Effectiveness of the Aedes aegypti Mosquito Vector Control Program in Southeast Asia

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REVIEW ARTICLE

Effectiveness of the *Aedes aegypti* Mosquito Vector Control Program in Southeast Asia

ABSTRACT

Dengue is still a major vector-borne disease problem in the world. It is caused by infection with the Dengue virus, which can be spread through a vector in the form of the *Aedes aegypti* mosquito. One of the ways to reduce the incidence of dengue infection is by controlling vectors. This study aims to analyze the effectiveness of vector control of the *Aedes aegypti* mosquito on the dengue incidence in Southeast Asia. This study is a systematic review that examines articles with experimental research designs and cluster randomized controlled trials. The scope of this research area is limited to Southeast Asian countries during the last ten years. Four journals have significant results in reducing the number of *Aedes aegypti* mosquitoes. Three journals that discussed the output in the form of the Larva Density Index (LDI) show a decrease with significant results. Both journals that discussed biological control (*Bacillus thuringiensis israelensis*) got significant results in decreasing Pupal Density (PD). The two journals on chemical control (*permethrin*) that discussed the outcome of the presence or absence of IgG seroconversion show insignificant results. The researchers reviewed two studies that discuss chemical control, which is *permethrin*. Moreover, those studies also examine the four studies that discussed biological control: *Mesocyclops* and *Bacillus thuringiensis israelensis*. All control methods are considered effective. However, among the three vector control methods studied, the control with *Bacillus thuringiensis israelensis* is the most effective method.

Keywords: *Aedes aegypti*, Dengue, Dengue Control Program, Southeast Asia, Tropical Disease

INTRODUCTION

Dengue is still a major vector-borne disease problem in the world. It is a disease caused by infection with the Dengue virus, which can be spread through a vector in the form of the *Aedes aegypti* mosquito. According to WHO, dengue infection is most often found in tropical and subtropical areas, as well as urban and semi-urban areas (1). The dengue virus infects about 128 countries in the world, with an estimated 390 million dengue infections that occur annually and is the most common mosquito-borne disease in the world (2). In 2020, there were 95.893 cases of dengue fever in Indonesia. The number of deaths due to dengue was 661 cases spread across 472 districts or cities in 34 provinces (3). Meanwhile, in Malaysia, it was recorded that the number of cases of DHF found was 9.270 cases, and the number of deaths was 5 cases during the period from January to May 2021. Afterward, in the Philippines, there were 17.630 cases of DHF, and the number of deaths was 63 cases during the period January 1 to March 27, 2021. Meanwhile, in Singapore, there were 2,217 cases of DHF during the period January to April 2021 (1).

The impact of dengue infection can be asymptomatic and symptomatic. The severity of the symptoms can vary, ranging from flu-like symptoms, headache, nausea, rash to bleeding gums, abdominal pain, and persistent vomiting (4,5). The severe dengue infection can be fatal and cause death, which is requiring appropriate management. But, until now, there is no specific therapy that has been found to treat dengue infection but symptomatic therapy (1). Therefore, clinical monitoring of dengue fever must be carried out regularly to get better results (6).

Various ways can be done to control the incidence of dengue, such as environmental management. It is an effort to modify or manipulate the environment by not allowing stagnant water, closing tubs or containers filled with water, not piling up and throwing away items that are no longer needed, regulation of temperature and humidity, as well as using mosquito nets. Fogging and the mosquito larvae eradication programs based on the 3M+ slogan (the indonesian slogan which consist of the words: draining, closing, and burying) are the most frequently used methods in Indonesia, but the implementation of fogging and 3M+ has not gone well (7). Another method recommended by WHO is to control the vector chemically and biologically. chemical control, namely the use of larvicides, repellants, insect repellent spray, and fogging (1). Insecticides that have been used throughout the world are organophosphates, for example phenitrothion, fenthion, and malathion; and pyrethroids, for example cypermethrin, deltamethrin, and permethrin (8). While biological control, namely by using natural predators of mosquitoes such as dragonflies, frogs, birds, and fish. Then, it can also use the protozoan Ascogregarina culicis, the bacterium Wolbachia pipientis, spores of entomopathogenic fungi (Beauveria bassiana and Metarhizium anisopliae), and Bacillus thuringiensis (Bti) (9).

Of these several methods, it is still not clear which is the best and most effective way to control dengue vectors, especially in Southeast Asia. Therefore, this study aims to systematically review and analyze the effectiveness of dengue vector control methods where divided into chemically, biologically, and environmentally.

