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Technical document for the implementation of interventions based on generic operational scenarios for *Aedes aegypti* control

Pan American Health Organization

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REGIONAL OFFICE FOR THE Americas

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1 Introduction

Arboviral diseases such as dengue, chikungunya, and Zika fever, transmitted mainly by the *Aedes aegypti* and *A. albopictus* mosquitoes, are public health problems in the Region of the Americas.

The dengue virus (DENV) continues to be responsible for the highest global burden of disease, especially in the Region of the Americas. It is endemic in more than 30 countries, with an estimated 13-53 million cases annually and a case-fatality rate of 1.2% (WHO, 2009; Bhatt *et al.*, 2013). The Region is also subject to explosive and epidemic outbreaks of chikungunya and Zika fever. The chikungunya (CHIKV) and Zika (ZIKV) viruses are found in every country in the Americas except Canada, Chile, and Uruguay (Nsoesie *et al.*, 2016; Messina *et al.,* 2016).

The recent outbreak and rapid spread of ZIKV in the Americas drew attention to the importance of organizing and strengthening *A. aegypti* control activities (Ferguson *et al.*, 2016) and keeping all health systems in the Hemisphere on constant alert. Also worrisome is the potential reemergence and risk of reurbanization of the yellow fever virus, which in Brazil has caused explosive outbreaks in the wild, although some of them have occurred in proximity to urban centers (WHO, 2018).

Historically, the operating costs and capital expenditures for the maintenance of *A. aegypti* prevention and control programs have been high, due to the use of control methods that emphasize high coverage, mainly with insecticides (Fitzpatrick *et al.*, 2017). Moreover, to date, the traditional routine methods to control the *Aedes* vector (physical elimination of habitats to reduce breeding sites; larvicides; and adulticides) have had only a limited and temporary impact on disease prevention, either because they are not very effective or their coverage is limited (Bowman *et al.,* 2016; Tun-Lin *et al.*, 2009).

Urban areas have the highest burden of the diseases transmitted by *A. aegypti,* due to their high population density and dynamic, in addition to the inherent problems in their health service infrastructure, water supply, and refuse collection. Hence, they still pose a real challenge for vector control. Vector control programs focus their coverage on the individual, housing, block, housing section, or neighborhood, but rarely entire cities, since no public health program has enough human resources to cover every household. Furthermore, vertical programs do not consider the heterogeneity and diversity of *A. aegypti* ecological scenarios or local transmission cycles (Barrera Pérez *et al*., 2015).

Multiple factors influence the transmission of arboviral diseases and operate simultaneously on different spatial and temporal scales, creating complex transmission, persistence, and dispersal patterns (Vázquez-Prokopec *et al.*, 2010 b; Vanlerberghe *et al*., 2017, Bisanzio *et al.*, 2018). The identification of these transmission patterns and their scale of operation is urgently needed, given the current epidemiological situation in the Hemisphere.

When human, material, and financial resources for local public health interventions are limited, it is necessary to stratify the risk at the following lower levels: housing section, neighborhood, area, or sociodemographic unit (Vanlerberghe *et al.*, 2017). This stratification identifies the most important strata – that is, the areas at greatest epidemiological-entomological risk – on which to focus interventions for better transmission prevention and control (Gómez Dantés *et al.*, 1995).

For stratification at the city or local level, spatial analyses are needed that help to identify transmission patterns and their scale of operation. However, it is also necessary to determine and select the most cost-effective intervention and evaluation tools and strategies for each scenario (anticipatory measures) and their timely implementation (Barrera *et al.,* 2000; Gómez Dantés *et al.*, 2011; Vanlerberghe *et al.*, 2017). This is essential for achieving the desired impact on transmission.

The purpose of this publication is to provide a framework for planning and implementing *A. aegypti* surveillance, prevention, and control activities through risk stratification to support the development of potential operational scenarios at the local level. Operational scenarios serve as a reference for selecting the best tools for vector control and using them more efficiently.

2

Updating *Aedes aegypti* surveillance and control methods

National *A. aegypti* surveillance and control programs in the Region have structures that differ in terms of their components and organization. The majority are based on the management model known as the “integrated management strategy for dengue prevention and control in the Americas” or IMS-dengue (San Martín and Brathwaite, 2007).

This section does not seek to provide an exhaustive analysis of each component or of how components interact in each country but, instead, will focus solely on the entomological component of integrated vector management (IVM) which includes the activities involved in *A. aegypti* surveillance and control.

2.1. Bioecology of *Aedes aegypti* and its importance for surveillance and control

The behavior, biology, and ecology of *A. aegypti* pose unique mosquito control challenges. Humans inadvertently facilitate the vector’s reproduction in dwellings and other private structures to which health inspectors or health brigades have no direct access. It has been shown that a high proportion of closed dwellings or dwellings whose residents deny access to these personnel is a determinant of failure in *A. aegypti* control (Chadee, 1988).

In its immature stages, the mosquito often develops in necessary containers (water storage tanks or drums, water dishes for pets, etc.). Its habit of resting, biting, and even laying eggs inside the home isolates and protects it from outdoor insecticide space spraying (Castle *et al.*, 1999; Perich *et al.*, 2000).

Another important characteristic is that *A. aegypti* can transmit arboviruses even at very low population densities. Mathematical models suggest that one female biting one person per day is enough to produce local transmission of dengue in areas with temperatures of 28°C and herd immunity of 0%-67% (Focks *et al.*, 2000).

Another salient characteristic is the significant reproductive capacity of *A. aegypti,* whose potential is maximized when it is found in low densities, as occurs in the wake of control measures. Furthermore, in recent years, *A. aegypti*'s use of cryptic aquatic habitats such as storm drains in streets or dwellings, septic tanks, elevated tanks, etc., has frequently been described. These breeding sites cannot be located visually due to their hidden or inaccessible nature, are immune to traditional vector control methods, can produce more mosquitoes than other types of containers, and pose the risk of dengue transmission (Barrera *et al.*, 2008; Manrique Saide *et al.*, 2013; Russell *et al.*, 1993).

