Aedes aegypti CONTROL PROGRAMMES IN BRAZIL

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SUMMARY

Mosquito-borne diseases are among the most significant challenges facing societies around the world. In Brazil, current official epidemiological reports show increasing numbers of cases of mosquito-borne diseases, such as chikungunya, dengue, yellow fever and Zika, which are spreading to new areas of the country. Therefore, it can be stated that current methods used for the management of mosquito vectors in Brazil, established since 2002, have been ineffective. Thus, there is a necessity for readjustment or updating of the *Aedes aegypti* control programmes that are being applied in Brazil. As recommended by the World Health Organization (WHO), the best way to combat these pathogen vectors is an integrated approach where several convenient and compatible control techniques are combined to efficiently reduce or potentially eliminate a targeted insect vector population. In this manuscript, we updated a review published in 2015 by the same authors about *Aedes* control programmes in Brazil showing their basic concept and the principal components of *Aedes* integrated control programmes. Strategies such as public education, community engagement and responsibility; mechanical elimination of mosquito breeding habitats; the use of larvicides and adulticides; massive collection of eggs and adults using traps; and the reduction in the vector population through the promotion of sterility of mosquitoes by ionizing radiation, use of symbiont bacteria such as *Wolbachia*, or genetic modification, are discussed. The Brazilian experience to test and evaluate some of these technologies is described and compared with strategies to prevent and manage mosquito populations in other countries. It is concluded that there are new control methods that can be integrated on an area-wide basis to suppress mosquito populations successfully. Nevertheless, epidemiological studies are also needed to evaluate their impact on disease transmission, in addition to the proof-of-concept that they suppress mosquito populations.

Key Words: Mosquito control methods, community engagement, Projeto Aedes Transgênico, population suppression, integrated vector management (IVM), genetically modified mosquitoes, vector-borne diseases, Plano Nacional de Controle da Dengue (PNCD)

1. INTRODUCTION

1.1. *Aedes aegypti* Primary Vector of Arboviruses

Aedes aegypti (L.), the yellow fever mosquito, is the primary mosquito vector of various arboviruses such as yellow fever (YFV; genus *Flavivirus*), dengue (DENV; genus *Flavivirus*), Zika (ZIKV; genus *Flavivirus*) and chikungunya (CHIKV, genus *Alphavirus*).

Yellow fever is endemic in tropical areas of Africa, as well as Central and South America. Symptoms include fever, headache, jaundice (origin of the name “yellow” fever), muscle pain, nausea, vomiting, and fatigue. A small proportion of patients develop severe symptoms and approximately half of those die within 7 - 10 days (WHO 2018).

Dengue is endemic in more than 100 countries and is one of the most serious public health problems in the world. Clinical manifestations of dengue virus infection include high fever (40°C) that can be accompanied by severe headache, pain behind the eyes, muscle and joint pains, nausea, vomiting, swollen glands or rash. It is estimated that worldwide, about 40% (2500 million people) of the human population is at risk of contracting dengue fever, and about 390 million people are each year becoming infected with the disease. In 2016, more than 2.38 million cases of dengue were reported in the Americas, of which 1.5 million cases occurred in Brazil, i.e. a threefold increase in cases as compared with 2014 (WHO 2009, 2016a).

A ZIKV infection brings complications and consequences such as microcephaly in babies and the Guillain-Barré syndrome, and their neurological complications are being intensively investigated. Symptoms are generally mild and include fever, rash, conjunctivitis, muscle and joint pain, malaise or headache that last for 2–7 days. However, most people with Zika virus infection do not develop symptoms. Since the 1960s, ZIKV disease has been reported in Africa, Asia, the Pacific islands, and the Americas, but since 2015, its geographic range has expanded rapidly (WHO 2016b). Currently, the ZIKV has been reported in more than 84 countries, territories or subnational areas in the world (WHO 2017a). Between 2015 and 2017, more than 200 000 confirmed autochthonous cases of ZIKV were reported in the countries and territories in the Americas, as well as 3323 confirmed cases of congenital syndrome associated with ZIKV infections. Of these ZIKV cases, a majority (134 057) were reported in Brazil (PAHO/WHO 2016).

CHIKV has been identified in over 60 countries in Asia, Africa, the Americas and Europe. The disease is characterized by fever and is frequently accompanied by joint pain, which is often very debilitating and lasts for a few days or weeks. In 2016, there were more than 150 000 laboratory confirmed cases of chikungunya fever in the Americas. Brazil reported 146 914 confirmed cases, followed by Argentina (322 confirmed cases) and Paraguay (38 confirmed cases) (PAHO/WHO 2014; WHO 2016c, 2017b).

All the above-mentioned viruses are transmitted by *Aedes* spp. when the female mosquitoes take a blood meal from a viremic human host and bites another non-viremic human host. These mosquitoes are distributed throughout tropical and subtropical territories, where they largely overlap, explaining their current scenario of co-infection (Furuya-Kanamori et al. 2016; Rückert et al. 2017).

1.2. Why Vector Control?

The co-distribution and/or co-transmission of vector-borne diseases pose a challenge for public health in endemic and epidemic regions of the world, in particular also in Latin America (Furuya-Kanamori et al. 2016; Rodriguez-Morales et al. 2016; Carrillo-Hernández et al. 2018; O Silva et al. 2018; Suwanmanee et al. 2018). More than 80 % of the global human population lives in areas where they are at risk of contracting at least one vector-borne disease and more than half lives in areas where they are at risk of contracting two or more of these diseases (PAHO 2016). Vector-borne diseases mainly affect poorer populations and impede economic development through direct and indirect medical and other costs such as loss of productivity and tourism (WHO 2017c).