METHODS

Research Type and Design

This study is a systematic review that uses articles with experimental research designs and cluster randomized controlled trials. These trials cover research areas in Southeast Asian countries. The data search in this study was conducted online and done on June 11, 2021.

Research Literature of Search Criteria

The criteria for searching research literature using the PICO (Population, Intervention, Comparison, and Outcome) method as shown in table 1. The population characteristics used are people in Southeast Asia. It is with the intervention group that is considered as the dengue infection prevention program and the effectiveness of various dengue infection prevention programs as a comparison. The outcome is the dengue infection rate.

Data Types and Criteria

The following are the inclusion criteria used in table 1:

Technique of Data Collection

The data collection in this systematic review is by taking six scientific research articles from English-language international journal publications in PDF format. The article searches are conducted using the PubMed and ScienceDirect search engines by the keywords dengue infection AND Southeast Asia AND dengue vector control AND *Aedes aegypti*. In the search for articles, the limitations of 2012 to 2021 are used. Based on the search results through search engines using the keywords in question, the articles are then selected based on the title and abstract. After being filtered again based on the inclusion and exclusion criteria, six articles are obtained that matched. The next process is grouping the data based on the variables that are going to be discussed. Furthermore, the data synthesis is conducted to obtain a systematic study related to the effectiveness of controlling the *Aedes aegypti* mosquito vector on the incidence of dengue infection in Southeast Asia (Figure 1).

Data Analysis and Synthesis

The data are analyzed qualitatively descriptively. Afterward, examining how the effectiveness of controlling the *Aedes aegypti* mosquito vector affects the incidence of dengue infection in Southeast Asia. In this study, the data analysis will be formed in a table discussing the results of the answers to the research question that seeks to conclude the effectiveness of the control of the *Aedes aegypti* mosquito vector on the incidence of dengue infection in Southeast Asia according to the expected outcome.

RESULTS

There are 333 articles obtained from two sources: PubMed and ScienceDirect, by using certain keywords. For example, dengue infection AND Southeast Asia AND dengue vector control AND *Aedes aegypti*. Through a screening process based on the presence or absence of access, inclusion, and exclusion criteria. According to the evaluated parameters, the final results obtained are 6 articles.

Of the six studies, there are two studies discussing the effectiveness of permethrin as vector control, two studies that are discussing *Mesocyclops*, and two other studies discuss *Bacillus thuringiensis israelensis* (Bti). The outcome is the number of Aedes aegypti vectors with different forms of the dependent variable. As shown in Table 2, five journals provide an output in the form of the number of *Aedes aegypti* mosquitoes, four of which stated that they had a significant result in that there was a decrease in the number of mosquitoes after the intervention using permethrin by Kittayapong et al., *Mesocyclops* by Nam et al., and Bti by Setha. et al. and Bohari et al. Of the four journals that both studied biological control, only three of them are two studies on *Mesocyclops* and one study on *Bacillus thuringiensis* (by Bohari et al.). Those studies discuss the outcome in the form of the *Larva Density Index* or LDI. However, only the administration of *Bacillus thuringiensis* shows a significant reduction in LDI. Both journals discussing biological control, namely the intervention of *Bacillus thuringiensis* both calculate the outcome in the form of *Pupal Density* (PD) and show a significant reduction in PD after the intervention.

Both journals on vector control in the form of chemical control using permethrin also discussed the outcome of the presence or absence of dengue IgG seroconversion after the intervention. However, both studies show insignificant results. There is one journal in each that provides output in the form of House Index (HI) and Breteau Index (BI). Yet, both are accompanied by Container Index (CI) numbers. Only research by Bohari et al. includes the calculation of Ovitrap Index (OI) with significant results and Incidence Rate (IR). The journal compares the results before and after the intervention, as well as between the intervention group and the control group.

DISCUSSION

Dengue is an infectious disease caused by the dengue virus and is transmitted by mosquitoes of the *Aedes* genus (10). Until now, dengue is still a major health problem that can cause morbidity and economic burden, especially in tropical and subtropical countries (11). Various prevention efforts are carried out to reduce and overcome the incidence of dengue infection in the world, one of which is by controlling the vector. Various prevention efforts are conducted to reduce and overcome the incidence of dengue infection in the world. One of them is by controlling the vector. The control of vectors based on the mechanism can be grouped into environmental management, chemical control, and biological control (1).

