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DENGUE VECTOR CONTROL APPROACHES: EXISTING OPTIONS AND THE WAY FORWARD

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Abstract: *Aedes* mosquitoes are crucial vectors of many significant viral infections. The intensifying and convoluted threat of dengue on a global scale warrants enhanced approaches to mosquito control. This short communication aims to provide an overview of the various types of environmental, biological, plant-based and chemical control strategies employed worldwide to curb dengue outbreaks which are worthy of reflection. The use of synthetic insecticides as the predominant method to reduce the spread of dengue has been widely adopted, albeit with caution. The prolonged dependency and repetitive usage of chemical insecticides has been associated with negative ecological and physiological dangers, necessitating the pursuit of alternative strategies to augment existing methods of mosquito control. This review aims to discuss the effectiveness of existing insecticides and the potential use of natural larvicides of botanical origin against dengue using literature sourced from electronic databases. Although many studies have utilised plant-based derivatives as naturally occurring pesticides, their efficacy needs to be further investigated which forms the rationale behind this review.

Keywords: Dengue, environmental control, biological control, larvicides, chemical control.

Introduction

The increasing global incidence of dengue fever (DF) is alarming. It is transmitted by the *Aedes (Stegomyia)* mosquito which can lead to hospitalisation and death in many parts of the world (Jing & Wang, 2019). DF is widespread, present in more than 100 countries with cases reported across Southeast Asia, America, Africa, Eastern Mediterranean and the Western Pacific (Medlock *et al.,* 2015; Guo *et al.,* 2017). Approximately 2.5 billion individuals living in endemic regions are vulnerable to dengue and severe dengue infections with an estimate of 400 million cases occurring each year. Infections regularly show symptoms following the two weeks of incubation, followed by an acute onset. Mortality rates can be as high as between 5% and 20% (Guzman *et al.,* 2010; Linares *et al.,* 2013; Jing & Wang, 2019) and can result in the impairment of health services and grave economic losses.

The resurgence of DF and its increased severity may be due to various factors including climate change, urbanisation, globalisation and ineffective vector control intervention. Asia is one of the most seriously affected regions, representing 70% of cases reported globally (WHO, 2020). In Taiwan, five outbreaks were reported with more than 1,000 cases of DF documented (Yang *et al.,* 2014). Similarly, Malaysia, often witnesses an increased risk of DF in uban and peri-urban areas with high transmission rates occurring during rainy and monsoon seasons. DF/has now spread to new areas including Europe. From observations made by Vaux *et al.* (2019), there is an ongoing invasion of *Ae. albopictus* into the United Kingdom due to ground vehicular traffic that is anticipated to escalate.

The principal concept to minimise dengue transmission is to reduce mosquito densities and eliminate potential breeding sites. However, frequent, repetitive and excessive use of synthetic insecticide may lead to harmful consequences such as destabilisation of an ecosystem and environmental pollution (Jirakanjanakit *et al.,* 2007; Sarwar *et al.,* 2009). As such, environmental management, biological and plant-based alternatives are often employed in conjunction with the use of chemicals to curb dengue. The most suitable vector control method to apply largely depends on the behaviour and local ecology of the *Aedes* mosquitoes, the availability of resources, the cultural context in the area, the adequacy of coverage and the viability (WHO, 2009). More often, a combination of vector-control methods employed synergistically could help maintain low-level vector populations (Guzman *et al.,* 2010).

Most endemic countries have implemented strategies to improve outbreak response by enhancing the global surveillance capacity (Guzman *et al.,* 2010). The Thailand Public Health Ministry for instance, like many other Southeast Asian countries has relied on the usage of chemical insecticides to control dengue vectors since the 1960s (Kittayapong *et al.,* 2006). Malaysia too has been aggressively fighting dengue since the 1970s. Many household surveys, larvicide, fogging and Ultra-Low Volume (ULV) activities were conducted as a part of the dengue control programme over the years. Similarly, this is also observed in other countries such as Oman from 2018 to 2019 (Vythilingam & Wan-Yusoff, 2017; Al-Abri *et al.,* 2020).