Despite the emergence of new viruses transmitted by *Ae. aegypti*, dengue continues to be one of the most important public health problems in Brazil, considering the burden of disease and the great potential for evolution to death (Martelli et al. 2015; Araújo et al. 2017). Between 2013 and 2016, the cost of hospitalizations for dengue paid by Brazil's publicly funded health care system (known by the acronym SUS) was BRL 68.1 million (SHS 2017). In addition, dengue contributes to the loss of healthy years of life, affecting a large number of people from all age groups, causing some degree of disability during the infection period and deaths, mainly in children (Araújo et al. 2017). The application of remediation measures during epidemic periods can drastically reduce its cost through a more effective prevention programme using entomological surveillance, integrated with area-wide vector control strategies, resulting in the prevention of several diseases and increasing human population life quality in the target area.

In Singapore, for example, the haemorrhagic fever induced by dengue infection became a significant cause of death in the 1960s, affecting especially children. A vector control programme was implemented from 1968 to 1973, using data from entomological and epidemiological surveys to develop a strategy that was based on entomological surveillance, larval source reduction, public education, and law enforcement. The philosophy of the programme was to carry out vector control before the disease is detected as a means to reduce disease transmission. Singapore successfully controlled *Ae. aegypti* population and as a result, DENV infections were reduced and disease incidence remained low for a 15-year period. However, this success proved to be temporary, and the disease incidence increased again in the country in the 1990s (Ooi et al. 2006). The development of a local entomological index correlates the increase of new areas with breeding sites more susceptible to dengue transmission (Ong et al. 2019). In addition, cases of other arboviruses were reported, such as CHIKV in 2008 (Leo et al. 2009) and ZIKV in 2016 (Maurer-Stroh et al. 2016).

The reduction in the density of the *Ae. aegypti* population, the resurgence of DENV and appearance of other diseases transmitted by this vector seems like a paradox. However, it is speculated that several factors may have contributed to an increase in dengue incidence in Singapore: 1) decreased herd immunity after 30 years of low dengue exposure, 2) an increase in the proportion of adult infections, 3) virus transmission occurring outside houses, 4) the adoption of a reactive rather than a pro-

active approach to vector control, 5) the presence of asymptomatic persons, and 6) a continued introduction of the virus through increasing numbers of travelers returning from endemic areas (Ooi et al. 2006; Ooi and Gubler 2009). Moreover, peridomestic areas, where other competent vectors were present (*Aedes malayensis* (Colless) and *Aedes albopictus* (Skuse)), were not included in the vector management programme (Mendenhall et al. 2017), and hence the programme was not following area-wide principles.

In the 20th century, classic vector control strategies to reduce populations of mosquitoes that transmitted malaria, yellow fever and dengue temporarily reduced the impact of these diseases in several countries using mainly insecticides (NASEM 2016). However, the current distribution of vector-borne diseases in the world shows that these and other disorders are re-emerging and/or spreading to new areas. This means that the full potential for preventing disease transmission is not applied as it should. There are factors that contribute to the failures such as technical complexity, costs and logistic needs, complacency and environmental concerns about insecticides (Townson et al. 2005).

1.3. *Aedes aegypti* Control in Brazil

Control of *Ae. aegypti* in Brazil has been implemented according to the guidelines outlined in the National Plan for Dengue Control (in Portuguese, *Plano Nacional de Controle da Dengue* - PNCD) (MS/FNS 2002), which is aligned with the Integrated Management Strategy for Dengue Prevention and Control in the Region of the Americas (known by the abbreviation IMS-Dengue) approved in the Resolution CD44.R9 adopted by the 44th Directing Council of the Pan American Health Organization/World Health Organization (PAHO/WHO 2003; San Martín and Brathwaite-Dick 2007).

The main objective has been to promote a model for prevention and control of dengue that incorporates national and international experiences and emphasizes the need for change in previous models, including also the decentralisation of the vector control programme so that each municipality is responsible for the control with the support from the State Department of Health and the Ministry of Health (MS/FNS 2002; Tauil 2002; Brasil 2009; PAHO 2018). The main actions involve epidemiological surveillance, vector control, patient care, integration with primary health care, environmental sanitation actions, integrated health education actions, communication and social mobilization, training of human resources, social and political support and evaluation of the programme (MS/FNS 2002, 2009; Braga and Valle 2007; Araújo et al. 2015).

The strategies involve the participation of 'Community Health Agents' (CHA) that are responsible, together with the local community, to promote the mechanical (removal or elimination of potential breeding sites) and chemical control (insecticides) with the objective of guaranteeing the sustainability of the elimination of breeding sites by real estate owners, in an attempt to break the chain of transmission of dengue. Other actions also recommended by the Brazilian Ministry of Health include installations of screens on the doors and windows to prevent the entry of the adult mosquito, in addition to the use of predators or pathogens with

potential to reduce the vector population (biological control). Among the available predators are fish and aquatic invertebrates, which eat the larvae and pupae, and pathogens that release toxins including bacteria, fungi and parasites (Zara et al. 2016).

Since the mid-1980s, temephos (organophosphate) has been the main insecticide used against larvae of *Ae. aegypti* in Brazil. However, since 2002, mosquito populations in half of the country have become resistant to temephos (Chediak et al. 2016). As a result, pyriproxyfen, an insect growth regulator that mimics a natural hormone and interrupts insect development, was introduced in 2014 for the suppression of *Ae. aegypti* larvae (MS 2014a). Since 2009, malathion (organophosphate insecticide) has been used to control adults, replacing the use of pyrethroids after the identification of high levels of knockdown resistance registered (Martins et al. 2009). Concentrations of the all insecticides currently used, as well as the applied bioassay protocols, are those recommended by the WHO (2013) and the Brazilian Ministry of Health (MS 2014b).