The most critical aspect in *A. aegypti* control is the resistance of the mosquito's eggs to desiccation, meaning that they can remain viable in containers for months. This adaptation confers great population resistance to control measures and adverse environmental phenomena such as droughts. No commercial ovicides are currently available at this time, and larvicides are not long-acting enough to extend beyond egg viability. In the dry season, many batches of *A. aegypti* eggs lie dormant on interior container surfaces. When the rainy season arrives, these containers fill up with water that ultimately reaches and covers the eggs, prompting the emergence of the larvae. This phenomenon occurs on a massive scale in container reservoirs, leading quickly to high adult populations of this mosquito. This makes *A. aegypti* highly resilient and able to recover after natural or human disturbances (Barrier, 2015 a).

Finally, insecticide resistance in *Aedes* populations is compromising the effectiveness of chemical control of arboviral diseases (Vázquez-Prokopec *et al.*, 2017); this is particularly important for local control programs, the majority of which choose synthetic chemical insecticides as the first option for mosquito control. Insecticide resistance in *A. aegypti* in particular has intensified and spread over the past decade. The reemergence of dengue worldwide, accompanied by increased use of chemical interventions in response to major and recurrent outbreaks, and long-term dependence on pyrethroids for urban vector control have been key factors in the rapid and widespread growth of insecticide resistance (Ranson *et al.*, 2010; Smith *et al.*, 2016; Vontas *et al.*, 2012).

2.2. Entomological surveillance

The common purpose of all entomological surveillance programs for *A. aegypti* control is to identify changes in the geographical distribution of this mosquito, obtain relative measurements of its populations over time, evaluate the coverage and impact of vector control measures, monitor the susceptibility and resistance of *A. aegypti* populations to the principal insecticides used in vector control (PAHO, 2017), and more recently, monitor the presence of arboviruses in mosquitoes (entomovirological surveillance).

Entomological surveillance (potentially) includes systematic sampling of all stages in the development of *A. aegypti*: egg, larva, pupa, and adult. Selection of the indicators and sampling methods (including the sampling effort) depends on the surveillance objectives and infestation levels (Table 1) and, of course, the available capacity to implement them. It is generally recommended that indexes of pupae and/or adults, rather than indexes based on ovitraps and larval sampling, be used as indicators of risk or success, since adults (females) are the last link in the chain of transmission and have high epidemiological value.

Although the usefulness and relevance of larval indicators in the identification of transmission risk areas and levels have been questioned (Bowman *et al.*, 2014), they are most often the first to be used, since, based on the visual inspection of containers, they do not require highly skilled technical personnel and are useful for obtaining information in the short term. The reliability of larval indexes can be affected by the presence of cryptic breeding sites; it is therefore recommended that the existence of these breeding sites in the study area be ruled out (Barrera, 2016).

Although indicators based on pupae or adults are the most preferred for measuring infestation levels and transmission risk, and even establishing transmission density thresholds (particularly for DENV), these thresholds have not been fully validated in the field and their capacity to predict transmission risk has not been solidly demonstrated (Barrera, 2016).

Entomological surveillance systems in some countries have recently included insecticide susceptibility monitoring and the determination of resistance mechanisms (through biochemical and molecular tests). These systems provide evidence to aid in the selection of insecticides, a key element of comprehensive resistance management strategies.

According to the global guidelines (CDC, 2010; WHO, 2013), these studies may consist of:

- the evaluation of formulations or new compounds for control (bioefficacy tests);
- bioassays to determine the susceptibility to insecticide resistance and its intensity;
- determination of resistance mechanisms with biochemical and molecular tests (detection of mutations).

By including these studies in a regular systematic monitoring program, it will be possible to determine baseline resistance levels and, in time, gain a better understanding of the resistance profiles of local mosquito populations, which is necessary for adopting the best resistance management strategy. Thinking that resistance can be reversed, implementing a management strategy is always beneficial in terms of long-term cost effectiveness.

Although less common in *A. aegypti* surveillance and control programs, arbovirus surveillance in adult mosquitoes for timely detection of areas at risk for transmission (that is, with infected mosquitoes) triggers an immediate anticipatory control response.

Also proposed is the use of non-entomological indicators potentially associated with mosquito breeding sites, such as the distribution and density of human populations, socioeconomic and housing conditions, the public services situation, climate, etc., which would serve as indicators of the risk of viral transmission. These indicators measure the vulnerability of a geographical area or region to the transmission of viruses by *A. aegypti*. However, as with the entomological indicators, the sensitivity and specificity of vulnerability indexes have not been validated epidemiologically. Furthermore, they can vary with the conditions that determine the risk of viral transmission in different geographical areas of a country.

In any case, the most informative entomological surveillance methods should be employed in the entomological-epidemiological scenario, based on the available capacity to implement them. The method should be tailored to local programs before its routine use. Finally, methods based on pupae or adults are preferable.

Table 1. Entomological indicators (available methods) and main entomological indexes for *A. aegypti* surveillance

Surveillance method	Usefulness	Advantages	Disadvantages	Principal entomological indicators
Sampling with ovitraps	• Provides information on the distribution, both spatial (presence/ absence and clustering) and temporal (fluctuation), of female mosquitoes. • Monitoring of infestation/ reinfestation in areas free of the vector or with low transmission. • Evaluation of interventions based on the control of adults. • Provides material for identifying colonies and conducting susceptibility/ insecticide resistance studies and/or searches for the virus.	• Economic. • Performed with limited personnel with extensive coverage in a short time. • Unintrusive. • Requires little maintenance. • Is highly sensitive for monitoring the impact of control intervention.	• Disadvantageously competes with existing breeding sites, which may be more attractive, potentially yielding erroneous information. • The relationship with respect to the abundance of adults is not clear.	• Ovitrap positive index (OPI): Number of houses with ovitraps positive for *Aedes* per 100 houses. • Mean eggs per trap (MET): *Aedes* egglaying rate.
Larval sampling	• Provides knowledge about infestation levels (houses and the abundance of breeding sites in a given universe) prior to the implementation of control measures and about the impact of these measure, especially those for controlling breeding sites with specific clean-up activities and/ or the use of chemical or biological larvicides.	• It is one of the measures (and in many cases, the only measure) most often used to describe the degree *A. aegypti infestation.* • Provides information about the most abundant larval habitats.	• Depends on visual location of containers in the domestic setting and is rarely applied in other settings or public spaces, limiting the identification of important cryptic breeding sites.	• Index (HI): Number of houses with immature *Aedes* per 100 houses. • Container Index (CI): Number of containers with *Aedes* larvae per 100 containers with water. • Breteau Index (BI): Number of containers with immature *Aedes* per 100 houses.

