pyriproxyfen also gave 100% larval mortality in the laboratory; however, the study did not include any field trials (Buckner et al., 2017; Snetselaar et al., 2014). Another approach used a combination of oil and pyriproxyfen to enhance the attachment of the particle on female mosquitoes and increase the transfer of pyriproxyfen to the oviposition sites (Wang et al., 2014).

An Innovation of Autodissemination Device

An autodissemination station is a new device that has shown promising results in different settings. This device significantly reduced *Aedes* mosquito populations and subsequently inhibited the transmission of dengue cases. In general, most autodissemination stations use a similar concept of attracting mosquitoes to lay their eggs into the traps. Female mosquitoes were then contaminated with pyriproxyfen and transferred the particles to other breeding containers. Some autodissemination stations were developed with their own unique features while still maintaining the basic concept of autodissemination. It is important to determine the effectiveness of prototype autodissemination stations based on their ability to serve as a lethal ovitrap, high mosquito attraction, low cost, biodegradability, and ease of maintenance (Gaugler et al., 2012). These stations are described below and may become widely available with a significant impact on dengue control programs. Thus, a comparative study of autodissemination devices is warranted.

Auto-Dissemination Augmented by Males (ADAM)

Auto-Dissemination Augmented by Males (ADAM) was developed by using a combination of autodissemination and autocidal concepts, and by enhancing the abilities of male *Aedes* mosquitoes (Mains et al., 2015). This technique uses mosquitoes as a transporter to transfer pyriproxyfen via mating attempts, and subsequently, it will transfer the pyriproxyfen to cryptic breeding sites during the oviposition. Corbel et al., (2017) found a significant cross-contamination between males and females who were suitable to release the ADAM in areas of low density *Aedes* populations. Although the density of adult mosquitoes declined after four weeks of treatment, further studies on the mosquito behavior, study area with a different ecological context, as well as the size of the field trials are needed to validate the efficacy of ADAM in the vector control program (Corbel et al., 2017).

In2Care Mosquito Trap

The In2Care mosquito trap has been approved by the United States Environmental Protection Agency (EPA) for use by professionals against *Aedes* mosquitoes. It is the first commercial trap that controls both larvae and adult mosquitoes using pyriproxyfen and *B. bassiana,* a fungus with slow-killing abilities on adult mosquitoes, which can be disseminated by affected female mosquitoes. During the oviposition, female mosquitoes will touch their tarsal on a gauze contaminated with pyriproxyfen and *B. bassiana*. Both agents will stick to the mosquito bodies and be able to disseminate pyriproxyfen to other breeding sites within their flight range (Buckner et al., 2017). The In2Care mosquito traps manipulate the behavior of female mosquitoes by "skip oviposition" and finding cryptic breeding sites. At the same time, the *B. bassiana* spores will grow hyphae, feed upon the bodies, reproduce and kill the mosquitoes within 18 hours (Ragavendran et al., 2017).

AedesTech Mosquito Home (AHM)

AedesTech Mosquito Home (AHM) works by using a "pull" and "push" control strategy combined with the lure-kill technology to reduce *Aedes* populations and interrupting dengue transmission. It has the potential to target larval breeding sites that cannot be reached by traditional larvicidal applications (cryptic breeding sites). The “pull” component uses a formulation with an attractant ingredient lure against female mosquitoes to breed inside the AHM while the “push” component refers to the contaminated mosquitoes dispersing after ovipositing their eggs. In this method, female mosquitoes are used as a carrier for the transfer of insecticide to other containers, and thus disseminating the insecticide to the larval habitats (Liang et. at., 2019). The AHM devices have been designed with a sustainable feature in which gravity is used to control the level of water in the casing. During evaporation, water is released in the casing, filling it back to the pre-set level and the evaporation rate will always be kept at the optimum level which is sufficient for the development of *Aedes* from egg to pupae.

STATUS AND ONGOING STUDIES IN MALAYSIA

Studies on autodissemination using pyriproxyfen are not well established in Malaysia. Most of the studies conducted were only to evaluate the effectiveness of pyriproxyfen against *Aedes* spp. mosquitoes. In a study by Nazni et al. (2015), a total of 350 autodissemination devices were deployed in three apartment blocks consisting of 27 storeys with ten-unit houses per floor. Four units of autodissemination were placed at each level at a distance of 5 m from apartment units. After the exposure periods, there were no viable larvae in the traps, and a significant reduction in number of dengue cases was observed from 53 cases (2013) to 13 cases in 2014. Another study was carried out to explore the additive impact of targeted outdoor residual spraying (TORS) and deployment of autodissemination devices (ADD) in Johor Bharu, Malaysia. Unfortunately, there was no significant effect on the mosquito populations following the combination of TROS and ADD (Hamid et al., 2020).

CONCLUSION

Vector control programs for arboviruses transmitted by mosquitoes are facing many obstacles. However, with new advances and technologies, it may be viable in the foreseeable future. One of these advances is autodissemination which is a self-delivery technique that manipulates the behavior of mosquitoes to carry insecticides and disseminate it to cryptic breeding sites. Autodissemination has shown promising results in several countries and can be considered as additional tools in a vector control program.

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