Despite the risk of favouring the rise and dispersal of resistant populations, and the consequent lack of alternative insecticides to the currently available malathion against *Ae. aegypti* adults, the Brazilian Ministry of Health intensified insecticide spraying against *Ae. aegypti*, as a response to the Zika and chikungunya epidemics. The reliance on a strategy that was mainly based on chemicals to bring the *Ae. aegypti* population under control gave the human population in Brazil a false conception of security (Augusto et al. 2016). The unprecedented spread of vector-borne diseases clearly highlights the challenges faced by everyone, not just the health agencies. Multiple control tactics will need to be used for the management of vector-borne diseases, and this will only be possible if an integrated vector management (IVM) approach is selected. An IVM approach was adopted in 2004 by WHO for all vector-borne diseases and involves a rational decision-making process for the optimal use of resources, to improve cost-effectiveness, ecological soundness, and sustainability of disease-vector control (WHO 2004, 2008, 2017c). The outcome of IVM is improved human capacity and strengthened infrastructure to increase the well-being, and not only protecting human population against disease. The WHO recommends integrated control of the mosquito vectors, mainly those of dengue. Control activities should target *Ae. aegypti* (or any of the other vectors depending on the evidence of transmission) in all its immature (egg, larva, and pupa) and adult stages (WHO 2017d). The critical components of *Aedes* integrated vector management programme in Brazil are illustrated in Fig. 1.

2. EDUCATION, COMMUNITY ENGAGEMENT AND RESPONSIBILITY

2.1. General Overview

Of primary importance in any IVM strategy is training of health personnel in community-based participation so that the local population can understand and hence participate in several aspects of vector control (Gubler and Clark 1996; Ulibarri et al. 2016). Vector control also requires national level support to provide strategic direction, technical expertise, and training, aside from the development of norms and indicators to monitor the progress of operational activities.

Figure 1. Integrated control programme for *Aedes aegypti* populations in Brazil.

The distribution and incidence of vector-borne diseases are determined by ecological factors, but they are also influenced by the behaviour of humans. Thus, vector control interventions that incorporate human population engagement are more likely to be successful as they offer the opportunity to take into account community problems (Townson et al. 2005).

The WHO has prepared and made available guidelines to assist national programmes with the design and implementation of social mobilization and communication strategies aimed at dengue fever prevention and control. The approaches to social mobilization are known by the initials “COMBI” (Communication-for-Behavioural-Impact) that integrate the participation of different members of the community, from households to political leaders. COMBI represents a set of marketing, education, communication, promotion, advocacy and mobilization approaches with the same goal, i.e. to ensure sustained community participation to combat *Ae. aegypti* and as such, to promote the health of community members (Parks and Lloyd 2004; Tapia-Conyer et al. 2012).

2.2. The Brazilian Perspective

In Brazil, the Municipal Health Secretariats have begun to manage and execute PNCD actions with the support of the States and the Ministry of Health, with most funding provided at the federal level. Engagement of the communities and education of the public in the control of *Ae. aegypti* does not mean to bombard people with information about mosquitoes or vector-borne diseases. In Brazil, it has happened that despite growing levels of public knowledge about mosquitoes and their control, many people are not taking the required basic actions such as the elimination of larval sources (Claro et al. 2006). Nevertheless, a study conducted in Ribeirão Preto (south-eastern Brazil) reveals the relevance of educational campaigns and educational health programmes using different types of media to reach different community levels to transmit the necessary information (Alves et al. 2016).

Caprara et al. (2015) developed an eco-health programme, based on community engagement, developing and distributing educational and informative material. They also promoted workshops for the community and developed activities to involve the community directly, such as mobilization of schoolchildren and the elderly, organization of meetings and active participation during campaigns to remove/relocate breeding sites. Although the overall result shows that there was still an increase in the mosquito population after the rainy season (which also corresponded to the end of the experiment), the non-treated site had a significantly higher increase in mosquito density compared to the treated area during the same period (Caprara et al. 2015).

The key to educational campaigns is achieving a long-term modification of the behavioural of the general public that must be conscious of its own actions and be responsible for the surrounding environment. In support, a recent Brazilian sanitary legislation allows the application of fines in the case of impediment or difficulty when implementing sanitary measures that aim at the prevention of the diseases and their dissemination (Brasil 2016).

2.3. Innovations and Experiences of Other Countries

Community engagement and information activities were performed in Brazil during the entire mosquito population suppression *Projeto Aedes Transgênico* (2010-2013 described in Section 7) that relied on the release of genetically modified mosquitoes (GMM) (Capurro et al. 2016). These activities, carried out before and during the mosquito release project, showed positive results and provided guidance for the design of similar public engagement plans in other regions or countries. This pioneering study in continental America showed that full transparency was crucial to make the public aware of all aspects of the mosquito release project, particularly in this case involving genetically modified organisms.

The work from Sommerfeld and Kroeger (2015) reviews community-based vector control interventions in different countries in Latin America that are fighting against dengue and using educational campaigns, chemical and non-chemical strategies, including new approaches such as waste management. The authors mention that these strategies involving the community require establishment of a

prolonged interaction with control services, municipalities and other public actors, proving to be rewarding during the process and with excellent potentials for sustainability, however, they were time-consuming and costly at the beginning. The results of community participation programmes used in Mexico showed that continuity of these activities in long-term campaigns is a prerequisite to achieve the desired goals (Tapia-Conyer et al. 2012). However, governments are often reluctant to invest and support these initiatives, and consequently, these programmes are often relegated to serve as epidemiological projects during dengue outbreaks.

3. MECHANICAL CONTROL

3.1. General Overview

In general, mechanical control consists of the elimination of *Ae. aegypti* larval breeding sites from domestic and peridomestic areas, and the application of measures that prevent the contact between humans and the vector. The interventions include changing the environment through cleaning and removal of possible habitats suitable for any stage of *Ae. aegypti* and *Ae. albopictus* to prevent or minimize vector propagation. This entails covering water storage containers, disposing of non-biodegradable waste, and installing mosquito screens on windows, doors and other entry points, in addition to the use of mosquito bed nets. Local government agencies must take responsibility for the clean-up of public spaces and to eliminate illegal dumps and discarded tyres (Arunachalam et al. 2012; US-EPA 2017; WHO 2017e).