Permethrin

Permethrin, based on its chemical structure, is a type I pyrethroid insecticide, which can be used as a chemical vector control. Pyrethroids have an insecticidal effect by intervening with voltage-gated sodium channels (VGSC) on vector neuron membranes, binding open channels, and preventing re-closure., thereby prolonging the potential action causing the vector to experience paralysis or knock-down, resulting in vector mortality (12). In addition to having an insecticidal effect, pyrethroids have a spatial repellent effect and contact irritant effect, as well as excito-repellency, which is the reason for the use of pyrethroid insecticides such as permethrin for clothing (13). The results of a study conducted by Pattamaporn Kittayapong et al. (2017) and Tsunoda et al. (2013) showed that permethrin was effective in reducing the number of Aedes mosquito vectors, although it was applied with 2 application methods and 2 different research locations. Kittayapong et al. impregnated permethrin in school uniforms in Thailand and was shown to reduce the incidence of dengue and the number of Aedes aegypti mosquitoes caught in the classroom compared to control schools (14,15).

Meanwhile, Tsunoda et al. in Vietnam impregnated 2% permethrin in mosquito nets (Olyset® Net) and reduced the Container Index (CI), House Index (HI), the percentage of positive containers for immature *Aedes* mosquitoes ($p<0.05$), and the dengue seroconversion rate was lower than the control area(15). This Olyset® Net has previously been developed as a mosquito net for protection against the bite of the malaria mosquito vector and reduced the prevalence of malaria by 45.7% in India (16). Olyset® Net (permethrin 2%) reduces mosquito landing effort and increases flight time, thereby preventing female mosquitoes from laying eggs in containers installed with Olyset® Net. The use of permethrin on clothing may cause side effects. It is seen in the study by Kittayapong et al. (2017), where a number of students experienced mild skin irritation. Hence, they had to be withdrawn from the study (14). According to Marlie Hartley (2010), the use of permethrin can cause allergic dermatitis in individuals who have allergies to chrysanthemums, ragweed plants, or turpentine, although this is rare. In addition to possible side effects, the knock-down value (after 1 hour) and mortality (after 24 hours) in mosquitoes decrease rapidly after 4 washes, and the efficacy of permethrin is calculated to be below 20% after 20 washes (14).

Several findings also reported the possibility of mosquito resistance to pyrethroids which underlies a recent study to develop Olyset® Net containing only 2% permethrin and combining it with other substances. Pennetier et al. (2013) (17) at Bennin combined Olyset® Net (2% permethrin) with Piperonyl-Butoxide (PBO) 10g/kg, which has known as Olyset® Plus. Meanwhile, Koffi and colleagues (2014) (18) at Central Côte d'Ivoire combined Olyset® Net with pyriproxyfen, an insect growth regulator (IGR) to form Olyset® Duo. A combination of 2% permethrin with other substances has proven to be more effective in reducing the number of mosquitoes, including pyrethroid-resistant mosquitoes.

Mesocyclops

Mesocyclops is used as a form of biological mosquito control that is non-toxic and inexpensive because it has a high reproductive capacity (19). Mesocyclops works by preying on the larvae of Aedes aegypti so that it can break the life cycle of the mosquito (20). The results of a study conducted by Nam and colleagues (2012) (21) with community-based Mesocyclops intervention showed a significant decrease in the number of Aedes aegypti mosquitoes with an average decrease of 98.8%.

In 4 of the 5 communities, no incidence of dengue is found after the serological analysis. The results of this study are in line with the results of research by Tran et al. (2015) (22) on 100 randomly selected households in the community. It was found that the Mesocyclops intervention program reduced larval density by more than 98% during the program intervention period conducted by the government. However, in the last period of program intervention by the government, there was an increase in larval density and the number of Aedes aegypti mosquitoes, as well as a decrease in the number of Mesocyclops after the transfer of program responsibility to the community. This can happen due to a lack of public knowledge about effective methods of mosquito control management with Mesocyclops, considering that limited food and poor care will inhibit Mesocyclops populations. Although no incidence of dengue occurred, this cannot be said to be related to a decrease in the number of Mesocyclops and an increase in the number of Aedes aegypti mosquitoes. This is because many other factors affect the incidence of dengue, such as weather, dengue virulence, the immunological status of patients, and population density (22). Both studies were conducted community-based in Vietnam in different locations and time periods. The intervention of the two studies was carried out by inserting Mesocyclops as a biological agent into water containers. Based on these two studies, Mesocyclops proved to be effective as a biologic agent in dengue vector control.

