Chapter 6

Challenges for the Introduction and Evaluation of the Impact of Innovative *Aedes aegypti* Control Strategies

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http://dx.doi.org/10.5772/intechopen.79862

Abstract

Innovative control tools for the dengue, chikungunya and Zika vector *Aedes aegypti*, such as genetically modified mosquitoes and biological control and manipulation with the bacteria *Wolbachia*, are now becoming available and their incorporation into institutional vector control programs is imminent. The objective of this chapter is to examine the technical and organizational mechanisms together with the necessary processes for their introduction and implementation, as well as the indispensable indicators to measure their entomological effect on vector populations and their epidemiological impact in the short, medium and long term as part of an integrated vector management approach.

Keywords: dengue, chikungunya, Zika, *Wolbachia*, SIT, RIDL, entomological surveillance, epidemiology

1. Introduction

The tools and strategies that have been implemented in recent decades to control the *Aedes aegypti* mosquito face an efficient vector of various viruses [dengue, chikungunya, Zika and yellow fever, which together are known as *Aedes*-borne diseases (ABD)] that has a great capacity for adaptation to human and urban habitats (domesticated).

Improvements in the quantification and control of this mosquito in urban environments and the transmission of ABD require a reformulation of current control strategies, as well as a stronger focus on reducing vector abundance, preventing human-vector contact and finally, reducing virus transmission [1, 2]. Due to the multiplicity of co-circulating viruses transmitted by the *Aedes* mosquito and the absence of effective treatment or vaccines against these infections, the development of long-term strategies for managing the populations of the *Aedes* mosquito has become a public health priority.

Traditional mosquito control strategies have consisted of nonintegrated vector management of the immature (larvae) mosquito stage and of the use of insecticides that have fairly low—and temporary—mortality rates in adult female mosquitoes. Effective and sustained control by these methods and intervention is impeded by a number of obstacles: effective coverage of all breeding sources, lack of personnel needed, the need of continuous insecticide re-application, the transitory nature of their effects, the false sense of security that they generate and the dependence fomented in both the affected communities and the mosquito management programs.

On February 1, 2016, the World Health Organization (WHO) declared the Zika virus, along with microcephaly and the other associated neurological disorders, a public health emergency of international importance (public health emergency of international concern, PHEIC) [3]. The Zika outbreak rapidly reached across not only the Americas, but also 75 other countries and territories; its control continues to be a long-term challenge to public health even after the declaration of the end of the state of emergency by the WHO Emergency Committee in November of 2016.

Due to this emergency, the scientific community; entrepreneurs and international, regional, and national governmental programs in areas endemic to *Ae. aegypti* and ABD are researching on innovative alternative methods of vector control. WHO has expressed its support for developing and upscaling three novel approaches to controlling the *Ae. aegypti* mosquito: the sterile insect technique (SIT), the release of insects carrying dominant lethal genes (RIDL) and the release of *Wolbachia*-infected mosquitoes.

We find ourselves looking to the possible incorporation of various technological innovations whose application in the field of public health offers positive (theoretical) prospects of success along with new opportunities for enhancing the effectiveness of control programs; however, there are also technical and operational challenges that must be considered before incorporating these innovations into the inventory of mosquito management tools [4].

2. Methods of intervention for *Aedes aegypti* control

Vector control is a complex task. There are a number of options available for different stages (eggs, larvae, pupae and adult) of the mosquito populations; a variety of available tools (physical/mechanical, environmental, biological, chemical and behavioral preventive measures) and different goals for each strategy (covering containers to avoid egg-laying, eliminating breeding sites in order to diminish larval densities, spraying insecticides to kill and reduce adult mosquitoes or installing barriers that diminish vector-human contact). The ultimate goal of each strategy is diminishing transmission. However, experience has shown that there is no "magic bullet" that is effective, lasting, affordable and easy to implement.