3.2. The Brazilian Perspective

Dengue is a disease that has ecological, biological and social factors involved in its transmission. The dynamics of *Ae. aegypti* breeding sites are closely linked to human behaviour; therefore, elimination of larval sites through household interventions is an efficient way to reduce the mosquito population. In Brazil, the removal of breeding sites is the responsibility of households. Periodically the community health agents, and the 'Endemic Disease Control Agents' (EDCA) visit houses looking for possible breeding sites, but they are mainly responsible for non-residential properties, and if necessary, integrate chemical (insecticide) application (Zara et al. 2016).

Chaebo and Medeiros (2017) investigated five conditions for an effective strategy for dengue control policy implementation through co-production, which they defined as the strategy for policy implementation resulting from technological, economic, and institutional influences. Initially the technical, economic, normative, cognitive and structural conditions were analysed and as a result they stated that technical, economic and normative conditions are interdependent, and changing one will change the others. In addition, the authors added two extra conditions to implement policy using co-production that they defined as cognitive and structural conditions. Including these conditions to the main study, the authors state:

"We believe, it is impossible to successfully undertake policy implementation via co-production unless users recognize that an important problem exists and are able and willing to undertake the necessary co-production actions" (Chaebo and Medeiros 2017).

Unfortunately, besides the responsibilities of authorities, the communities often wait for the public vector control services to carry out the task of controlling mosquito breeding sites. In some cases, communities are fully aware of the threats leaving breeding sites and their responsibility to eliminate them, but they are not involved in the programme, and this paradigm needs to change. In integrated vector control, the householders must be stimulated to interact with vector control staff and to ensure appropriate interpersonal communication (Arunachalam et al. 2010).

3.3. Innovations and Experiences of Other Countries

The effect of encouraging community members to eliminate *Ae. aegypti* breeding sites showed a favourable impact in studies carried out in the Caribbean (Rosenbaum et al. 1995), Latin America (Tapia-Conyer et al. 2012), Thailand (Suwannapong et al. 2014), Pakistan (Zahir 2016), USA (Healy et al. 2014), and many other parts of the world (Spiegel et al. 2002; Kay and Nam 2005; Vanlerberghe et al. 2009; Sanchez et al. 2012). There is a consensus among health authorities that this measure is an essential component of environmentally sustainable mosquito control programmes. A recent mathematical model for dengue control developed by Carvalho et al. (2019) confirms that, even though the combination of mechanical and chemical approaches is the most suitable one instead of using them separately, it is still insufficient to eliminate disease transmission completely.

4. MASS-TRAPPING

4.1. General Overview

Different models of traps are available to monitor *Ae. aegypti* and *Ae. albopictus* populations, and they can generate baseline data that are essential to guide control operations. They can also be included in the entomological surveillance to improve mosquito population density prediction prior to epidemic periods (Honório et al. 2009; Degener et al. 2014). An increased number of deployed traps can be used to reduce the target mosquito population, i.e. the gravid females are attracted to the oviposition traps (ovitrap) and are killed when making contact with the oviposition substrate that is impregnated with insecticides, or lethal ovitraps, collecting eggs that are subsequently killed by an insecticide-treated ovistrip (Paz-Soldan et al. 2016).

According to a review on mass-trapping interventions for suppression of urban *Aedes* by Johnson et al. (2017), successful deployment is achieved with a high area coverage (>80%), a pre-intervention and/or additional source reduction, the direct involvement of community members for sustainability, and the use of new-generation traps (such as the Autocidal Gravid Ovitrap – AGO, or Gravid *Aedes* Trap – GAT) to outcompete remaining water-holding containers.

In areas where *Ae. albopictus* co-exists with *Ae. aegypti*, eggs or larvae collected in ovitraps need to be taken to the laboratory for species identification at the larval stage or maintained until adult emergence. In those areas, the AGO is a good alternative to monitor mosquito populations (Caputo et al. 2015). These traps are

simple, specific and efficient for gravid females, and their integration with other chemical or biological control methodologies can contribute significantly to decrease mosquito populations. However, their use is laborious, which is a disadvantage for deployment over large areas of action. Combining mass-trapping of adults, with the use of larvicides, can have a more significant impact on *Ae. aegypti* populations than using each of these methods alone (Regis et al. 2008).

4.2. *The Brazilian Perspective*

Mass-trapping is not currently used for mosquito control in any vector control programme in the country; however, several works have assessed the effect of lethal ovitraps, and the results were promising in several situations (Regis et al. 2008, 2013). A modified ovitrap containing *Bacillus thuringiensis israelensis* (*Bti* – see next Section) that kills any larvae developing inside was evaluated in north-eastern Brazil. The *Bti*-treated trap can safely remain in the field for up to two months and during that time can collect more than 7000 eggs/trap (Regis et al. 2008), of course depending on the initial population density.

Deployment in urban areas of ovitraps treated with the pyrethroid deltamethrin reduced the density of the adult female population by 40% (Perich et al. 2003). The study involved the placement of 10 ovitraps/residence (five inside and five outside) for 12 weeks in two municipalities in Rio de Janeiro, and the sampling of 30 houses per intervention neighbourhood. The authors mentioned that although lethal ovitraps were not designed to be a control method to be used alone, their results show that lethal ovitraps could provide an inexpensive, simple, environmentally benign way to be integrated into vector control strategies (Perich et al. 2003).

Sticky ovitraps with an adhesive strip, rather than an insecticide-treated oviposition surface that traps the ovipositing females when they land, have been used for surveillance in areas with high mosquito insecticide resistance. A study was conducted for 17 months to suppress mosquito populations in the Amazon region through a mass-trapping system using sticky ovitraps. The authors conclude that this intervention alone was not able to show mosquito population suppression, and they indicate as probable reasons a lack of buffer zones, which allowed mosquito migration from other areas, the lack of an area-wide approach due to the small size of the treated area, and insufficient collection efficacy of the trap or inadequate number of traps/household (Degener et al. 2015).