Surveillance method	Usefulness	Advantages	Disadvantages	Principal entomological indicators
Pupal sampling	• Indicator of the abundance/density of adult mosquitoes. • Identification of the breeding sites that produce (contain at a particular time, e.g., time of the year and in certain breeding sites) the highest proportion of pupae, which suggests that they also produce the highest proportion of adult mosquitoes.	• Identifies the most productive breeding sites to focus on their control. • Indicates transmission risk through the pupa and population count.	• Requires exhaustive sampling, with the consequent investment of time. • Requires trained personnel.	• Pupa/person index per hectare, block. • Productivity: Estimate of the relative importance of each type of breeding site, calculated from the percentage of *Aedes* pupae in the total collected, by type of breeding site.
Adult sampling	Direct measurement of the abundance of adults, with high epidemiological value, especially if there is a search for viruses.	• It is the recommended theoretical indicator for measuring infestation contact infection risk of transmission. • Provides an estimate of the population per unit of area (housing).	• Can be an intrusive method. • Requires an investment of time, equipment, and trained personnel, elevating its costs.	• Adult house index (AHI): Number of houses with adult *Aedes* per every 100 houses. • Adult density index (ADI): Relative abundance of the *Aedes* vector.

The reliability of the information from entomological surveillance systems will depend on the spatial (coverage) and temporal (frequency) scale in which the indexes are obtained. The information will be valid only for the area monitored (block, neighborhood, housing section, etc.) and the moment that the sampling was done and cannot be generalized to a larger scale, since environmental conditions change from place to place and mosquito populations fluctuate in time and space (LaCon *et al*., 2014).

2.3. Vector control

The purpose of vector control is generally to prevent mosquito bites, maintain "acceptable" mosquito population densities, minimize vector-human contact, and reduce the longevity of adult females (Foster and Walker, 2002). Vector control measures are expected to reduce the incidence and prevalence of vector-borne diseases and their associated morbidity and mortality to an acceptable level (that does not exceed the capacity of health systems to provide care) or, if possible, to eliminate them. Eradication of *A. aegypti* populations is possible but rarely lasts; thus, the mandate of control programs is more to keep vector populations at levels below a certain threshold than to eliminate them (McCall and Kittayapong, 2007).

A. aegypti control strategies can be classified as:

1. **Search and destroy:** The control agent is taken to the location where the mosquitoes are expected to be found and includes all the control techniques in use: removal or alteration of containers in which water accumulates in houses and public areas; the use of larvicides and space and residual insecticide spraying. For this strategy to work, access to the majority of sites where *A. aegypti* is expected to breed or rest is necessary.
2. **Attract and kill:** This strategy uses attraction – physical (color, size), chemical (smell), or both – to attract *A. aegypti* to capture stations such as mosquito traps or to feeding stations with pesticide-laced sugar (poisoned feed). These techniques are innovative and are undergoing field testing. To be effective, the trap must be highly efficient, sufficient traps must be distributed per dwelling, and the majority of dwellings must be treated. This type of approach is beginning to yield very good results (Barrera *et al.*, 2017; Barrera *et al.*, 2018) and lends itself very well to community participation, due to its high degree of acceptance.
3. **Autodissemination of the control agent:** This strategy uses the mosquitoes themselves as control agents through mass releases (mainly of males) to eliminate or sterilize the mosquitoes found in nature. For example, males infected with entomopathogenic bacteria or fungi, mosquitoes that carry aquatic environmental contaminants that inhibit the emergence of adults, and irradiated or genetically modified mosquitoes can be released (Alphey *et al.*, 2013; Bellini *et al.*, 2013; Mains *et al.*, 2015; O'Connor *et al.*, 2012; Scholte *et al.*, 2004). For these techniques to be effective, it is necessary to have males with a normal ability to fly and copulate; to release sufficient quantities of males in proportion to the wild males; to release them often enough; to keep females from being released with the males; and to achieve effective coverage, bearing in mind especially the limited dispersal of adult *A. aegypti*

2.3.1. *Aedes aegypti* control methods*i*

Control methods vary with the stages of the *Aedes* life cycle that they affect (Table 2). Their use in each program depends on the cultural context and available implementation capacity. The World Health Organization (2008) advocates that these methods be implemented under an IVM system consisting of an array of interventions often implemented simultaneously (in synergy) and selected on the basis of knowledge about the local factors that influence the biology of the vector, transmission, and the morbidity of the disease so as to optimize the resources for vector control (McCall *et al*., 2009).

A. aegypti control in the Region of the Americas depends on local control programs organized in the ministries of health with a certain level of community participation to promote proactive control of immature mosquito habitats (e.g., reducing, eliminating, adapting or modifying potential breeding sites) and the adoption of personal protective measures, supported by educational campaigns, environmental management, and legislation as basic measures.

The principal available control methods are presented in Table 2.

Physical or chemical control of immature and adult *A. aegypti* is an important part of integrated strategies for arboviral disease prevention and control in the majority of countries in the Region. However, the impact of these interventions on *Aedes* abundance and DENV transmission has been called into question. Most authors conclude that there is no solid evidence of the effectiveness of the interventions carried out by local vector control programs (Ballenger-Browning and Elder, 2009; Bowman *et al*., 2016).