Since then, the strategies for dengue prevention and control in Malaysia have focussed on five key thrusts as recommended by the World Health Organisation (WHO) including:

(1) Implementing elements of integrated vector management (IVM)
(2) Enhancing public health surveillance by harnessing collaborative linkages and health information systems
(3) Strengthening emergency planning and response plans
(4) Establishing capacity building interventions, and steering training courses and workshops in the field
(5) Conducting competitive research and development projects that focus on dengue prevention (Ong, 2016)

Similar methods and policies are also in place in neighbouring countries. There is a plethora of information in the literature on existing control measures that warrant an update, synthesis and integration of findings. Furthermore, there is a conceptual debate regarding the benefits, efficacy and practical certainty of the options, forming the rationale of the study. This review aims to explore the relevancy, potentiality and applicability of prevailing methods.

Methodology

The literature for review was conducted using electronic databases and scientific search engines namely Scopus, PubMed, Springer Link, Wiley Online Library and Science Direct. For the literature search, the terms ("dengue"), ("dengue fever"), ("dengue outbreak"), ("environmental control"), ("biological control"), ("chemical control"), ("plant-based larvicides") were considered as a means of selecting articles that focus on dengue control. The keywords were used as is or in combination with other terms, using an "and" "or" during the search. In the initial screening process, an analysis of the information available in the title, running head, abstract and keywords was performed. In the subsequent step, articles were selected and excluded if they did not meet the following criteria:

(1) The articles were not written in English
(2) The articles were not published in peer-reviewed journals
(3) The articles did not focus on the subject of dengue control
(4) Articles that did not capture the essence, purpose and
(5) Articles that did not capture the objectives of this study

Furthermore, references cited in the reference list in the selected articles were also used to examine and search for additional literature. Such articles were analysed in terms of relevancy and subjected to the same eligibility evaluation as previously mentioned.

Environmental Control of Dengue Outbreak

The behaviour of *Aedes* mosquitoes can be influenced by the changes in present-day human lifestyle and urbanization (Sumayyah *et al.,* 2016). *Aedes aegypti* can make use of the wide variety of human-made surroundings in a built-up environment with its ancestral counterpart *Ae. aegypti formosus* which was naturally dependent on tree-hole habitations. The vector can effortlessly colonise new regions of the world because the eggs are easily transported and can withstand drying. However, the species is not able to withstand the cold winter temperature because its eggs are incapable of enduring harsh climates and they go through a diapause (Vaux *et al.,* 2019). Similar to *Ae. aegypti*, the eggs of *Ae. albopictus* can survive drying for several months. In this way, it can distribute itself universally with ease due to the physiological nature of its eggs, its close association with human interactions and the escalation of globalisation (Fontenille & Toto, 2001). The import of used tyre trade poses an environmental risk that is beneficial for *Aedes* mosquitoes. The inner surfaces of tyres are capable of moving the dry eggs from one place to another as seen in countries such as France, Italy and the Netherlands (Medlock *et al*., 2012; Vaux *et al*., 2019). Dengue continues to flow and circulate to new areas, including places that were previously inhibitory.

Environmental management commonly involves planning, performing and monitoring activities to modify environmental factors to minimise, eliminate or deprive these vectors of favourable breeding sites (Wang *et al.,* 2020). Environmental control programmes are typically community-driven and reduce the sources of vector propagation by eradicating, adjusting or recycling larval habitats. Examples of environmental management strategies are summarised in Table 1.

Implementation of such interventions in tandem with health promotion campaigns necessitates environmental review and investments in infrastructure manpower and

Table 1: Three types of environmental management

Type	Definition	Examples
Environmental modification	Changes or transformations that aimed to decrease larval habitats. The changes are often lifelong/long-standing	Strengthening physical systems. E.g., water supply installations to rural communities and the development of good quality water distribution facilities
Environmental manipulation	Temporary changes involve managing “essential” containers where the vectors breed	Disposal of solid/household waste/tyres/containers to decrease larval habitat or potential breeding sites of dengue vectors
Adjustment of human behaviour or habitation changes	Goals to lessen host-vector contact	Using mosquito net during the daytime and installing mosquito screening on windows

(World Health Organisation, 2009)

management of resources. This includes the provision of safe water supplies and improving the present solid waste disposal management/collection system (Guzman *et al.,* 2010; Ong, 2016). This requires the promotion of health literacy, collective interest and cohesive strategies from all relevant authorities involved as well as economic valuations particularly in developing countries to ensure long-term sustainability. Community-driven interventions conducted in Asia and Latin America have led to a reduction in vector densities (Bowman *et al.,* 2016). Furthermore, findings by Ouédraogo (2018) revealed that well-organised, community-based interventions are feasible and have shown to be effective in controlling dengue in Africa.