4.3. *Innovations and Experiences of Other Countries*

Like the Brazilian experience, *Ae. aegypti* populations were significantly reduced in Thailand when lethal permethrin-treated ovitraps were deployed in conjunction with other interventions such as source reduction, use of screen covers, and biological control. In this case, they also evaluated the impact on dengue transmission and the proportion of DENV IgG–IgM positives in the treated areas, which were reduced from 13.46% to 0%, whereas those from untreated areas increased from 9.43 to 19.15% (Kittayapong et al. 2008).

A previous study using lethal ovitraps, also in Thailand, showed a 49-80% reduction in the mosquito population in an experiment over 30 weeks (Sithiprasasna et al. 2003). In Cairns, Australia, the acceptance by households of a mass-trapping scheme allowed the comparison of different types of lethal ovitraps in three separate trials. The results suggest that a high trap density can collapse a mosquito population over time (Ritchie et al. 2009).

The AGO, baited with an attractant and containing an adhesive card placed inside the trap entrance that serves as an autocidal oviposition substrate, was developed by the Centers for Disease Control and Prevention (CDC) to catch gravid *Ae. aegypti* females (Mackay et al. 2013). The AGOs placed in 85% of residences in four communities of two municipalities in Puerto Rico between November 2015 and February 2016 to control *Ae. aegypti* mosquitoes significantly reduced the prevalence of CHIKV IgG antibodies in participating communities without any other control tactic used (Lorenzi et al. 2016).

5. LARVAL CONTROL

5.1. General Overview

Larvicides are biocides used against immature mosquito stages and their use fits well within environment-friendly management strategies (except in emergency situations). Larval control can minimize the need for widespread use of insecticides to kill adult mosquitoes. Larvicides are used by vector control staff to treat water-holding structures and containers in public places, whereas the general citizen is supposed to do the same to treat fountains, septic tanks, pots and pools on private properties. The use of larvicides should be restricted to containers that are not used for drinking, and that cannot be covered, dumped or removed (CDC 2017a). Widely used is *Bti*, a bacterium marketed commercially as a biological larvicide to control insects relevant to public health. It is safe for humans, but when ingested by mosquito larvae, lethal endotoxins proteins are produced during the bacterium sporulation, killing the larvae before reaching adulthood (Federici et al. 2007; Ibrahim et al. 2010). An alternative is the auto-dissemination approach, that can be augmented by the release of males which were tainted with pyriproxyfen, a juvenile hormone analogue, and who will contaminate females during mating or directly the larval habitats (Bouyer and Lefrançois 2014).

5.2. The Brazilian Perspective

In Brazil, *Bti* is used since 2002 when resistance to the organophosphate larvicide, temephos, was observed (Suter et al. 2017). In those cases, *Bti* can be used alone or in association with different chemical larvicides such as pyriproxyfen (MS/FNS 2009; Suter et al. 2017). Recent bioassays with Brazilian populations of *Ae. aegypti* and *Ae. albopictus* that have been exposed for many years to insecticides, in particular *Bti*, showed that both species are equally susceptible to *Bti*, suggesting that the same application rates may be used where the species co-exist (Suter et al. 2017).

A study in Manaus (northern Brazil), using pyriproxyfen, showed not only mosquito mortality, but also that adult emergence was reduced more than 10 times (Abad-Franch et al. 2015). They concluded that this approach is very promising to complement current mosquito control strategies, which heavily rely on the difficult task of detecting vector breeding sites and therefore perform poorly.

In some contexts, however, the application of larvicides by public health services can be complicated. Many *Aedes* breeding sites are small, sheltered and difficult to locate (cryptic habitats). Therefore, depending entirely on breeding site treatment or removal is complex, requiring a combined strategy. Therefore, auto-dissemination methods are an alternative to overcome these limitations, as they rely on the oviposition behaviour of adult mosquitoes and their attraction to breeding sites. The auto-dissemination method to control *Aedes* mosquitoes requires artificial adult resting sites (dissemination stations) to which adult females are attracted and where they are contaminated with pyriproxyfen when entering the station and then contaminate breeding sites with lethal levels of pyriproxyfen (Caputo et al. 2012; Unlu et al. 2017).

5.3. Innovations and Experiences of Other Countries

In a study carried out in Thailand, about 61.8% of water containers were treated with *Bti* and temephos, and the rate of positive containers (with larvae) was reduced from 13.8% in untreated areas to 3.7% in treated areas ($P < 0.001$) showing the combined approach of *Bti* and insecticide were effective in achieving the result in the target area (Arunachalam et al. 2010).

The autodissemination approach was tested in the USA with pyriproxyfen-treated males and showed, in combination with another insecticide, a decline in the *Ae. albopictus* adult population by around 74-78% (Unlu et al. 2018). In a similar approach using only pyriproxyfen, the male mosquitoes were shown to be vehicles of insecticide in areas with low mosquito densities to intoxicate potential breeding sites before the seasonal emergence of the target population (Mains et al. 2015). These males can also contaminate the females, increasing even more the affected breeding sites, interrupting the development of immature offspring. On the other hand, a study only using pyriproxyfen conducted in Florida showed that there was no apparent pupal mortality during the study period (Lloyd et al. 2017).

In Southeast Asia, larvivorous fish, e.g. from the genus *Gambusia*, that feed on mosquito larvae are often used in pots that decorate houses and terraces (Araújo et al. 2015) (Fig. 2). This practice is also employed as a non-insecticidal method to control malaria vectors in India and Africa (Kamareddine 2012; Kant et al. 2013; Walshe et al. 2013). However, the use of fish to control mosquito larvae is feasible and effective only in breeding sites that are easily identified and in those as observed in Asian culture (Chandra et al. 2008).

