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Control methods for *Aedes aegypti*: Have we lost the battle?

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ABSTRACT

The past twenty years have been a period of remarkable innovation in *Aedes* vector control, and several methods with varying success rates have been used. Here we discussed the main intervention categories of vector control applied nowadays and their main weaknesses. It is urgent to have more efficient design and management of control programs, and the requirement for studies to evaluate and compare methods must be prioritised. The world must better articulate actions and cooperate with other sectors beyond health; it is necessary to work together with managers and entomologists in action plans and adapt them to the condition of each region.

The mosquito *Aedes* (Stegomyia) *aegypti* is responsible for the propagation of many arboviral pathogens in the Americas, with more than half a billion people at risk of diseases every year [1]. With new epidemic waves of dengue, Zika, and chikungunya, *Ae. aegypti* continues to be a major public health problem due to its highly anthropophilic behaviour and attraction to man-made containers for breeding sites [1]; this species is exceptionally domestic among other vectors [2]. In addition to the aforementioned well-known arboviruses, *Ae. aegypti* mosquitoes can also transmit many other endemic viral diseases such as yellow fever, Mayaro fever, and eastern equine encephalitis [3].

Considering that there are no satisfactorily effective vaccines for each circulating arboviruses transmitted by *Ae. aegypti*, attempts to control the dissemination of these diseases have focused on mosquito [4]. The control of *Ae. aegypti* has been failed despite extensive efforts and diverse control methods that have been employed for decades [5]; the control programs were successful in only three instances: the Pan American *Aedes* eradication program in the 1960s, the vector control efforts in Cuba and Singapore. These programs all led to long periods of low dengue incidence. However, these programs all face challenges in sustainability and hence the re-emergence of dengue particularly in the Americas and Singapore [6]. There are some successful examples where the global dissemination of the yellow fever virus has considerably been suppressed, for example via vaccination as a requirement for international travellers to endemic countries [1]. However, such resources are not yet feasible for dengue fever.

The Dengvaxia vaccine, developed by Sanofi Pasteur, is authorized for use in many Southeast Asian countries and has shown limited efficacy in children and adolescents [7]. The main issue that prevents more widespread use of Dengvaxia in adults is that unlike childhood vaccination, there is no systematic program for vaccinating adults. These are driven mostly by demand rather than through public health programs. Moreover, there is a paucity of safety data in older adults, particularly since this vaccine was made using the yellow fever 17D genomic backbone and there are safety concerns about yellow fever vaccination in those above 60 years old [8]. Despite preventive attempts such as vaccines, many dengue and yellow fever cases still appear globally. Thus, efforts to reduce the dissemination of the pathogens, such as mosquito control, are fundamental [3]. There are some well-reported historical examples of yellow fever and dengue being eradicated or substantially reduced by *Ae. aegypti* control measures [6]. Unfortunately, these achievements are exceptions that are frequently impermanent [2].

The past twenty years have been a period of remarkable innovation in *Aedes* vector control, and several methods with varying success rates have been used. The main intervention categories were as follows: (1) chemical control: insecticides and chemical larvicides; (2) habitat management; (3) non-chemical larvicides: larvivorous fish, oil coating, and mass trapping of immature forms of mosquitoes; (4) population replacement techniques; and (5) genetic methods [3] (Fig. 1). However, implementing an integrated mosquito control management, in which all appropriate techniques for a specific area are employed, is most successful. Bowman et al. [9] carried out a rigorous literature review and demonstrated the remarkable paucity of reliable evidence for the effectiveness of any dengue vector control method. The authors concluded that standardised studies of higher quality to evaluate and compare methods must be prioritised to optimise cost-effective dengue prevention.

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Insecticides have been widely used for mosquito population reduction and have been shown to be efficacious. Dichlorodiphenyltrichloroethane (DDT) was successfully used to eliminate *Ae. aegypti* in 19 countries during the 1950s and 1960s (Smith, 2016). Over the years, DDT resistance has appeared, and this compound has now been discarded in vector control procedures [3]. Besides, there is DDT persistence in the environment and hence contamination of the food chain. Currently, one of the most commonly used chemical components for mosquito control is temephos, an organophosphate larvicide, applied to water storage containers to limit mosquito breeding. Nevertheless, studies have shown no strong evidence that temephos use is correlated with a decrease in dengue cases [10]. Another widely used chemical larvicide is *Bacillus thuringiensis israelensis* (Bti), a gram-positive bacterium that is pathogenic to mosquitoes [11]. Habitat management consists of eliminating mosquito breeding sites. Countries use an association of techniques such as grassroots community engagement, collaboration between different public health sectors, public health training, and punitive procedures in mosquito control. Nonetheless, naturally, *Aedes* mosquitoes live in urban and semi-urban areas. In urban areas, it is challenging to eliminate breeding sites because of pollution and inappropriate garbage disposal, overpopulation, suboptimal wastewater management, and intermittent water supply. In semi-urban areas, the natural water collection sites cannot be eliminated [3].