***Bacillus thuringiensis israelensis* (Bti)**

Of the six journals reviewed, there are two journals that discuss biological vector control using the bacterium Bacillus thuringiensis israelensis (Bti). Bacillus thuringiensis (Bti) will form parasporal crystals composed of protoxin proteins. These protein crystals are toxic when eaten by mosquito larvae, bind to intestinal epithelial cells, and cause holes in the intestines so that the larvae die (23). Bti has been used as mosquito control for more than 30 years and has been shown to be non-toxic to humans and other animals. Based on a study conducted by Setha and colleagues (2016) in Cambodia and Bohari et al. (2020) in Malaysia, it showed that containers or containers treated with Bti during treatment and post-treatment experienced a decrease in the number of pupae, and even the number of pupae became less. None at all compared to containers or containers that were not treated with Bti ($p<0.05$) (24,25).

According to Setha and colleagues (2016) (24), treatment with Bti strain AM65-52 at 8g/1000L, the same dose used in the previous study, can significantly suppress the formation of Ae aegypti pupae ($p<0.05$). In addition to suppressing the formation of pupae, according to research conducted by Setha et al. (2016) (24), Bti also reduced the number of Ae aegypti mosquitoes counted during treatment and post-treatment ($p <0.05$). Meanwhile, the research conducted by Bohari and colleagues (2020) (25) in 2015 showed the results that Bti treatment proved effective in reducing the AI (Aedes Index), larval density index (LDI) ($p <0.05$), ovitrap index (OI) ($p<0.05$), and Incidence Rate (IR) compared to areas that did not receive Bti treatment. Bohari and colleagues (2020) also investigated the use of Bti with the wide spray method, which turned out to be able to reach larval habitats that are difficult to detect. An evaluation confirmed that Bti droplets were able to penetrate barriers and settle in water containers among dense vegetation, as well as on the first level of buildings up to 5 meters above the ground. The Bti solution with a concentration of 125 grams/12 liters is said to be efficacious for 21 days after treatment. From these two studies, it can be concluded that Bti is the most effective in controlling vectors, as stated by the CDC in 2017.

CONCLUSION

Based on the results of a systematic review of six studies, it can be concluded that all control methods studied are effective in controlling *Aedes aegypti* as a dengue vector. The researchers review two studies that discussed chemical control, namely permethrin, and four studies that discussed biological control, namely *Mesocyclops* and *Bacillus thuringiensis israelensis*. Among the three vector control methods studied, the control with *Bacillus thuringiensis israelensis* is the most effective method. Further studies are needed on the advantages and disadvantages of each vector control method. In addition, adjustments are also needed to existing environmental and community conditions so that vector control methods can be more effective.

CONFLICT OF INTEREST

None of the author have any conflicts of interest to disclose

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-nor-profit-sectors

ETHICAL STATEMENT

Not applicable

AUTHOR CONTRIBUTIONS

All author participate in writing the manuscript, had read and approved the final manuscript

FIGURE

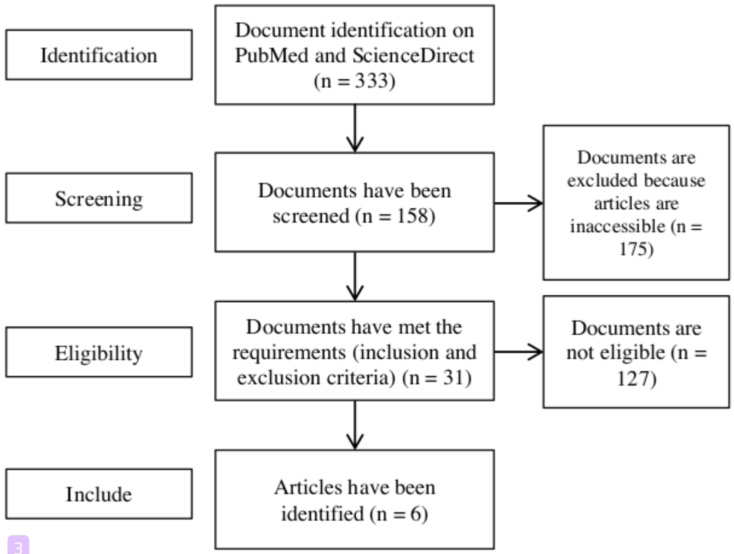

Figure 1 Diagram of preferred reporting items for systematic review and meta-analysis (PRISMA)