Specifically, the effectiveness of ultralow volume (ULV) space spraying (ground or aerial) has been questioned, given the very low probability of contact to affect domestic populations of *A. aegypti* (Castle *et al*., 1999; Perich *et al*., 2000). ULV space spraying is recommended as an emergency response to outbreaks to rapidly reduce adult mosquito populations, but its effect is temporary (Esu *et al*., 2010; Pilger *et al*., 2010). Its main function is to eliminate infected adult mosquitoes, but it is not a tool for managing vector populations. The latest scientific data suggests that the efficacy of interior ULV space spraying in reducing domestic mosquito populations may be greater than 60% (Gunning *et al*., 2018) and even greater than 90% (Perich *et al*., 2003).

One alternative recently recommended by the World Health Organization is residual treatment – in particular, indoor residual spraying in *Aedes* resting sites in the home. Although the heavy investment of time and human resources that it requires has limited its widespread adoption in control programs, the evidence shows that when done properly, indoor residual spraying can have a greater impact on the size of *A. aegypti* populations and DENV transmission (Vázquez-Prokopec *et al.*, 2010 b; Vázquez-Prokopec *et al.*, 2017) than other adult control methods and result in higher intergenerational mortality.

Encouraging results have been observed with a somewhat similar approach consisting of the use of screens/netting impregnated with long-lasting insecticides (with a useful life of three years declared by the manufacturer) to control mosquito vector populations. The results of some studies conducted in Haiti, Venezuela, Mexico, and Guatemala suggest that installing screens on doors or windows (Che-Mendoza *et al.*, 2015; Che Mendoza *et al.*, 2018), hanging mosquito nets as curtains in doors and windows (Lenhart *et al.*, 2008; Rizzo *et al.*, 2012; Loroño-Pino *et al.*, 2013) or using them as container covers (Kroeger *et al.*, 2006) could be effective in reducing *A. aegypti* populations in the home as protection against the vector. Screens/mosquito netting, with or without insecticide, on doors and windows are a significant protective factor linked to a reduction in the number of mosquitoes in the home (Waterman *et al.,* 1985; Che-Mendoza *et al.*, 2015). In light of these results, certain countries in the Region – Mexico and Brazil in particular – are promoting "*Aedes*-proof homes" (dwellings without *A. aegypti* breeding sites and with screens/mosquito netting in doors and windows) as a key element for integrated management of the arbovirus vector.

These studies show that when properly implemented, vector control methods can have a significant entomological and epidemiological impact. It is generally accepted that the existing tools and strategies are effective in reducing the transmission of diseases spread by *Aedes,* provided that they are properly implemented in control programs (WHO, 2016).

In any vector control strategy, it is always essential to include a community participation or social mobilization component to guarantee a greater impact (Alvarado-Castro *et al.*, 2017; Bowman *et al*., 2016; Erlanger *et al.,* 2008).

New technologies have been developed that focus on population suppression or substitution through the mass release of irradiated, genetically modified, or *Wolbachia* infected mosquitoes (Table 2). However, they are still in the trial phase to verify their impact and determine how to implement them. (A review of the PAHO article [2018a] on the assessment of new technologies for the *A. aegypti* control is recommended.)

Table 2. Principal methods available for *A. aegypti* control in the Region of the Americas (adapted from PAHO, 1994 and McCall and Kittayapong, 2007)

Method	Description	Mode of application	Examples	Impact
Chemical control	Control of immature stages (eggs, larvae and pupae).	Larvicides can be applied manually (when the breeding site is accessible) or with ground or aerial equipment to cover a large treatment area in less time.	Synthetic chemical larvicides (temephos, chlorpyrifos, fenthion, pirimiphos-methyl).[1] Biorational larvicides:[1] growth regulators (methoprene, pyriproxyfen), inhibition of chitin synthesis (benzoilfenilureas) derived from bacterial toxins *(Bacillus thuringiensis* var. *israelensis and spinosad).*	Its efficacy is greater when the immature mosquito is restricted to a low number of small, accessible breeding sites.
	Control of adults	Adulticides can be applied as residual treatment on surfaces inside and outside of dwellings (residual spraying with hand pumps) or as space treatments (cold or hot ULV space spraying with portable or hand-held, vehiclemounted, or aerial equipment).[2]	The majority of local programs control adult populations with insecticides from the principal chemical groups recommended by the WHO Pesticide Evaluation Scheme (WHOPES) for interior and exterior fumigation[3] (pyrethroids, organophosphorus compounds, and carbamates) or with the insecticides accepted by the local authorities in each country.	ULV fogging aims to immediately reduce the densities of female mosquitoes, their longevity, and other transmission parameters; it is recommended in epidemics, but its effect is temporary. Residual spraying attempts to reduce vector-virus-human contact through a longacting (3-6 months) household chemical barrier[4], eliminating, discouraging, or repelling the mosquitoes.

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[1] http://www.who.int/whopes/Mosquito_Larvicides_Sept_2012.pdf
[2] WHO, 2003a.
[3] WHO, 2006.
[4] WHO, 2015.

Method	Description	Mode of application	Examples	Impact
	Personal protection	Commercial household insecticides (aerosols, spirals, and foggers); repellents (natural or synthetic); barriers, whether or not insecticide impregnated (mosquito canopies, curtains, and nets) and paints that release insecticides (least common).	Commercial insecticides for household use are the most frequently used products. The principal active ingredient in the vast majority of them is a pyrethroid. The recommended repellents are those with active ingredients such as: • DEET (N, N-diethyl-3-methylbenzamide); • IR3535 (3-[N-Butyl-Nacetyl]- aminopropionic acid, ethyl ester); • Picaridin, also known as KBR 3023 and Icaridin (2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester); • *Corymbia citriodora* oil (lemon-scented eucalyptus) or p-Menthane-3,8-diol (PMD).[5]	They can reduce vector-human contact in two ways: acting as a physical barrier and through their insecticidal or repellent effect.
Biological control	Control of immature stages (larvae and pupae)	Introduction of agents that parasitize, compete, or in some way reduce populations of the species.	Restricted to the use of some fish species[6] – for example, *Gambusia and Poecilia* (Poeciliidae) and copepods (Copepoda: Cyclopoidea),[7] preferably indigenous.	Although their effectiveness has been proven in the operational context in specific habitats and containers, they are rarely used on a large scale in the Region of the Americas.