Studies carried out in Mexico have shown that larvivorous fish can reduce larval and pupal numbers in household water containers, but there was no evidence of a reduction in DENV infection (Morales-Pérez et al. 2017). In villages of Karnataka, South India, the introduction of fish, e.g. the guppy *Poecilia reticulata* (Peters) and *Gambusia affinis* (Baird & Girard), combined with information, education and

communication campaigns, had a significant impact on the density of the *Aedes* population and decreased the prevalence of chikungunya (Ghosh et al. 2011). This method is harmless to humans and exhibits minimal risks of mosquito resistance. Besides, the fish are cheap to produce in most cases, saving resources that could serve for other needs. However, in some cases, these invasive fish can be negative effects on biodiversity (El-Sabaawi et al. 2016).

Figure 2. Larvivorous fish in water containers in Southeast Asia (Araújo et al. 2015).

6. ADULT CONTROL

6.1. General Overview

Adulticides are intended to impact a significant number of infected adult mosquitoes in a short time through surface (indoor) and/or spatial (outdoor) treatments with insecticides of residual or low residual activity. The indoor residual spraying (IRS) consists of the application of long-acting chemical insecticides on the walls or others surfaces of houses in a given area using backpack sprayers. A recent review using seven databases evaluated the effectiveness of indoor spraying of insecticides and showed the effect on adult mosquitoes is high immediately after application (Samuel et al. 2017). These spraying activities are usually carried out by staff of the vector control programmes, but the general public can also buy commercial adulticides for use in their homes.

Space spraying is recommended only in emergency situations when people in a large area are at risk of infection, or mosquito densities are very high. The insecticides can be applied by backpack sprayers, trucks or airplanes. When cases of the disease are detected in the early stages of an epidemic, emergency space spraying can reduce disease transmission quickly. However, applying other vector control measures such as larviciding or environmental modification help provide longer-term control as a part of an integrated mosquito management programme (CDC 2017b; MS 2017a; WHO 2017b, 2017f).

6.2. *The Brazilian Perspective*

In 2016, the Brazilian Government published law No. 13.301 of July 27, 2016 that allows the incorporation of adult vector control mechanisms through aerial spraying upon approval of sanitary authorities and scientific evidence on the efficacy of the measure (MS 2017b). However, in the same year, the Oswaldo Cruz Foundation (FIOCRUZ) issued a technical note stating that there are risks to human health related to the spraying of a neurotoxic product such as malathion in urban areas. They considered that it not only posed a threat to the environment and the population's health, but it is also of little efficacy in the combat of *Ae. aegypti*, which in its adult stage lives mainly within the domiciles (FIOCRUZ 2016).

6.3. *Innovations and Experiences of Other Countries*

The Florida Keys Mosquito Control District used aerial sprays with insecticide (naled) and bacterial larvicides to reduce *Ae. aegypti* populations in urban areas of Key West, Florida, USA (CDC 2017c; Pruszyński et al. 2017). The aerial applications of *Bti* caused a significant decrease in adult female populations throughout the summer because, in Key West, larvae of this mosquito develop in micro-containers around human habitations. The advantage of aerial spraying of larvicide is the area-wide coverage over and around urban areas achieved in a short period and in the case of Key West, the aerial application of larvicide was effective in controlling the *Ae. aegypti* outbreak (Pruszyński et al. 2017).

7. POPULATION SUPPRESSION INTEGRATING THE STERILE INSECT TECHNIQUE, THE INCOMPATIBLE INSECT TECHNIQUE, AND GENETICALLY MODIFIED MOSQUITOES

To improve the Brazilian dengue vector control programme, it is mandatory to use the principles of IVM to minimise financial and personnel requirements and be able to cover the target geographic area to be treated with the chosen vector control methods. Furthermore, improved monitoring and evaluation tools for vector control should be developed and applied, and relevant training must be performed based on necessity (Horstick et al. 2010).

As described above, suppression of disease-transmitting mosquito populations is still mainly based on insecticides (larvicides and adulticides). A reduction in

mosquito densities is the most reliable method to decrease pathogen-host contact, which will reduce the probability of humans becoming infected. Nevertheless, the long-term use of chemical compounds has selected for mosquito populations resistant to them, resulting in the increase of the number of cases in endemic areas and the spread of diseases transmitted by these insects into entirely new areas (Campos et al. 2015; Díaz et al. 2015; Zanluca et al. 2015; Luksic et al. 2017).

Other population suppression approaches are therefore under development and evaluation, and these could be integrated into the currently used IVM approaches. These methods have the benefit that they can reduce vector populations in a target area, without causing the selection of resistance as promoted by insecticides (Bourtzis et al. 2016). They have in common the release of sterilized male insects (because male mosquitoes do not blood-feed and therefore do not transmit diseases), and the monitoring of the sterile and wild male populations in the target area (Lees et al. 2014). These males must be mass-reared to achieve the required numbers to promote suppression of the target population. After release, an efficient monitoring system is needed to be able to follow the vector population fluctuation and if required, to adjust male production and release rates (Hood-Nowotny et al. 2006; Vreysen 2021).

The first of these approaches is the Sterile Insect Technique (SIT), which uses an ionizing radiation source (gamma or X-ray) to sterilize the mass-reared males that will be released into the open field in numbers 10-100 times larger than the wild-type population. The high sterile to wild male overflooding ratios increase the probability of a mating of a wild virgin female with a sterile male (Vreysen et al. 2014; Dyck et al. 2021). For more than 50 years, the SIT has proven to be an effective control tactic to suppress agricultural insect pests such as moths, fruit flies, screwworm and tsetse flies (Hendrichs and Robinson 2009; Klassen et al. 2021). With support from the international scientific community through the International Atomic Energy Agency (IAEA) and the Food and Agricultural Organization of the United Nations (FAO), several countries like Brazil, Cuba, Italy, France (La Réunion), Mauritius, Mexico, Thailand, USA and others have or are initiating pilot trials against mosquitoes on a small to medium scale as a proof-of-concept (Lees et al. 2021).