The purpose of vector control is to maintain populations at "acceptable" densities, to minimize vector-human contact (to prevent mosquito bites) and to reduce the longevity of female adult mosquitoes, in order to reduce the health problem to a manageable level that does not surpass the capacities of local health systems. The ambitious campaign (1947–1970) promoted by the Pan American Health Organization (PAHO) to eliminate *Ae. aegypti* from the continent was one of the great Latin American public health events due to the extent of its achievements throughout the continent. Eradication is not plausible for *Ae. aegypti*, elimination was a goal pursued in the past, but the desirable goal is now control.

We are challenged by different stages of the vector's life cycle which develop in different environments (air and water) and in different types of breeding sites (natural and artificial), made of a variety of materials (plastic, metal, cement, clay, glass, etc.) and have different productivity, different uses (some may be disposable and others able to be controlled) and can be either permanent or seasonal. This variability in type of vector breeding sites imposes diverse challenges for control—whether it can be sporadic (cleaning campaigns), continuous (use of larvicides or larvivorous fish), or permanent (physical elimination)—and it is not realistic to expect that these differences require a homogenous strategy. The characteristics of the different types of breeding sites require a variety of customized strategies so that the control may be effective and sustainable.

The diversity of available vector control strategies and their implementation in each operation are related to the resources available, the cultural context in which the interventions are performed and the overall capacity for applying them appropriately and with sufficient coverage. These factors can and should be included in the integrated vector management (IVM) approach promoted by the WHO [5, 6]. IVM is based on a spectrum of intervention strategies, frequently utilized in synergy and applied simultaneously, that are selected based off of knowledge of local factors influencing the vector's biology and the disease's transmission and morbidity, with the goal of optimizing resources for vector control.

As dengue spread on the last decades, the idea of vector control replaced that of vector elimination, because the magnitude of the problem surpassed the capacity of institutional responses (vertical programs) and incorporated new approaches such as community participation; biological control of larvae (copepods, *Bacillus thuringiensis* (Bti) and fish); physical control (mosquito nets, curtains, clothing, etc., all impregnated with insecticide); chemical control (repellents, larvicides and novel insecticides); behavior change communication [7] (BCC) and communication for behavioral impact [8, 9] (COMBI); integrated management in the comprehensive control of vectors (EGI-Dengue, 2003) [10] and even the design of multidisciplinary approaches, such as an eco-bio-social emphasis [11]. The incorporation of so many different approaches is a clear sign of the complexity entailed in facing this mosquito.

Despite new vector control strategies being introduced with the goal of diminishing transmission, entomological monitoring indicators were never adapted to the new demands of the programs, and the traditional indices designed to measure the presence and absence of larvae and containers, which were never linked to the risk of transmission, were maintained [12].

The introduction of technological innovations—such as the use of *Wolbachia*, the genetic modification of mosquito (GMM) populations, and/or the use of irradiated mosquitoes—that promise better coverage, impact and sustainability propose to improve the effectiveness and durability of control interventions. Nevertheless, the innovations also present organizational and procedural challenges that must be attended before, during and after their introduction as control measures.

3. Innovations to biological and genetic manipulation of mosquito vectors

The strategies for genetic and biological control/manipulation with *Wolbachia* of mosquito vectors (GMM/BCMW) propose an attack on the mechanisms directly responsible for the proliferation of mosquito populations. Allowing the mosquitoes' reproductive dynamics be the tool for spreading the intervention means that we will allow the modified populations to disperse naturally (through repeated releases) so that little by little the mosquitoes go about occupying the territory of wild populations to the point of reaching our objective by replacing them in their function as vectors or by suppressing them as a species.

The mechanism of dispersion and coverage that is proposed is the male mosquito vector itself; these male mosquitoes will find their female counterparts and transmit the control measure before these females lay their eggs, undiscriminating as to preferred breeding site and location. The progeny (eggs, larvae and adults) will incorporate the intervention naturally and will maintain it in the population that emerges from their lineage (desirable). In essence, the dispersal and upkeep of the intervention will be a product of biological mechanisms rather than human intervention.