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[5] Allow 3-7 hours of protection, depending on the concentration of these ingredients (Rodríguez *et al.*, 2017; Uc-Puc *et al.*, 2016).

[6] WHO, 2003b.

[7] Benelli *et al.*, 2016.

Method	Description	Mode of application	Examples	Impact
Environmental management	Modificación	Permanent physical change in the characteristics of the habitats of immature mosquitoes.	Installation of a reliable piped water supply network, frequent household solid waste collection services, permanent filling or leveling of habitats (flooded floors and ceilings), drainage of public spaces.	Aimed at altering the environment to prevent or minimize the spread of the vector and vector-human contact through the destruction, alteration, elimination, or recycling of empty (unuseful) containers that serve as habitats of the vector.[8]
	Manipulation	Temporary changes that affect the main features of the vector's habitats.	Mass elimination, cleanup, recycling, storage, and solid waste destruction campaigns with community participation, including container cleaning (interior washing) and manipulation (physical protection, use of netting or covers).	
	Structural changes in mosquito havens or human dwellings and in human behavior	Action to reduce human-vector contact, such as the installation of screens/mosquito netting in windows, doors, and other points of entry and the use of canopies while sleeping in the daytime.	Installation of screens/ mosquito netting in doors and windows or other points of access, paints and wall coverings to eliminate habitats and natural havens.	
New technologies	Control of adults		Release of males infected with bacteria of the genus *Wolbachia*. Release of genetically modified mosquitoes. Mosquitoes sterilized through irradiation. Autodissemination of autocides by mosquitoes.	In the evaluation phase, through pilot field studies in the Region of the Americas: Brazil, Colombia, Mexico, Cuba, and the United States.

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[8] WHO, 1982.

3 Operational scenarios for *Aedes aegypti* surveillance and control

3.1. Surveillance, prevention, and control strategies

Local vector control programs often use the available epidemiological and entomological information from the integrated surveillance system to evaluate, identify, and prioritize risk areas for the introduction of vector control interventions (Hernández Ávila *et al*., 2013). The integrated vector management strategies generally used by the programs are:

- **Routine prevention activities.** In the absence of transmission (interepidemic period), the activities are concentrated in sites with recent transmission (to eliminate vertical transmission of infections) or in areas of high entomological risk (determined by entomological surveillance). As part of environmental management, some programs implement clean-up campaigns or hold public events with community participation to eliminate *Aedes* breeding sites, whether for preventive purposes or before cases appear; these strategies can have an immediate effect, reducing potential mosquito reproduction sites (Barrera Pérez *et al*., 2015).
- **Response to case reporting.** When cases are reported, targeted control measures are taken in the area surrounding the residence of the case (up to a 300 m radius). Targeted treatment is a key element of the early phases of transmission control, when there is initial evidence of peridomestic transmission of DENV around the index case (Martínez Vega *et al*., 2015). Once the chain of transmission has been established, DENV spreads throughout the community through the movement of cases. Targeted treatment often consists of an intensive assault on mosquitoes in the residence of the suspected or confirmed case, using a wide range of simultaneous

interventions (applied in synergy). The effectiveness of this approach is highly dependent on early case detection and epidemiological documentation on the site where the infection may have occurred. This technique has successfully been used in non-endemic areas where each case is investigated in depth, including the places visited in the days prior to the onset of symptoms (work, homes of family members). A major constraint is that while most DENV and ZIKV infections do not produce symptoms, asymptomatic people can infect the mosquitoes.

- **Outbreak response (emergency response).** This includes a series of synchronized extensive vector control measures implemented in one or more sectors of the city or locality (neighborhoods, housing sections, or areas) when transmission is generalized or persistent and the number of reported cases exceeds the capacity to respond with targeted treatment surrounding the case. Due to the cost involved, these measures rarely cover an entire locality, but there are some examples of aerial spraying. This strategy generally involves steps for immediate action to reduce adult mosquito populations and, hence, transmission. Since epidemics can last several months, routine control measures are always intensified.

One of the main limitations of *A. aegypti* control programs is that they tend to be reactive – that is, they are deployed in response to the reporting of apparent clinical cases (based on the operational definitions of “case”), directing vector control activities to the area surrounding the customary residence of the case. Furthermore, they largely depend on interventions with chemical insecticides, mainly ULV space spraying or, in some cases, synchronized control measures (both chemical and physical) in a defined risk area. These interventions face enormous staffing and resource constraints during major outbreaks, complicated by the underreporting and delayed reporting of cases characteristic of passive surveillance systems (Vázquez-Prokopec *et al.*, 2010a).

As a result, many of these routine control interventions have not yielded the desired results (Bowman *et al.*, 2016; Horstick *et al.*, 2010), due to their inadequate coverage, temporary effects, lack of implementation as an integrated strategy, and, finally, but no less important, their intensity only during transmission periods – that is, in emergencies. Program sustainability is key, since mosquito populations rapidly recover with the relaxation of prevention measures (Nathan, 2012).

The evidence indicates that collaboration between local government agencies and the affected communities is essential for guaranteeing the long-term success and sustainability of an *A. aegypti* control program (Espinoza Gómez *et al.*, 2002; Pilger *et al.*, 2010).

Furthermore, there are insufficient resources to cover all urban areas. Local control programs must improve their use of information systems so that decisions can be made taking epidemiological, entomological, and other data into account to identify priorities (at-risk areas or periods) and mount interventions with special emphasis on high-risk areas and periods.

Bisanzio *et al.* (2018) used historical data from dengue, chikungunya, and Zika cases to locate the dengue transmission hotspots, which were associated with the areas where the other two diseases had been introduced and case clusters found. The information routinely collected as the basis for decision-making has value added that is currently underutilized in *Aedes* control.