Regarding non-chemical techniques, the objective is to disrupt the life cycle of mosquitoes, consequently limiting their dissemination. Captured immature mosquitoes can be eliminated in ovitraps or larval traps, which are attractive breeding surfaces. The efficiency of oil coating in larval control is limited for *Ae. aegypti* mosquitoes. Some species of larvivorous fish, such as *Gambusia affinis*, have been known to eat mosquito larvae, thus decreasing the density of immature vector populations in water bodies. However, this does not apply to small breeding sites that are widely used by *Ae. aegypti*. The more successful program is the introgression of *Wolbachia* into wild-type *Ae. aegypti* to render the mosquitoes less able to transmit dengue virus. This program was tested in a randomized cluster-controlled trial and showed 77% efficacy, which is comparable to the efficacy of vaccination [12]. *Wolbachia* is an intracellular, maternally inherited, and endosymbiotic bacterium that naturally infects many insects. *Wolbachia* is responsible for reproductive modifications, such as cytoplasmic incompatibility, which causes the generation of offspring to become unviable when an uninfected female mates with an infected male [13].

Genetic manipulation is comprised of many modalities for mosquito control. The sterile insect technique requires the production and release of sterile males into the environment, decreasing the reproductive capacity of the target wild mosquitoes and consequently reducing the population size. Classical sterility is caused by radiation and more recently, by genetic manipulation. This technique induces the death of mosquito offspring after mating. However, irradiation method to sterilize male mosquitoes suffer from a lack of fitness of irradiated mosquitoes to compete with wild-type males for females. Variations of this system, such as the release of insects carrying a dominant lethal mutation (RIDL), have also been employed [14]. Genetic strategies for the generation of refractory mosquitoes include the expression of specific proteins, antibodies, or changes in cell signalling. For example, RNA manipulation methods are currently being investigated to minimize viral replication within insects [14]. Nevertheless, genetically manipulated mosquitoes are GMOs and the issues of acceptance of GMOs, whether rightly or wrongly, affect its acceptance as a public health control tool.

On analysing cases of successful and ineffective programs, two important concerns were identified: program design and management, especially sustainability, goal setting, surveillance, and assessment, and the requirement for more efficient *Ae. aegypti* control tools [2]. There are diverse reasons for the failures. The expanded area of disorganized urbanization has increased the number of breeding sites for *Ae. aegypti*; rapid global movements increase the probability of mosquito and virus spread; poverty hampers the efforts of individuals and communities to implement efficient measures - even when resources for reducing mosquito populations are available, they are often inadequately applied [2]. An important challenge involves scaling up locally effective initiatives. Bowman et al. [9] raised an important issue regarding control programs: the authors stated that, today, there is a common perception that *Ae. aegypti* control 'has failed' or that existing methods will not decrease dengue transmission, and therefore we should discard current approaches and invest in alternative strategies [9]. As they have shown in their review, this assumption is incorrect. There is little reliable evidence from appropriately designed trials to reach a conclusion about any of the control methods available.

The world must better articulate actions and cooperate with other sectors beyond health to control and minimize vector-borne diseases. It is essential that vector control programs work together with city managers, environmentalists, entomologists, engineers, and departments that administrate water and sanitation, as we will experience seven out of ten people occupying cities and urban regions globally by 2050 [15]. This implies that a decrease in the number of breeding sites for *Ae. aegypti* by amplifying access to piped water is required. We also need to clear waste, promote drainage, and keep the environment clean. These measures could be implemented in present-day towns and smaller cities, which will eventually expand into larger cities in the next 20 or 30 years [15]. Thus, acting locally with city mayors and communities can make a big difference and evolve resilience in reducing mosquito-borne diseases. A crucial evaluation of vector control methods and those under development should guide a research agenda for determining which existing techniques work best, and how to best combine state-of-the-art vector control with vaccination [16]. For example, Hladish et al. [17] evaluated dengue management options in an endemic setting in Mexico

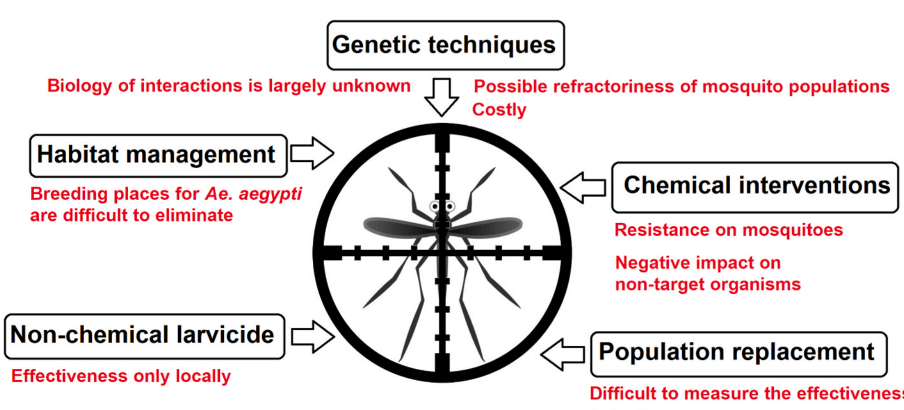

Fig. 1. The principal intervention categories of *Ae. aegypti* vector control applied nowadays and their main weaknesses.

that combine vector control measures and vaccination. They found that the vaccines and targeted indoor residual spraying combination still outperformed either single approach, but the modest benefit of combining interventions implies lower cost-effectiveness per incremental investment compared with either intervention alone.