Interventions consisting of biological manipulation and genetic control of vectors, furthermore, share many characteristics that again distinguish them from the traditional methods. Among these are as follows: (1) dependence on vertical (maternal) transmission of heritable elements (resistance genes and *Wolbachia*), (2) specificity in regard to affected species, (3) environmental friendliness, (4) harnessing of natural reproductive instincts, (5) noninvasiveness of domestic spaces and (6) large-scale application (indispensable). A common challenge of these innovations and of traditional measures of control is to achieve the coverage necessary to be effective and sustainable.

In general, these innovations to vector manipulation are based on two strategies that can be organized according to the results obtained (population elimination vs. replacement) or to the implantation dynamics (self-sustainable or self-limiting).

Population elimination/suppression: aimed to affect the demographics of the vector population with the goal of eliminating it from the area or reducing it to a low level that will not maintain transmission.

Population substitution/replacement: This strategy seeks to replace wild populations with modified populations that are resistant to the viral infection. One of the most novel mechanisms that produce resistance to infection is transinfection with *Wolbachia*. Other mechanisms are effected through the incorporation of transgenes that—by way of impacting the vectors' survival, physiology (flight, feeding) or susceptibility to the infection—indirectly reduce the mosquito's vectorial competence (interference).

Self-limiting: This strategy implicates the abundant and repeated release of mosquitoes in order to maintain the flux of the genetic change in the target population. It is reversible with the discontinuation of releases.

Self-sustaining: This strategy proposes repeated releases of modified mosquito populations sufficient to establish themselves as the dominant population (replacement), to the end of their persisting in the population even while there may be unforeseen risks.

4. Paradigm shift, focus and objective

One of the most important changes upon incorporating GMM-BCMW into the *Aedes* and ABD control programs is a *paradigm shift* in passing from emphasis on the larval stages to the direct impact on adult populations. These innovations in *Ae. aegypti* control direct efforts to the reproductive capacity or its competence as a vector, rather than the breeding sites. The theoretical assumption is based on the key elements for vector control centered on adult mosquitoes (abundance, survival, incubation periods, biting rate, etc.) [13]. However, directing control toward adult mosquitoes requires information that is not currently produced in traditional control programs.

Traditional programs of control direct their efforts toward larval stages, reducing breeding sites abundance and the density of larvae in houses and containers, while they attack adult mosquitoes with insecticides that have limited coverage, short duration and low mortality at the population level. The focus and objective of integrated vector management (IVM) are directed to the control of mosquito populations through multi-sector interventions with a multidisciplinary and/or eco-bio-social focus based on changes to community practices, achieved by way of educational interventions.

GMM-BCMW are not technologies that can be used in case of emergency (outbreak control). Focus is directed to the reduction, suppression (elimination) or substitution of *Ae. aegypti* populations; but in all cases, they should be visualized within the IVM scheme as complimentary tools. Traditional vector control programs imposed a strong component of entomological surveillance (larval monitoring) not correlated to epidemiological surveillance (incidence of infection and disease); this favored control responses (reactive) before the increase of entomological indicators, without relating them to transmission risk (risk thresholds). This has resulted in reactive interventions based on detection of an increase in breeding sites or of the number of cases that frequently have late entomological effects but no epidemiological effect. With and IVM approach it is expected to use surveillance as a predictor of risk; the identification of priority areas for interventions and to promote actions before, during and after periods of epidemics. In the case of GMM-BCMW, surveillance should be improved so it can be a powerful (proactive) tool that permits entomological, epidemiological and viral surveillance.

5. Challenges to entomological surveillance

Entomological surveillance has been employed to (1) determine changes in the geographical distribution of *Ae. aegypti*, (2) obtain relative measurements of *Ae. aegypti* populations through time and identify areas of "high" infestation or periods of growth in vector populations and (3) evaluate the impact of anti-vector interventions. These indicators cannot be used straightforwardly to estimate the risk of virus transmission in the population at a certain time or location.