Finally, the construction of operational scenarios that define the high-risk areas and periods creates an opportunity for proactive (preventive), rather than reactive, action, maximizing the impact on arbovirus transmission. The models show that chemical interventions of proven effectiveness (such as residual household spraying with insecticides that the mosquito populations are not resistant to) could reduce the number of dengue cases by almost 90% in the first year and by an annual 78% in the first five consecutive years, as long as they are widely and proactively implemented (at least 75% of dwellings treated once a year before the high-transmission season) (Hladish *et al.*, 2018).

3.2. Surveillance, prevention, and control strategies by operational scenario

The construction of generic scenarios for *A. aegypti* surveillance, prevention, and control is the starting point for determining the most cost-effective intervention strategy in each potential scenario to rationalize resources.

The first step, on a macro scale, is to classify or stratify locations in a country or district. This will require information on environmental and sociodemographic variables and the entomological-epidemiological history. Scenario construction should be based on the risk of transmission. A key element of this classification is the availability of DENV incidence data as the main variable for constructing the different scenarios, since it is available in most countries and is very simple to obtain with a minimally structured epidemiological surveillance system (based on clinical case reporting by the network of health units and case confirmation through serology, clinical surveillance, and laboratory testing).

Thus, in constructing the risk scenario, decision makers should look at historical transmission records in each area. The following scenarios have therefore been suggested for *A. aegypti* control in the Region of the Americas (PAHO, 2018c):

- Areas with no transmission but with entomological risk (just the presence of *A. aegypti*): Urban areas with no reports of autochthonous cases of DENV and with limited populations of the vector in dwellings.
- Areas with low DENV transmission: Urban areas with below-average incidence in the past five years, according to the data generated by the epidemiological surveillance system. Transmission is occasional and there are established, but limited, populations of the vector.
- Areas of moderate DENV transmission: Urban areas with below-average incidence in at least three of the past five years, according to the data generated by the epidemiological surveillance system. With established populations of the vector, transmission is highly seasonal and concentrated in the period (weeks) that defines the rainy season.
- Areas of high DENV transmission: Urban areas with above-average incidence in at least three of the past five years, according to the data generated by the epidemiological surveillance system. There are established populations of the vector, persistent transmission, and several outbreaks during the year, with a seasonal pattern, with severe cases reported.
- Epizootic: Urban areas with the presence of the *A. aegypti* or *A. albopictus* vectors near wild places, with reports of non-human primates dead of or sick with yellow fever.

Table 3. Basic variables or indicators related to the epidemiological characteristics and vector related and demographic factors, by operational scenario, that should be included in country information and surveillance systems

Components	Scenarios				
	No transmission	Low transmission	Moderate transmission	High transmission	Epizootic
Epidemiological characteristics	Identification of the highrisk period and location of groups vulnerable to DENV, ZIKV, and CHIKV (children, the elderly, and pregnant women).	DENV, ZIKV, and CHIKV incidence rate per epidemiological week by age group and locality. *Surveillance in the transmission stage.*	DENV, ZIKV, and CHIKV incidence rate per epidemiological week by age group, by locality. Hospitalization and case-fatality rates. Proportion of cases by type of arbovirus. *Continuous surveillance.*	DENV, ZIKV, and CHIKV incidence rate per epidemiological week by age group, by locality. Hospitalization and case-fatality rates. Proportion of cases by type of arbovirus. Proportion of arbovirus coinfections. *Continuous surveillance.*	Cumulative incidence of yellow fever cases in nonhuman primates. Cumulative incidence of cases in humans. *Surveillance in the transmission stage.*

Components	**Scenarios**				
	No transmission	**Low transmission**	**Moderate transmission**	**High transmission**	**Epizootic**
Vector-related factors	Ovitrap positivity index (OPI). Egg density index (EDI). Insecticide susceptibility bioassays. *Surveillance in sites with transmission risk.*	Ovitrap positivity index (OPI). Egg density index (EDI). Larval indexes: House index (HI), Breteau index (BI), Container index (CI) by type of container. Characterization of the types of larval habitats. Insecticide susceptibility bioassays. *Surveillance in transmission stage.*	Ovitrap positivity index (OPI). Egg density index (EDI). Larval indexes: House index (HI), Breteau index (BI), Container index (CI) by type of container. Characterization of the types of larval habitats. Environmental risk factors (e.g., vacant lots, cemeteries, tire disposal facilities, markets, densely populated areas with high mobility). Insecticide susceptibility bioassays. *Continuous surveillance.*	Ovitrap positivity index (OPI). Egg density index (EDI). Larval indexes: House index (HI), Breteau index (BI), Container index (CI) by type of container. Characterization of the types of larval habitats. Pupa and/or adult indexes: abundance of adults per dwelling and/or identification of productive breeding sites. Entomovirological surveillance (diagnosis of virus in mosquitoes). Environmental risk factors (e.g., vacant lots, cemeteries, tire disposal facilities, markets, densely populated areas with high mobility). Insecticide susceptibility bioassays; biochemical and molecular tests. *Continuous surveillance.*	Ovitrap positivity index (OPI). Egg density index (EDI). Characterization of the types of larval habitats. Insecticide susceptibility bioassays. *Monitoring in sites with transmission risk.*

Components	Scenarios				
	No transmission	Low transmission	Moderate transmission	High transmission	Epizootic
Demographic factors	Population size (inhabitants). Population density (inhabitants/km²). Percentage of urban population (%). Total dwellings.	Population size (inhabitants). Population density (inhabitants/km²). Percentage of urban population (%). Total dwellings. Percentage of women of reproductive age (%).	Population size (inhabitants). Population density (inhabitants/km²). Percentage of urban population. Total dwellings. Percentage of women of reproductive age (%). Percentage of migrant population (%).	Population size (inhabitants). Population density (inhabitants/km²). Percentage of urban population. Total dwellings. Percentage of women of reproductive age. Percentage of migrant population. Percentage of dwellings without piped water. Percentage of dwellings without refuse collection. Proportion of pregnant women by block, neighborhood, or area.	Abundance of non-human primates in the area and number of primates with disease compatible with yellow fever; number of nonhuman primate deaths from yellow fever.