Category	**Inclusion**	**Exclusion**
Languages	*English, Indonesian*	*Others*
Objectives	Biological, chemical, and mechanical dengue vector control (environmental management)	*Others*
Outcome	Number of vectors of *Aedes aegypti*	
Population	All people in Southeast Asia	All people outside Southeast Asia
Publication Type	*Original article*	*Review article, meta-analysis, systematic review, case series, background article, commentary, editorial,* etc.
Study design	*Cross sectional/ case control/ cohort study/ cluster randomised controlled trial/ experimental*	*Others*
Study duration	2012-2021	*Others*

Table 2. Research results

No	Title	Author	Location	Design, Number of Samples, Time, and Period	Intervension	Outcome of measurement	Outcome
1.	Mitigating Diseases Transmitte by Aedes Mosquitoes: A Cluster Randomised Trial of Permethrin Impregnate School Uniforms	Kittay pong, P. *et al*	Distrik Plaeng Yao, Provinsi Chachoeng sao, Thailand	Cluster-Random is ed Controlled Trial. 10 schools, 1811 students, ages 6-17. June-November (5 months)	Impregnation of school uniforms with *permethrin* liquid	The incidence of dengue infection, the number of *Aedes aegypti* mosquitoes (with BG-S trap), and knock-down within 1 hour, and mortality within 24 hours of *Aedes aegypti* mosquitoes (with WHOPES cone tests)	**Incidence of infection:** 57 of 1655 students with paired serum samples proved to be infected with new dengue, that is 24 at school control (3.7%) and 33 at school treatment (3.3%). **The number of A. aegypti mosquitoes:** Mosquito catches were significantly lower in the treatment school than in the control school. **Knock-down (1 hour) and mortality (24 hours):** The percentage is almost 100% to 4 washes, after 20 washes, the efficacy is <20%. Knock down decreased at a linear rate of about 4.7%/week and mortality at 4.4%/week.
2.	Field trial on a novel control method for the dengue vector, Aedes aegypti by the systematic	Tsunoda et al	Tan Chanh City, Long An Province, Vietnam	Cluster-Randomised ed Controlled Trial. 313 (trial) and 363 (control) House Ladder. August 2008-February 2009	Intervention with Olyset® Net water container lid (containing 2% permethrin) and pyriproxyfen	Percentage of immature Aedes mosquitoes, HI, CI, and dengue seroconversion rate (IgG anti-dengue ELISA)	**Percentage immature mosquito:** lower positive after treatment (trial) compared to with area control. After 2 post month treatment, area treatment with Olyset® Net experience drop significant and lower compared to area control (value p<0.001, OR area treatment 0.7 and OR control area 1.0). moon girl Dec and Feb when combined, that in the area treatment has percentage positive container lower than area control (value x2 test

	use of Olyset® Net and pyriproxyfen in Southern Vietnam						6.38 and value P <0.05). **Container Index (CI):** gradually decreased on October-February (trial) compared to with CI area control, except 'concrete tank cylinder' on the moon February. **House Index (HI):** before treatment, HI trial area more Tall compared to area control. After treatment, HI area decreased trial last October increase gradually month December-February. HI control area continues to increase August-February. Seroprevalence of anti-dengue IgG: in healthy residents of the trial and control areas did not differ significantly. Seroconversion was observed at 23 of 37 seronegative cases in the trial area (62.2%) and 44 of 59 seronegative cases in the control area (74.6%).
3.	Social sustainability of Mesocyclops biological control for dengue in South Vietnam	Tran et al	Chanh An, Mang Thit district, Vinh Long province, Vietnam.	Experimental. 100 random houses. 2008-2013 (55 months)	Intervention with *Mesocyclops*	LDI, IBI, CI, Mesocyclops prevalence	**0 Month =** LDI 105%, CI = 40%, BI 140%, percentage of mesocyclops = 27%. **18 Months =** LDI 15%, CI = 1%, BI = 2%, percentage of mesocyclops = 75%. **55 Months =** 30% LDI, CI = 10%, BI = 55%, percentage of mesocyclops = 37%
4.	Community-Based Control of Aedes aegypti By Using	Nam et al	Southern Vietnam	Cluster-Randomised Controlled Trial. 14 communities with 124. 743	Intervention with Mesocyclops	Larva Density Index (LDI), number of adult Aedes aegypti, number of	**Number of adult mosquitoes:** Mean ± SD of adult females decreased from 0.93 ± 0.62 to 0.06 ± 0.09, the average decline is 98.8%. 6 communities: no adult mosquitoes, 1 community of which no larva/pupae were found (immature).