Entomological indexes: There are various indicators (indexes) and methods to detect or monitor *Aedes* populations (egg, larval, pupal and adult stages) in relation to their location (containers, home or geographical area). The indicators were initially qualitative (negative/positive breeding sites or houses) and evolved toward being quantitative in order to identify the number of mosquitoes, though without specifying density, productivity or breeding site relevance (cryptic). The indices are not sufficiently exact to identify the risk of transmission [14].

One element of the evolution of control programs has been the slow innovation of entomological monitoring indicators, an area dominated by the traditional *Stegomyia* indexes used in the campaign to eliminate *Ae. aegypti* in the fight against yellow fever: house (HI), container (CI) and Breteau (BI) indexes. These indices were useful in the extent to which they indicated the (qualitative) presence and absence of the vector in a campaign that sought its elimination and attempted to evaluate the endeavors toward physical elimination of breeding sites (positive breeding sites or houses). The focus now turned toward the reduction in density (rather than the elimination) of the vector, and these indicators have lost their usefulness [15, 16].

The need for better indicators led to indices of pupae and oviposition, closer life stages to the ideal measure of adult (female) mosquito populations, which would allow for a better approximation of the estimated risk of transmitting dengue [17, 18]. These indicators of entomological risk did not reduce or eliminate the challenges to evaluate the interventions because the need to relate density and/or the threshold of the different vector stages to risk of transmission still persists [19–21].

The use of "nonentomological" (though associated with infestation and facilitators of vector-human contact and epidemiological risk) indicators has also been proposed and ought to be considered in order to better understand the dynamics of dengue transmission—for example, density and distribution of human populations, socioeconomic conditions, living and public services, climate, etc. [22–27].

The selection of indicators and surveillance methods depends on the objective of surveillance (density reduction, risk detection and outbreak prevention), the levels of infestation and the capacity for implementation. Nevertheless, there is little evidence showing that the control programs employ systematic monitoring of vector populations—in particular, monitoring of adult females—in order to measure infestation and risk of dengue transmission [18, 28, 29]. In the best of cases, programs still employ indices of infested sites/breeding sites [29, 30] in order to establish "areas" of transmission risk without demonstrating the predictive capacity of these indices as indicators of dengue transmission risk in the last 50 years [31].

The limitations of these methods for measuring mosquito populations are the absence of a "gold standard," the fact that all measurements have a range of error (they are not precise) and that only a proportion of the total mosquito population (eggs, larvae or adults) is measured. Furthermore, it must be understood that the risk of transmission can occur in various locations and not necessarily where the measurement and/or intervention is performed and that in the selection of methods of measurement and entomological monitoring, precision is always sacrificed. This is to say that, despite being less precise, easier and cheaper methods are chosen over those (e.g., adult surveys) that require more resources and thus are more expensive [32].

An additional challenge is the combination of strategies (not yet their integration) and the differentiated evaluation of their impact, since while one intervention can modify the physical availability of breeding sites, it does not necessarily result in a decrease of vector density nor control the most stable and productive breeding sites. On the other hand, there is insufficient evidence to support the idea that achieving a lower egg or larval density through a variety of available interventions has an impact on the rate of disease transmission. Nevertheless, the combined use of old strategies and/or the incorporation of new vector control tools imposes various challenges: (1) the use of indicators that measure more specifically the density of mosquitoes in all stages of development in order to more concretely evaluate all available modes of intervention, (2) the definition of risk thresholds and (3) that the programs demonstrate their capacity (in terms of human resources, equipment and finances) to be executed with the coverage and frequency necessary to make them valid [1, 2].

6. Challenges to epidemiological surveillance

The evaluation of interventions to control *Ae. aegypti* faces diverse challenges regarding the potential impact they may have on the risk of transmission not only of dengue but also of other arboviruses recently associated with the region's epidemiological profile: Zika, chikungunya and yellow fever. The first challenge is estimating the impact derived from the disease that may be affected and the second in measuring the direct impact of the interventions on the vector populations in all of their stages and their relation to transmission risk (vectorial competence and capacity).