3.2.1. Information systems and surveillance by scenario

It is important to determine the basic variables that should be included in country information and surveillance systems for each risk scenario constructed. The variables can be divided into three classes: 1) epidemiological characteristics; 2) vector-related factors; and 3) human demographic factors. Table 3 lists various indicators to include in the construction of a conceptual model; they range from simple, inexpensive daily practices (e.g., passive surveillance of cases, use of ovitraps in risk areas) to more sophisticated and expensive practices (e.g., entomological sampling and the definition of environmental risks) to very expensive, highly specialized activities that require trained personnel (e.g., detection of the virus in mosquitoes, detection of coinfection in humans, and molecular studies to determine the insecticide resistance profile in mosquito populations). These indicators should be tailored to each country, considering the availability and quality of the data.

3.2.2. Interventions by scenario

While no single surveillance and control strategy is applicable to all scenarios, general activities can be grouped and described for each situation. In ascending order of complexity based on the scenarios constructed, the intervention package would include the following elements (see Table 4):

- Environmental management and legislation.
- Control and physical elimination of breeding sites, with health promotion and community participation (educational campaigns).
- Physical or chemical treatment of habitats, targeting key containers (productive breeding sites).
- Targeted treatment around cases (100-300 m radius).
- ULV space spraying with extensive coverage.
- New technologies that have had an epidemiological impact.

Environmental management and legislation. The persistence of transmission in major urban centers is associated in part with deficiencies in household sanitation, piped water distribution, and solid waste collection. The new vision aims to ensure that the community knows about environmental risks in the home and work environment.

In addition, it is important to engage municipalities or departments in the promotion of organized social participation in the medium term, correct deficiencies in water and solid waste management systems, and reduce environmental risks. For example, public health legislation and regulations can mandate interventions to reduce environmental risks in facilities that pose a high risk to the adjacent population: tire disposal facilities, workshops, metalworks, scrapyards, junkyards, recycling plants for PET (polyethylene terephthalate) containers, vacant lots, etc.

The responsibility for vector control should not fall to the health sector alone but to all sectors, including the local or municipal authorities. The human development and housing sector can promote the use of mosquito netting or screens in doors and windows as a way to improve the quality of dwellings and prevent vector-borne diseases (Vázquez-Prokopec *et al.*, 2016). It is essential to create local health councils or committees that will host meetings with the regional or local government, health units, academic institutions, public and private entities, and faith-based organizations to raise awareness and promote action to fight arboviral diseases. Furthermore, agreements should be reached in these meetings to implement the strategies and collaborate in a multidisciplinary fashion to ensure optimal and comprehensive results.

Control and elimination of breeding sites, with health promotion and community participation. Priority should be given to active organized social participation in the destruction of mosquito breeding sites through ongoing educational campaigns. This is especially important in areas where *A. aegypti* breeds in small empty containers in the home or places where potential breeding sites accumulate, such as car hoods, garbage dumps, recycling stations, etc.

Physical, chemical, or biorational treatment of habitats, targeting key containers (productive breeding sites). Physical or chemical treatment of habitats or breeding sites is perhaps the most effective measure for reducing *A. aegypti* population densities. However, the area to be treated may be extensive and impossible to cover. To curb the expansion of breeding sites, it is proposed that the most productive sites be targeted. The use of information on the pupal productivity of the different types of breeding sites to identify the most productive types (key containers) has been positively evaluated in different countries. Counting pupae and people (pupal/demographic surveys) is a technique for obtaining information on the epidemiological importance of the different types of water containers related to the risk of transmission and on the degree of suppression necessary to limit such transmission (Focks, 2003). These studies are useful in determining the importance of breeding sites and developing a strategy that targets the most productive sites. It is recommended that at least two pupal studies be conducted, one before and one after the rainy season. Classifying breeding sites according to their productivity will result in more effective and economical control if the measures employed target the most important breeding sites.

Targeted treatment around cases (100-300 m radius). Targeted treatment consists of intensive treatment of the residence of the suspected or confirmed case, using a range of interventions, often in combination and simultaneously applied (in synergy), that can include:

- The elimination of breeding sites, physically reducing their number or applying chemical or biorational larvicides.
- ULV space spraying (with vehicle-mounted or portable equipment), either perifocal or in the area surrounding the case's residence. The spraying can be done in the morning or at dusk, just once or in several weekly application cycles.
- Cold or thermal indoor spraying, which can be applied residually (rapid spraying of *Aedes* shelter and resting sites) or at ULV in or around the case's residence (adjacent dwellings or blocks). For more details on residual spraying, see the PAHO manual on indoor residual spraying in urban areas (OPS, 2018b).
- Promotion of preventive household and personal protection measures (e.g., use of mosquito canopies by vulnerable groups such as pregnant women).

ULV space spraying with extensive coverage. These interventions are reserved for outbreaks or epidemics when reported cases exceed the capacity for targeted treatment (emergency control). Preventive ULV space spraying (as an early response measure) should be confined to high-risk areas with transmission (see below).

New technologies. The type of technology and its use will depend on the capacity of the infrastructure and the program's technical personnel. For more information on new technologies, see the PAHO report regarding the subject (OPS, 2018a).

Table 4. Integrated vector-control interventions or intervention package under each operational scenario

Scenario	Intervention package
No transmission	• Environmental management and legislation. • Educational campaigns.
Low transmission	• Environmental management and legislation. • Educational campaigns. • Physical, chemical, or biorational treatment of habitats, targeting key containers. • Targeted case management.
Moderate transmission	• Environmental management and legislation. • Educational campaigns. • Physical, chemical, or biorational treatment of habitats, targeting key containers. • Targeted case management. • ULV space spraying with extensive coverage.
High transmission	• Environmental management and legislation. • Educational campaigns. • Physical, chemical, or biorational treatment of habitats, targeting key containers. • Targeted case management. • ULV space spraying with extensive coverage. • New technologies.
Epizootic	• Environmental management and legislation. • Educational campaigns. • Targeted (human) case management. • ULV space spraying with extensive coverage.

As a guide for risk stratification, the section below describes some of the methods used to define or classify risk areas, a basic step in selecting interventions according to their priority based on the risk and its time frame in the scenarios.