A similar approach is the release of males that are infected with symbionts that cause sterility without the use of ionizing radiation. The intracellular bacterium, *Wolbachia*, is a symbiont that is sexually transmitted and maternally inherited and can promote cytoplasmic incompatibility in embryos when the father is infected with a particular strain but not the mother (Sinkins 2004). This approach is called the Incompatible Insect Technique (IIT) (Zabalou et al. 2009) and is already under evaluation in several countries like USA (Mains et al. 2016), China, and in French Polynesia for *Aedes polynesiensis* (O'Connor et al. 2012). A related approach under evaluation in Australia, Brazil (Niteroi and Rio de Janeiro), Colombia (Bello and Medellín), and Indonesia (Yogyakarta) through the Eliminate Dengue and other campaigns (De Barro et al. 2011; Maciel-de-Freitas et al. 2012; Flores and O'Neill 2018) involves the release of both *Wolbachia*-infected males and females, resulting in population replacement by substituting the original population with a *Wolbachia*-infected population, this approach takes advantage of *Wolbachia*'s capacity to block pathogen transmission to the human host (Van den Hurk et al. 2012; Frentiu et al. 2014; Dutra et al. 2016).

The release of genetically modified mosquitoes (GMM) is the third population suppression alternative that is under evaluation, and so far, some programmes or trials have demonstrated success in reducing the mosquito population in the target areas Carvalho et al. (2015). This transgenic approach, which requires regulatory approvals and involves other issues, has a broad range of possibilities to interfere and trigger mosquito population suppression or population replacement by blocking disease transmission, due to its potential to manipulate, exclude or include new features at the genomic level of the target mosquito species (Handler 2002; Travanty et al. 2004; Catteruccia et al. 2009).

Brazil is one of the best locations to test and evaluate these new technologies, due to its diverse environments and extensive prevalence of arboviruses. Since 2002, Brazil has been implementing the PNCD to control dengue transmission and related diseases, such as chikungunya, Zika, and yellow fever. However, the efforts and strategies that are combined in the PNCD cannot entirely prevent disease dissemination; on the contrary, the number of reported cases only increases every year (Pessanha et al. 2009; SS-PE 2015; MS 2017c). Therefore, the inclusion of new technologies cannot alone change the vector density and transmission situation if their deployment is not carefully planned according to the specific characteristics and needs of each target area and taking advantage of the best characteristic of each of the technologies. Thus, it is necessary to combine and better apply where appropriate all these techniques as part of effective IVM approaches (Horstick et al. 2010; Bourtzis et al. 2016; Van den Berg et al. 2012).

7.1. Two-step Male Release Strategy – Integration of Techniques

Several models on the use of these innovative technologies, such as GMM, the IIT, the SIT and others, predict that it will take several seasons to suppress a targetted mosquito population, and even when achieving it, some virus transmission can still occur (Andraud et al. 2012; Chen and Hsieh 2012; Okamoto et al. 2013; Ndi et al. 2015). The IVM approaches can be improved by applying the suppression methods more effectively and based on mosquito biology. Models combining several techniques demonstrate the advantages of targeting different developmental stages and integrating different ways to suppress a population.

A two-step strategy was proposed to reduce mosquito populations and then block efficiently disease transmission (Carvalho et al. 2014). A first step involves the integration of any methods which have a significant impact decreasing the target vector population, such as the use of larvicides and adulticides, educational campaigns, breeding site elimination, the release of sterile males, which also can be carrying pyriproxyfen to suppress a population. Once the population has been suppressed, this should be followed by a second step, which could involve releases targeting population substitution (for example *Wolbachia*-infected females or GMM), in order to disrupt disease transmission entirely. The idea is first to reduce the mosquito population to extremely low levels, and then to substitute this residual population by one that is no longer able to transmit viruses, thereby obtaining the advantage of this low-cost combination strategy that can be implemented as part of IVM over larger areas (Fig. 3).

Figure 3. A schematic diagram of two-step male release strategy (Carvalho et al. 2014) using as an example a genetically modified mosquito (GMM) strain for population suppression and replacement.

Recently, some studies proposed transgenic constructions able to block the virus transmission with low impact on the overall mosquito fitness (Jupatanakul et al. 2017; Buchman et al. 2019). Strategies using RNA interference or RNA-based strategies targeting critical virus RNA's were already developed and tested under laboratory conditions and their fitness evaluated (Franz et al. 2006, 2014; Buchman et al. 2019). In addition, other strains targeting malaria parasites have also been developed for population replacement, entirely blocking the parasite transmission (Kokoza et al. 2010).

Nevertheless, it is a common evolutionary fact that without a stable gene drive mechanism such systems alone may not be enough to replace the population successfully, and over time will be displaced (James 2005). However, the use of new gene editing techniques, such as CRISPR-Cas9, provide an easier way not only to create strains for population suppression, but also for population replacement (Häcker and Schetelig, this volume). They may also eventually overcome the issue of gene drive resistance mechanisms that emerge in field populations (Champer et al. 2018). This resistance can originate from the drive itself, when cleavage is repaired and it changes the sequence of the target site, so that it can no longer be recognized, becoming resistant to future conversion.

A model provides that more than 100 generations are needed for the wild-type population to reach 50% of resistant alleles and the use of CRISPR-Cas9 can be an efficient way to provide stable strains for vector control programmes without the accumulation of genetical instability (Unckless et al. 2017). It is a matter of time for the availability and developing state of art of the gene drive technologies to provide further information on their behaviour in the genome and their ecological impact and long-term effects.

Further discussion among the scientific community, stakeholders and population regarding the advantages, risk assessment, and regulatory issues of using them are needed (Carter and Friedman 2016; Häcker and Schetelig, this volume; Nielsen, this volume).