Biological Control of Dengue Outbreak

Biological controls are methods used to reduce or alleviate pests using living organisms to feed on or challenge the target species. Effective biological control strategies are classically depended on the use of predacious species to reduce mosquito populations. This includes the use of larvivorous fish from the members of the Poeciliidae family such as *Gambusia affinis*, *Gambusia holbrooki*, *Poecilia reticulata* and *Poecilia latipinna* as well as fish that are farmed for human consumption such as species of tilapia (family Cichlidae), *Oreochromis niloticus* and *Oreochromis spilurus*, perch (family Percidae), for example, *Perca fluviatilis*, *Perca schrenkii* and *Perca flavescens* and grass carp (family Cyprinidae), for example, *Ctenopharyngodon idella* (Han *et al.,* 2015; Huang *et al.,* 2017) which have shown to cause reductions in the immature vector stages.

The predatory characteristics of mosquitoes within the genus *Toxorhynchites* such as *Toxorhynchites splendens*, *Tx. brevipalpis*, *Tx. moctezuma* and *Tx. Rutilus* on larvae is an essential feature in its practice as a biological control species (Huang *et al*., 2017, Donald *et al.,* 2020). The use of these non-biting mosquitoes provides an alternative sustainable method for the elimination of mosquito infections. In addition, the predation efficiency of crustaceans such as copepods mainly *Mesocyclops* and *Macrocyclops* species (Baldacchino *et al.,* 2017; Udayanga *et al*., 2019) and *Utricularia macrorhiza*, a carnivorous aquatic plant (Couret *et al.,* 2020) have been documented with minimum consequences on the environment.

The use of entomopathogenic fungi such as *Lagenidium, Coelomomyces, Entomophthora, Beauveria, Metarhizum* and *Culicinomyces* are known to affect mosquito populations and have been studied extensively with regard to disease transmission (Alves *et al.,* 2002; Scholte *et al.,* 2004). For instance, infections by *Beauveria bassiana* have been known to decrease the survival rate, feeding success and fecundity in *Ae. aegypti* (Huang *et al.,* 2017). *Lagenidium giganteum* has been described as being able to reduce the populations of *Ae. aegypti* and *Culex quinquefasciatus* larvae in artificial containers (Rueda *et al.,* 1990; Huang *et al*., 2017). Similarly, infections by *Metarhizium species* was found to be pathogenic to a wide range of mosquitoes of the *Aedes* and *Culex* genera (Alkhaibari *et al.,* 2016). Controlled experiments have therefore proven the effectiveness of entomopathogenic fungi in reducing mosquito populations.

The utilisation of the latest innovative techniques in biotechnology, including the use of genetically modified *Aedes* and *Wolbachia*-infected *Aedes is* also pivotal (Jing & Wang, 2019). For instance, maternally inherited endosymbiont bacterium *Wolbachia* A (wAlbA) and B (wAlbB) strains can naturally infect *Ae. albopictus*, resulting in cytoplasmic incompatibility (CI) (Nazni *et al.,* 2019; Ismail *et al.,* 2021). These intracellular bacteria function as reproductive parasites that can be used as a tool to suppress the mosquito population and hence, the infected progeny will have a vulnerability to viral pathogens (Bourtzis *et al.,* 2014; Vythilingam & Wan-Yusoff, 2017). This indeed is extremely promising. The implementation could however be hampered by financial and operational difficulties due to lack of facilities, the complexity of re-introducing these agents into the habitats (Guzman *et al.,* 2010), the short life expectancy of the genetically modified mosquitoes and the intricate life cycle and feeding behaviours of the biological predators as seen in Toxorhynchites sp. (Ong, 2016).