	Mesocyclops in Southern Vietnam			population. 2004-2010 (6 years).		immature Aedes aegypti, the prevalence of Mesocyclops	**Mesocyclops:** In > 50-liter containers increased from 12.77 ± 8.39 to 75.69 ± 9.17% during period 15-45 months. **Dengue incident:** There was no incidence of dengue in 4 out of 5 communities by serological analysis.
5.	Bacterial Larvicide, Bacillus thuringiens is israelensis Strain AM 65-52 Water Dispersible Granule Formation Impacts Both Dengue Vector, Aedes aegypti (L.) Population Density and Disease Transmission in Cambodia	Setha *et al*	Peani (trial) and Ou Ruessei (control) communes, Cambodia	Experimental. 1343 (trial) and 1595 (control) households with 3-4 containers per household. 2005-2006 (1 year).	Bacillus thuringiens is israelensis AM strain 65-52 and control without treatment	Number of pupae, number of adult Aedes aegypti mosquitoes	**(2005) Post-treatment:** 2 weeks; Peani commune 0 pupa & Ou Ruessei 50.42 ± 12.04 pupa in containers, 12 weeks: the number of adult mosquitoes continue to decline in the Peani commune. **18 Weeks:** The number of pupae in Peani commune is very low. **(2006) post-treatment:** 2 weeks: Peani commune 0 pupae, 10 weeks: Peani commune pupa count is still very low, **13 Weeks:** Peani commune pupae count increased, remained significantly lower than containers in Ou Ruessei commune. The adult Ae aegypti population in Peani commune was significantly suppressed until week 19 (end of surveillance). The lowest population was 1.82 ± 0.42/house 4 weeks post treatment. Meanwhile, during the rainy season, from 6-13 weeks post-treatment, an average of 3-13 mosquitoes/per house in Peani; 15-26 mosquitoes on Ou Ruessei. Mosquitoes in Peani peaked at 12.52 ± 2.45 at 13 weeks post treatment.
6.	Wide area spray of bacterial	Bohari et al	Sibu District, Sarawak,	Experimental. Trial (Z-7L): 2640;	Giving Bti via 2 ways; (1) by direct	Aedes Index(AI), Larva Density	**Aedes Index (AI):** Z-7L = 12,78 ± 4,06a (pre-treatment) and 0b (post-treatment).

	larvicide, Bacillus thuringiens is israelensis strain AM65-52, integrated in the national vector control program impacts dengue transmission in an urban township in Sibu district, Sarawak, Malaysia		Malaysia	Control (Z-5, Z,14): 1809 dan 2227 House Ladder. 23 week (5 week pre-treatment, 12 weeks of treatment, and 6 weeks of post-treatment; EW/epidemiological week 19-41)	into the receptacle for container in the and outside room and (2) wide spray especially for the outdoors. Z-7L as the intervention group, while Z-5 and Z-14 as the control group.	Index (LDI), Pupae Density (PD), Ovitrap Index (OI), dan Incidence Rate (IR)	Z-5 = 16, 42 ± 4,50a(pre-Treatment) and 5,03 ± 1,70a(post-treatment). a,b Show difference significant (p<0,05). **Larvae Density Index (LDI):** Z-7L = 0,26 ± 0,11a (pre-treatment) and 0b (post-treatment). Z-5 = 0,19 ± 0,09a(pre- treatment) and 0,09 ± 0,03a (post- treatment). a,b show Significant Difference (p<0,05). **Pupal Density (PD):** Z-7L = 0,05-0,1 (EW 20), 0 (EW 25-39), <0,05 (EW 40), 0,05-0,1 (EW 41). Z-5 = 0,1 (EW 23), 0,35-0,4 (EW 24), 0,05-0,1 (EW 36 and 40). **Ovitrap Index(OI):** Z-7L = 9,03 ± 3,90a (pre-treatment), 8,64 ± 2,30b(treatment), and 19,70 ± 5,00b(post-treatment). Z-5 = 6,70 ± 3,30a (pre-treatment), 21,10 ± 4,30a (treatment), and 45,60 ± 5,90a (post-treatment). **Incidence Rate (IR):** 2014 = There was an increase in the incidence of dengue from EW (epidemiological week) 25 until the end of the year. 397-1671/100,000 population in the three zones. 2015 = 460/100,000 (on EW 1-28) and 9/100,000 (on EW 29-52) on the Z-7L. 1527/100,000 (at EW 1-28) and 263 (at EW 29-52).

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