Systems of epidemiological surveillance now have the task of measuring, in the most precise manner possible, three infections transmitted by *Ae. aegypti*. Now things are complicated because the syndrome of fever and exanthema may be indicative of dengue, Zika and chikungunya. The diseases are also associated with other signs, distinctive symptoms and highly specific clinical complications (hemorrhages with severe dengue, chronic arthralgia with the chikungunya virus and congenital syndromes and neurological complications with Zika).

The estimate of the actual number of dengue cases, and now of Zika and chikungunya, is very difficult to calculate due to *biological problems* inherent to the infection, such as the number asymptomatic infections, or of unspecified fevers, which hinders the correct quantification of the impact of each of these illnesses. Clinical confusion regarding symptomatic fever/exanthema and discriminating diagnosis is reduced when complications are severe and chronic manifestations of each infection are observed. The *operational problems* are evidenced through the low demand of health services—especially during outbreaks—which results in under registration of cases when the person does not demand or lacks access to health services, medicates himself or opts for treatments of symptoms they already recognize through previous exposure to the problem.

Only patients with severe symptoms go to the doctor, and these are the best detected by the surveillance system. An additional operational problem is the lack of sensibility to clinical diagnoses of fever and the limited collection of samples in order to confirm diagnosis—even during an epidemic—now that normative processes restrict the collection of samples to only severe cases or those at the onset of an outbreak. Only those cases confirmed by diagnostic methods available in regional labs (serology and viral isolation) are recorded [33].

These circumstances impact the opportunity for vector control interventions (operational problem) since the presence of asymptomatic cases and unspecified or febrile patients are not registered early, and it is not until the accumulation of many cases that an increase in transmission is detected; it is at this point that control actions are initiated [34]. Among the *cultural problems*, or problems of perception, we find the familiarity with the sickness and its management given prior experience; fever is not considered an important risk to one's health and does not merit a visit to a doctor unless accompanied by more serious symptoms.

The necessity of improving detection, diagnosis and notification: Epidemiological surveillance of arboviruses faces two importance problems that occur in two different spaces: the community and health services. Given the clinical characteristics, an important number of cases do not demand health services due to their asymptomatic status or the unspecified fever that does not merit a visit to a doctor. Even many clinical cases do not consult medical services due to the patient having recognized and identified the case and knowing how to treat it. Due to this situation, we underestimate the number of cases and the detection of the illness and detection for those affected should be improved [35, 36].

In the health services sector, diagnosis and documentation related to cases should be improved by strengthening the capacities of health personnel and local laboratories. To accomplish this, the following are indispensable: (1) counting on clinical guidelines that facilitate the health personnel in the identification and treatment of clinical cases under surveillance (dengue, Zika and chikungunya) and that reduce the identification of false negatives, (2) establishing criteria for the collection of samples and having the supplies necessary for serological and/or viral confirmation of suspected cases, (3) improving the reporting of cases unconfirmed in the laboratory (probable/suspected) following the algorithms of differential diagnosis for the three illnesses, (4) encouraging the reporting of cases by epidemiological association in the case of an outbreak and (5) seeking mechanisms for notification of cases identified by private medical services [37].

7. Operational changes to the programs of control with *Wolbachia* and GMM

Evidence indicates that technological innovations should be viewed as tools complementary to vector control programs—tools whose introduction would be performed in carefully

http://dx.doi.org/10.5772/intechopen.79862

selected sites until the detection of evidence of the sustained impact and the reduction of potential risks of evolution in the manipulated species and introduced genetic or biological marker. It is believed that innovations would be used in places where traditional measures of control have little to no effect and where they may have an important epidemiological impact on transmission dynamics. However, as with any intervention—and especially with innovative interventions—there are some operational changes that will need to be considered for the programs of control with *Wolbachia* and GMM.