Plant-based Larvicidal Agents

Biologically active plant extracts are safe alternatives (Zhu *et al.,* 2008; Kumar *et al.,* 2012; Shoukat *et al.,* 2020), possessing insecticidal properties that can be used to avert and regulate outbreaks. Natural products pose less economic burden compared with other interventions. Such agents contain a myriad of potentially bioactive ingredients that can intercede and arbitrate standard biological processes of a vector and thus can alter and modify the virus's life cycle. Several botanical plants have shown their versatility in possessing natural pesticide abilities either in its crude form, extracted as an essential oil, or as bioactive fractions (Fallatah & Khater, 2010; Bilal *et al*., 2012). For example, *Lantana camara* exhibited larvicidal activity with a significant LC_{50} value against *Ae. aegypti* and is thus considered a potential larvicidal agent, which can be utilised for this vector (Kumar *et al.,* 2012). Plant extracts, essential oils and their secondary metabolites could also be used synergistically with favourable effects. For instance, Chansang *et al.* (2018) documented that the combination of essential oils isolated from rhizomes of *Cinnamomum verum*, *Alpinia galanga* and *Cyperus rotundus* alongside permethrin enhanced both its adulticidal toxicity and mosquitocidal efficacy against *Ae. aegypti.*

Extracts from *Zingiber officinalis, Achyranthes aspera, Trachyspermum ammi, Ricinus communis* and *Cassia occidentalis* have displayed significant larvicidal activities with LC_{50} values ranging between 55.0 and 74.67 ppm (Kumar *et al.,* 2012). Similarly, Musau *et al*. (2016) documented the larvicidal properties of *Ocimum suave*, *Plectranthus barbatus* A. *Azadirachta indica* A. *Juss*., *Adansonia digitata* Linn., *Lantana camara* and L. *Tagetus minuta* L. The larvicidal activity was dose-dependent and all extracts exhibited 100% mortality at 1 mg/ml. Such effects could have been a result of the actions of alkaloids and flavonoids that were in all the plants assessed. Furthermore, Pavela *et al.* (2019) documented findings obtained using more than 400 plant species, 29 of which revealed significant larvicidal activity with LC_{50} values less than 10 ppm against *Culex, Aedes and Anopheles*. The study outlined the vast array of different metabolites in plants with different modes of action as summarised in Table 2. Most of the mechanisms are similar to the mode of action of insecticides, justifying its timely permissibility to substitute synthetic insecticides.

Chemical Control of Dengue Outbreak

The International Programme on Chemical Safety (IPCS) is responsible to assess the health and environmental risks from exposure to chemicals that are often used during space spray applications, Indoor Residual Spraying (IRS) space treatment and the usage of Insecticide-Treated Nets (ITNs) as larvicides (Weeratunga *et al.,* 2017). This involves the evaluation of insecticides, larvicides and insect growth regulators such as pyriproxyfen (PPF), temephos (Abate), methoprene and the bacterium *Bacillus thuringiensis serovar israelensis* (Bti) H-14 and *Toxorhynchites* sp. (Ong, 2016).

Furthermore, preventive fogging and the use of Ultra-Low Volume (ULV) is often utilised during outbreaks in many Southeast Asian countries. Pyrethroids are mainly applied during indoor and outdoor spraying, whereas malathion, an organophosphate is often employed in ULV with concentrations of 96% (Vythilingam & Wan-Yusoff, 2017). Luz *et al.* (2011) explored the impact of vector-borne transmission controls for over five years and the findings revealed larval control resulted in environmental persistence of two months. In addition, the ULV application has an instant effect on the vector population while lasting for only one day. Space treatment with the use of chemical insecticides is ineffectual against *Ae. aegypti* mosquitoes due to the indoor breeding nature of the insect (Srinivas & Srinivas, 2015).

Table 2: Possible mechanisms of action of plant compounds

Compound	Chemical Group	Probable Mechanisms of Action
Visnagin, Khellin	Furanochromones	Phototoxicity; interactivity between transaminase and cytochrome P450 (CYP) dependent monooxygenase
Visnadin	Pyranocoumarins	Interactivity between transaminase and cytochrome P450 (CYP) dependent monooxygenase
Squamocin G	Acetogenins	Inhibition of NADH, neuronal toxicity, midgut damage, antifeedant activity, reduction of protein level
Artemisin	Sesquiterpene lactones	Generation of ROS
Piperine	Alkaloid amides	Feeding inhibition and prevention of normal embryonic development
Solasodine	Alkaloids	Developmental irregularity resulting in deformed pupae and adults
Spilanthol	Alkylamides	Adjustment of movement and muscular activity
Deguelin, Tephrosin Rotenone	Rotenoids	Impediment of protein synthesis and NADH activity
Emodin	Anthraquinones	Post-ingestive damage and antifeedant activity
Trichodesmine	Pyrrolizidine alkaloids	Genotoxicity and mutagenicity