Studies with machine learning and artificial intelligence using big data have shown to be promising and could become allies in the fight against mosquito vectors in the coming years, detecting the places with the highest risk for mosquito infestation and cases of arboviruses. The use of satellite imagery combined with digital mobile systems supported by a global positioning system (GPS) could also help improve the planning, management, and realization of mosquito control actions and provide a more efficient effort to prevent mosquito-borne diseases. By capturing the local relationships across the space, the authorities could design locally-specific strategies. This understanding is especially important where the control and prevention resources are limited. It is necessary to work together with managers and entomologists to apply new techniques in action plans and adapt them to the condition of each region.

References

[1] PAHO. Pan American Health Organization. Epidemiological alerts and reports. Available, https://www.paho.org/hq/index.php?option=com_topics&view=rdmore&cid=2217&item=dengue&type=alerts&Itemid=40734&lang=en. [Accessed 30 June 2022].

[2] Morrison AC, Zielinski-Gutierrez E, Scott TW, Rosenberg R. Defining challenges and proposing solutions for control of the virus vector *Aedes aegypti*. PLoS Med 2008;5(3):68–85.

[3] Weeratunga P, Rodrigo C, Fernando SD, Rajapakse S. Control methods for *Aedes albopictus* and *Aedes aegypti*. Cochrane Database Syst Rev 2017;8:4–23.

[4] Juarez JG, Garcia-Luna SM, Medeiros MC, Dickinson KL, Borucki MK, Frank M, Hamer GL. The eco-biossocial factors that modulate *Aedes aegypti* abundance in South Texas Border Communities. Insects 2021;12(2):183–95.

[5] Achee NL, Gould F, Perkins TA, Reiner JRC, Morrison AC, Ritchie SA, Scott TW. A critical assessment of vector control for dengue prevention. PLoS Neglected Trop Dis 2015;9(5):e0003655.

[6] Ooi EE, Goh KT, Gubler DJ. Dengue prevention and 35 years of vector control in Singapore. Emerg Infect Dis 2006;12:887–93.

[7] Godói IP, , Lemos LLP, De Araújo VE, Bonoto BC, Godman B, Guerra Junior AA. CYD-TDV dengue vaccine: systematic review and meta-analysis of efficacy, immunogenicity and safety. J Comp Effect Res 2017;6(2):165–80.

[8] Aguiar M, Stollenwerk N, Halstead SB. The risks behind Dengvaxia recommendation. Lancet Infect Dis 2016;16(8):882–93.

[9] Bowman LR, Donegan S, McCall PJ. Is dengue vector control deficient in effectiveness or evidence? Systematic review and meta-analysis. PLoS Neglected Trop Dis 2016;10(3):e0004551.

[10] George L, Lenhart A, Toledo J, Lazaro A, Han WW, Velayudhan R, Horstick O. Community-effectiveness of temephos for dengue vector control: a systematic literature review. PLoS Neglected Trop Dis 2015;9(9):e0004006.

[11] Lacey LA. *Bacillus thuringiensis* serovariety *israelensis* and *Bacillus sphaericus* for mosquito control. J Am Mosquito Contr 2007;23:133–63.

[12] Utarini A, Indriani C, Ahmad RA, Tantowijoyo W, Arguni E, Ansari MR, Simmons CP. Efficacy of Wolbachia-infected mosquito deployments for the control of dengue. New Engl J Med 2021;384(23):2177–86.

[13] Zabalou S, Riegler M, Theodorakopoulou M, Stauffer C, Savakis C, Bourtzis K. *Wolbachia*-induced cytoplasmic incompatibility as a means for insect pest population control. P Natl Acad Sci 2004;101(42):15042–5.

[14] Alphey L, McKemey A, Nimmo D, Neira Oviedo M, Lacroix R, Matzen K, Beech C. Genetic control of *Aedes* mosquitoes. Pathog Glob Health 2013;107(4):170–9.

[15] WHO. World Health Organisation. Global. Vector control response 2017–2030 (GVCR). Available: https://www.who.int/news/item/11-04-2022-genuine-intersectoral-collaboration-is-needed-to-achieve-better-progress-in-vector-control. [Accessed 30 June 2022].

[16] Wilder-Smith A, Gubler DJ, Weaver SC, Monath TP, Heymann DL, Scott TW. Epidemic arboviral diseases: priorities for research and public health. Lancet Infect Dis 2017;17(3):e101–6.

[17] Hladish TJ, Pearson CA, Toh KB, Rojas DP, Manrique-Saide P, Vazquez-Prokopec GM, Longini JIM. Designing effective control of dengue with combined interventions. P Natl Acad Sci 2020;117(6):3319–25.