Integration of interventions by level of application: A central element is the organization of interventions by level of application. We must keep on with simple practices, such as domestic hygiene (personal level); routine broad procedures such as breeding sites elimination campaigns; technically elaborated entomological sampling and larvicide application (community level); and even specialized, high-cost actions that require equipped, professional personnel, such as insecticide sprays (town level) or programs of medical attention for the correct handling of severe cases (national level). On the other hand, interventions aimed at urban infrastructure (access to potable water, garbage collection and a recycling system) ought to be incorporated bearing in mind that require high-level political commitment and substantial investments (municipal level).

An additional challenge is the integration of abovementioned interventions in order to perform them in a combined and sequential manner and differential intensity in accordance with the epidemiology of each area vulnerable to transmission. Although the available human and financial resources will generally define this, we must pursue on the objective to direct efforts to high-risk areas. The selection of localities in which to introduce these innovations for control should take into account the degree of risk in that area as well as the impact produced by the illnesses.

Program structure: The organization of the control programs has evolved from a vertical centralized structure ("Top-down")—independent of health services and with a "militarized" organization—to a more horizontal and decentralized structure, more tightly linked to services of surveillance and medical care and more participatory ("Bottom-up"). The advances toward a horizontal organization are variable, and in many programs, there exists a combination of both structures, in which the coordination is centralized. The need of coordinating all these processes—including the application of GMM/BCMW-based strategies—implies that programs that adopt these innovations ought to incorporate a centralized perspective, although the host communities ought to participate in the operational unfolding of the new technologies.

Implementation: The traditional control programs have an established procedural routine repeated each year, in the same season, with the same resources (human resources as well as physical, chemical and biological); however, the areas of control must be expanded and the actions intensified due to the increase in at-risk zones. In the case of IVM, it has been proposed that actions implemented should be differential in frequency and intensity in accordance with epidemiological risk.

Human resources and operational infrastructure: The vertical focus of traditional control programs developed a whole line of training for technical vector control personnel totally apart from promotional, preventative and educational health activities. This operational personnel was integrated in brigades separated from other health activities that were not exclusively linked to vector control. This resulted in an independent organization with equipment, vehicles, machinery and supplies (insecticides) that has been growing hand-in-hand with the problem. With IVM, a more rational use of resources is proposed, starting with the multi-sector and multidisciplinary nature (social participation) of the approach, where the social communication component is incorporated as a substantial element of this strategy.

The incorporation of GMM-BCMW into the vector control programs involves the components proposed for IVM, but also requires adaptation of the technology to the local conditions, as well as the development of an infrastructure of basic technology (insectariums and laboratories) to permit mass, sustained production, implementation and appropriate evaluation of the interventions. In this case, a specialized multidisciplinary group—in addition to technical personnel—is needed to achieve the introduction, monitoring and evaluation of new interventional strategies.

Coverage: A problem inherent to the traditional programs of control in urban and suburban areas in countries where ABD are endemic is their limited coverage; not all breeding sites can be protected or removed, and their productive potential cannot be eliminated with biological, chemical or physical agents. It is not possible to protect or control the totality of the most productive and stable breeding sites in urban centers due to their number, seasonal productivity, location and access ("cryptic" breeding sites).

The coverage of a vector control program functions at the level of the individual, the household, the block or neighborhood, but rarely at the town level. With the IVM programs, the target for intensive application of control efforts will be the neighborhood and towns at greatest risk; there are no claims that all affected areas, neighborhoods or towns will be covered. Coverage in the case of GMM-BCMW can include areas, towns, or medium-sized urban centers, since the mass release of treated mosquitoes cannot limit itself to blocks or a neighborhood. Thus, monitoring and maintenance in such broad areas is complicated by the necessity of technical and (specially trained) human resources and not presently contemplated by surveillance programs.