(Pavela *et al*., 2019)

The use of chemical insecticides is a convenient means of vector control but it has resulted in the vectors developing a resistance to the insecticide (Kamgang *et al.,* 2011). Vectors have evolved sophisticated mechanisms of resistance, resulting in a significant impediment to the existing control efforts (Tikar *et al.,* 2008; Kumar *et al.,* 2012; Deming *et al*., 2016; Hamid *et al.,* 2018; Wang *et al*., 2020). Resistance may arise as a result of alterations in host-vector systems resulting in changes in the rates of detoxification or sequestration of the chemicals used or as a result of genetic changes in the chromosomal genes of the vector which inhibits insecticide-target interactions (Hemingway *et al*., 2004; Ishak *et al.,* 2015). Table 3 summarises studies that have highlighted the impact of resistance as a result of the widespread use of chemical insecticides.

In terms of efficiency, ULV still shows promise in reducing the density of the *Aedes* mosquitoes. Marini *et al*. (2019) documented that ULV induced mortality in 40% of mosquitoes and prevented 4% of symptomatic cases in Brazil from 2015 to 2016. Nevertheless, Gunning *et al*. (2018) stated that ULV spraying has a short-term entomological effect, changes of which can be seen to revert in less than a month. Despite its widespread application, the rampant use of chemical insecticides can give rise to various health and environmental impediments (Kaur *et al.,* 2019). For example, the usage of organophosphorus such as malathion has been associated with a decrease in the secretion of insulin, the dysregulation of fat, protein and carbohydrate metabolism, changes in mitochondrial function and other body systems (Nicolopoulou-Stamati *et al.,* 2016). In addition, fogging and ULV treatment may cause long-term environmental pollution (Kaur *et al.,* 2019). Thus, the unfavourable consequences associated with prolonged use of chemical insecticides demand the exploration and development of alternative methods that are equally as effective but eco-friendly are much safer to use.

Table 3: Studies of resistance of *Aedes* mosquitoes toward conventional insecticide

Species	Location	Insecticide Tested	Resistance (Mortality Rate) (%)	Reference
Ae. aegypti	Santiago, Cabo Verde	*Bacillus thuringiensis var israelensis* (Bti), diflubenzuron, temephos, malathion, cypermethrin and deltamethrin	Deltamethrin, cypermethrin (<80%) and temephos	Rocha *et al.,* 2015
Ae. aegypti	Peninsular Malaysia	Permethrin	Permethrin (30%)	Rosilawati *et al.,* 2017
Ae. albopictus	Sabah, Malaysia	Malathion, dichlorodiphenyltrichloroethane (DDT), temephos, fenthion, bromophos, fenitrothion and chlorpyrifos	Malathion, temephos and DDT (<90%)	Elia-Amira *et al.*, 2018
Ae. aegypti	West Bengal of India	Malathion, DDT, permethrin, lambda-cyhalothrin, deltamethrin and propoxur	DDT (48-72%), propoxur (50-97%) and permethrin (50-63%)	Bharati and Saha, 2018

Conclusion

In summary, several strategies are ongoing on a global scale to alleviate the proliferation and propensity of vector-borne diseases including DF. No single intervention is deemed sufficient. The use of synthetic insecticides has been linked to ecological hazards including the resurgence of insecticide resistance which impacts human health. Similarly, other conventional approaches are less successful in curbing dengue outbreaks, following ecological, technical and economic reasons. This, therefore, necessitates the evaluation of other safe, readily available and eco-friendly options. Further studies are warranted with regard to the long-term effectiveness and sustainability of alternative agents as substitutes for synthetic products. Active engagement, coordination, promotion, and integration among researchers, healthcare authorities and the community are pivotal to strengthening, empowering, reinforcing and augmenting dengue intervention efforts.

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