7.2. Open Field Release Using the OX513A *Ae. aegypti* Transgenic Line and its Evaluation

Brazil and other countries have initiated the field assessment of the impact of some of these new technologies as part of IVM approaches. The first continental GMM release to suppress an *Ae. aegypti* mosquito population was carried out between 2011 to 2015 in two different cities, Juazeiro and Jacobina in the state of Bahia, in north-eastern Brazil. This *Projeto Aedes Transgênico* aimed at evaluating various aspects of a full IVM programme by using the OX513A transgenic line developed by the commercial company Oxitec Ltd. (Lee et al. 2009). Before the release of the genetically modified male mosquitoes in Brazil, several regulatory steps, as described by Carvalho and Capurro (2015), had to be performed. The most crucial approval was provided by the Brazilian National Committee of Biosafety, which regulates all research projects and products directly and indirectly involving genetically modified organisms, including a public review of the project that had no vote against it.

Due to all apprehensions around genetically modified organisms in plants and other organisms, the *Projeto Aedes Transgênico* initiated a pioneering communication plan to create adequate public awareness regarding the use of this technology and its purpose. Emphasis was likewise placed on community engagement and stakeholder participation during the execution of the project. This experience can serve as a model for other initiatives using the same approach (Carvalho et al. 2015; Capurro et al. 2016).

In the initial phase, some quality parameters of these GMM males were assessed in the target area/environment, such as flight range and longevity under field conditions. Based on this first phase, an assessment was made of the number of sterile male mosquitoes to be released to achieve population suppression, and the data compared with those of the first trial in Grand Cayman Island (Harris et al. 2011, 2012). This range-finding process, consisting of six weeks of releases and the three following weeks for evaluation (around 2800 males/ha/week were released in this first phase), was helpful in optimizing the release number and mass-rearing process. It was also crucial for the next phase involving overflowing the target area in Juazeiro with male mosquitoes for suppression purposes because it provided and confirmed parameters to initiate this suppression phase (Carvalho et al. 2015).

After the 17 months release period, around 95% of population suppression was achieved in Juazeiro, based on an indirect evaluation using a monitoring system with ovitraps. Afterwards, the study kept track of the GMM and wild-type populations after the suppression effect. The outcome was that when the releases were discontinued, the wild mosquito population returned rapidly to pre-control levels within 17 weeks due to immigration and other factors, such the eclosion of eggs that remained unhatched during the release phase (Garziera et al. 2017).

The second part of *Projeto Aedes Transgênico* included procedures for ground shipment of pupae to the city of Jacobina, around 300 km from the mass-rearing facility. This step also included optimizing the monitoring system, increased community engagement and awareness activities, and improved efficiency of mass-rearing procedures and release methods. The *Projeto Aedes Transgênico* was terminated at the end of the contract with the Bahia State Health Department. Again,

genetic monitoring of the GMM and wild-type populations continued post-suppression, indicating that portions of the transgenic strain genome became incorporated into the target population (Evans et al. 2019).

In parallel, as an independent initiative, Oxitec started a trial in Piracicaba and Juiz de Fora municipalities (in São Paulo state, south-eastern Brazil), following a similar approach and using the predetermined parameters established during the first two initial trials in the country (Paes de Andrade et al. 2016). So far these trials are service contracts directly performed with the municipalities without any support of the Brazilian Ministry of Health.

8. FINAL CONSIDERATIONS

Numerous activities are currently being integrated in Brazil to suppress *Ae. aegypti*, the vector of various arboviruses. Box 1 presents some important bullets summarizing the strengths, weaknesses, opportunities, and threats (SWOT) for the Brazilian vector control strategy.

Box 1. Strengths, weaknesses, opportunities, and threats of the Brazilian vector control strategy.

STRENGTHS	WEAKNESSES
<ul style="list-style-type: none"> • Strong research institutions • Decentralisation of the vector control • Existence of the National Plan for Dengue Control (PNCD) • Historical record of successful vector elimination • Reference research laboratories 	<ul style="list-style-type: none"> • Insufficient budget / trained staff • Insufficient public mobilization resulting in low community commitment and household participation and acceptance • Limited time required for data analysis resulting in poor management • Lack of consistent and frequent control strategy application
OPPORTUNITIES	THREATS
<ul style="list-style-type: none"> • Possibility to test new techniques in different biomes and urbanization levels • Use of different combinations and methods for vector control for specific conditions • Learning from different models and previous experiences (including other countries) 	<ul style="list-style-type: none"> • The continuous increase in reported arboviruses cases • Different vector species participating in disease transmission • Entry of new arboviruses promoting illness • Difficulty of treating increasing cases in big cities

PNCD activities and efforts are not enough to interfere with disease transmission by this vector. All have been recommended by WHO (Brasil 2009), however they have to be adapted to different levels of difficulty in different situations (for example, vector control in isolated small areas vs non-isolated, large and densely populated urban areas). Among the main reasons for the insufficient control are the low budget, lack of trained staff, insufficient insecticide application, insufficient public mobilization, and poor management. There is a need to increase vector control efforts all over the country, but at the same time to complement the adopted strategies with promising innovative approaches (Zara et al. 2016; Coelho 2012). There is the potential to exploit and include new methods as part of the IVM package in order to suppress more effectively and sustainably the mosquito populations and control disease transmission.

The current PNCD activities being performed should not be interrupted due to the advent of new technologies, but these can be validated and implemented as part of the IVM package. The range of approaches integrating new technologies is huge, and they have demonstrated that they can successfully contribute to mosquito population suppression and reduce disease transmission. In view of the proof-of-concept of these techniques (most of them carried out under Brazilian conditions), they are ready for the next step, which is their application as part of a long-term programme, not only to demonstrate their effect on mosquito populations, but also their impact on disease transmission.

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