Scale: One of the most important challenges for any vector control intervention is reaching a level of sufficient coverage (breeding sites, houses, people or communities) in order to effectively limit transmission. These technological innovations are proposed as intervention at a scale larger than that established by traditional vector control strategies. However, all of the processes of production, introduction and maintenance must be initially evaluated at an intermediate scale before considering their application at the regional or national level.

Their application for control of mosquitoes that transmit disease is today only viewed within the context of the strategy of integrated vector management (IVM). This implies necessary adaptations in control programs as regard production of biological materials as well as in relation to the operation, which should be designed in accordance with the technical specifications of the modified organisms.

Efficiency in large-scale production: In order to obtain the desired results, it is necessary to release a large quantity of mosquitoes (sterile, genetically manipulated or infected) into the environment in a reasonably short period of time that will allow for reduction and substitution of wild mosquito populations. Production, handling (separation), distribution and release may affect the capacity and competence of freed vectors. Production is easy to evaluate, but the same may not be said for the competence of the generated mosquitoes.

Quality: The performance, or *fitness*, of the vector should be evaluated, and there is not much experience with this sort of evaluation. Some factors to be evaluated are physical distinctions (pupa and/or adult size), survival rate, dispersal, mating capabilities, sperm quality, competition with wild or native species, and so on. Training of technical personnel and a specialized multidisciplinary group is needed.

Social participation: Social and community participation are essential to the acceptance, monitoring and evaluation of GMM strategies. Given the nature of the new GMM methods, communication with the communities is necessary in order to introduce these methods, which are conceptually very different from traditional methods of control.

Sustainability: The re-introduction of an eliminated species is possible if control interventions cease or diminish in intensity and frequency. Invasion or re-introduction from other nontreated areas requires a containment plan with geographical barriers to inhibit vector migration. The concerns are more environmental than health-related. The emptied niche may promote the invasion of a more dangerous, competent and effective species.

Costs: Cost-effectiveness studies of traditional control methods begin to be an important strategy in evaluating their potential and their degree of incorporation, and in defining the conditions that create for their maximum usefulness. The success of an intervention in terms of costs is subject to the context of where it is applied, the scale of implementation, the availability of personnel and appropriate equipment and the scale of the problem (endemic, epidemic, hyperendemic and introduction of new agents). Traditional control programs require resources in response to the growing magnitude and breadth of the problem. The investments associated with IVM increase costs because of the community and multi-sector participation and the necessary social communication, which touch on other relevant community issues. The incorporation of GMM-MBW needs to be accompanied by an important investment in infrastructure, personnel training, equipment and supplies, along with a strong social communication component that ought to be considered within the comprehensive cost of the program.

8. Final considerations

During the last decade, the WHO has been promoting IVM but has been using only those intervention methods traditionally available. Several innovative methods are being developed to complement the current control of *Ae. aegypti* populations and affect the transmission of ABD. Some show great potential, such as the use of GMM-BCMW, but are not yet available as part of institutional prevention and control programs. In addition to the challenges exposed earlier, other limitations include a lack of scientific and technological infrastructure of the quality and capacity necessary for the implementation of novel methods of mosquito control. This extends to laboratories, systems for the mass rearing of mosquitoes and processes such as quality control, transportation, field release, monitoring and evaluation of effectiveness. Both WHO and the Pan American Health Organization (PAHO) are offering their technical cooperation to support pilot studies using innovative methods. The technical advisory group on entomology in public health and vector control explicitly recommended to PAHO "Promoting rapid, robust and accelerated evaluation of new tools complementary to the control of *Aedes*, with particular attention to the use of mosquitoes infected with the bacteria *Wolbachia* and sterile and genetically modified insects."

Vector control programs do not use "single" methods. Innovations should be considered complementary tools to control programs, not substitutes. Traditional and/or new interventions of greater complexity can be implemented proactively using a risk stratification approach calling for different intensity and greater coverage in priority areas. However, we can anticipate complications on monitoring and evaluation, since there is little evidence and experience of multiple or combined interventions with intersectoral participation and IVM.

Traditional vector control has demonstrated limited impacts and transitory decreases in larval and adult mosquito populations. Monitoring of these traditional control programs is performed on an irregular basis throughout the year, without taking into account that there are important seasonal effects on vector populations. Furthermore, these evaluations are unstructured and usually not conduced at the time intervals necessary in order to estimate the magnitude and longevity of the effects on vector populations. In the case of GMM-BCMW, in addition to performing entomological monitoring to estimate the effects of suppression on target populations, in the case of substitution or population replacement strategies, it is necessary to include measurements of the reproductive and biological performance of the introduced populations.

Estimates of the effect of traditional actions (larval density) do not imply impacts on disease transmission (incidence). The IVM strategies share these limitations, although they diversify the indicators due to the multidisciplinary nature of their interventions. In the case of GMM-BCMW, the evaluations ought to incorporate continuous monitoring of adult mosquito populations (wild and introduced): their survival, performance (or *fitness*), competence as vectors or capacity to transmit the infectious agents, reproductive capacities, flight range, dispersal, and so on. The indicators should purvey information relevant to measuring the effects on reproductive capacity; reduction in infection and other entomological, epidemiological and even ecological parameters that describe the dynamics of adaptation of introduced populations.

Despite intense research on *Ae. aegypti*, we still do not have entomological parameters linking vector density to risk of transmission. It is also still difficult to define the transmission risk's direct impact on human populations and its duration (days, weeks and months) in mosquito populations—and even more difficult to count on indicators that allow for efficient evaluation of the effects of different vector control interventions on the impact of the illness within the community (infection, severity of clinical cases, mortality, etc.). These limitations are the same for GMM-BCMW, and we still need indicators that will correlate efficacy in terms of entomological parameters (reduction or substitution of mosquito populations) to effects on transmission of the illness.

Entomological surveillance is indispensable in order to monitor vector populations and to count on the basic parameters that allow for evaluation of direct impact on affected populations. Larval densities are not sufficient for evaluating the effects expected with the inclusion of these innovations, since the introduced populations are competing adults; as a result, it is necessary to evaluate adult density (males and females) as well as vector survival, mating habits, reproductive capacities (fecundity) and so on.

Last but not least, the success of any control intervention should be measured ultimately in terms of resultant decrease in infection transmission and in the impact of the illness on the community. This process entails decreased herd immunity in human populations and would introduce the risk of greater epidemics if the intervention measures lost intensity or effectiveness or were no longer applied. Decreased immunity augments the population's susceptibility, which results in lower vector density thresholds for transmission or risk of transmission.

Here, we have exposed some of the major challenges for the introduction, implementation and evaluation of innovative *Aedes aegypti* control strategies based on GMM/BCMW. Nowadays, they are still being evaluated to gauge their entomological impact; and evidence of epidemiological impact is desirable in the near future.

Other basic requirements for the adoption of technological innovations include a regulatory and legislative framework for their use in public health (Environmental, Biosecurity and Bioethics); following a set of Protocols & Portfolio having to do with safety, quality control, efficacy, and so on; and necessary integration with local vector control programs including agreement/acceptance by institutions and communities. In terms of administrative and financial requirements, we still need to resolve whether these technological innovations can be acquired under the current budget structure (as a product or service). In order to more quickly implement these new technologies, we need to develop a medium to long-term implementation and financing plan; production, distribution, monitoring and evaluation logistics and private-public partnerships.

Acknowledgements

To the Canadian Institutes of Health Research (CIHR) and IDRC (Preventing Zika disease with novel vector control approaches Project 108412) and Fondo Mixto CONACYT–Gobierno del Estado De Yucatán (Project YUC-2017-03-01-556). Abdiel Martin-Park is supported by the Cátedras–CONACYT program. Special thanks to Ana García-Moreno Malcolm for grammar corrections.

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