4 Risk stratification in the scenarios

Once the operational scenario for *A. aegypti* surveillance, prevention, and control has been constructed, the question of where the interventions should be directed or strengthened emerges.

The response lies in stratifying – that is, categorizing or classifying – the information to establish orders of importance. Stratification makes it possible to show where the greatest number or proportion of cases lies (assuming that the cases are not distributed uniformly among the strata), thus determining the areas of greater risk. It is customary for programs to stratify localities with a high risk of transmission by their history (mainly of DENV), the persistence of cases, and the population at risk (Gómez Dantés *et al.*, 2011). Spatial[9] stratification can also be used to determine the risk in localities by administrative unit – that is, housing section or neighborhood, area, sector, or some other administrative level, block, etc.

In cities where dengue is endemic, it has been shown that certain areas always have the highest incidence and persistence of transmission over time (Bisanzio *et al.*, 2018; Barrera *et al.*, 2000). For example, 70% of all dengue cases reported for several years in San Juan, Puerto Rico, were concentrated in the 35% of the urban area (Barrera *et al.*, 2000) with more deficient public services, more mosquitoes per dwelling, and higher population densities (Barrera *et al.*, 2002).

Similarly, in Merida, Mexico, dengue transmission hotspots (with 50% of the cases in 30% of the city) were statistically correlated with chikungunya and Zika hotspots, revealing high spatial coherence in the distribution of the three viruses (Bisanzio *et al.*, 2018).

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[9] The stratification can be non-spatial (e.g., cases can be stratified by sex, age, socioeconomic level, etc.) and spatial (geographical).

It should be noted that effective control of *A. aegypti* and arbovirus transmission in hotspots curbs the export of mosquitoes and viruses to other areas of the city where the conditions for transmission are not as favorable, leading to lower levels of the disease in untreated areas (Barrera *et al*., 2000; Vanlerberghe *et al.*, 2017).

Recognition of hotspots based on the history of infections is an important tool for establishing programs to prevent epidemics and developing more efficient and cost effective strategies.

4.1. Spatial stratification

Stratification at the city or local level requires analytical and theoretical methods to study the spatial patterns of the incidence or mortality of a health event. These patterns may appear as "unusual" spatial aggregates or clusters of a disease or areas where a disproportionate number of cases are concentrated (hotspots) (Lawson, 2010).

These patterns can be identified with simple descriptive methods, such as observation and visual analysis of the information (historical data on cases, incidences, or entomological data) with the aid of maps (visualization of the spatial data), or with more complex spatial analysis, such as geographical correlation studies (ecological analysis) and clustering of the disease (Table 5). Unlike visual methods, statistical methods make it possible to determine with greater certainty whether the unusual patterns are indeed the product of a disproportionate distribution of cases within specific areas of the locale.

The main objective of spatial epidemiology is to identify the spatial pattern of diseases – that is, to determine whether health events are distributed evenly, randomly, or aggregated in time and space (Tango, 2010). These health events could be identified as cases of arbovirus (clinically or laboratory-confirmed patients).

Before any analysis, it is important to identify the type of case data that is available to perform the spatial stratification:

- **Area data.** The spatial data consist of the number of cases per well-defined spatial subunit within a larger unit: for example, georeferenced cases of DENV clustered in subunits such as neighborhoods within a larger unit that would be the city. The data also can be clustered in arbitrary subunits of regular forms such as grids or any other geometric form.
- **Georeferenced data points (spatial point patterns).** The data consist of cases whose geographical coordinates have been recorded (usually the patient's customary

residence). These spatial data are generated by converting epidemiological data (home address of the incident cases) to spatial data. Health systems usually record cases with a physical address (house number, street, intersection, postal code, district, municipality, province or state, etc.), and the physical location is converted to geographic information in the form of latitude and longitude in a process called "geocoding." This is accomplished with open access geographic information tools.

Table 5. Main methods for studying the spatial patterns of a health event, in ascending order of difficulty, required data, and calculation power. Adapted from Vázquez-Prokopec (2018)

Methods	Mapping of case incidence and distribution	Interpolation (kernel density, kriging)	Hotspot analysis (LISA, Gi*)	Spatial effects models (GLMM, CAR, SAR, GWR)	Mathematical and simulation models
Examples	Incidence maps, case counts, individual cases.	*Aedes* egg density or cases (num./pop.), prevalence density maps (case density / population density).	Incidence hotand coldspots, clusters of high mosquito abundance.	Posterior incidence rates.	Number of susceptibles, incubating infections and immunity.
Advantages	Fast, directly obtained from databases.	Fast, obtained from databases with a minimum of data analysis.	Parameterization of data, which requires prior knowledge but not sophisticated skills.	Indicates spatial correlations, effects, time flows and herd immunity.	Maximum flexibility and interactions or spatial effects.
Disadvantages	Limited power to detect clusters; subjective.	No statistical evaluation; prone to biases if the bandwidth is not correctly established.	Must be validated with field data; prone to null results in the absence of data ("ND").	Scale-dependent (data scale), prone to null results with very scattered data; requires a high degree of training.	Many decisions for estimating parameters; affected by uncertainty; requires a highly trained analyst.

LISA: *local local indicators of spatial association;* **Gi*:** *Getis-Ord Gi statistic;* **GLMM:** *generalized linear mixed models*
CAR: *conditional autoregressive models;* **SAR:** *spatial autoregression;* **GWR:** *geographically weighted regression*).

Georeferenced cases can be added to an administrative sublevel and converted to area data through a process called "spatial joint" in the platform of a geographic information system (GIS). One of the virtues of using geographic information platforms is that they integrate data from different sources, making it possible to correlate entomological data such as collected mosquitoes (eggs or adults) with human epidemiological and demographic information.

There are several methods for identifying areas with the risk of transmitting dengue and other diseases borne by *Aedes*. These methods not only have advantages and disadvantages but depend on the type of data available (Table 5). Here, we will provide three examples, bearing in mind that the main requirement is that they employ robust statistical methods.

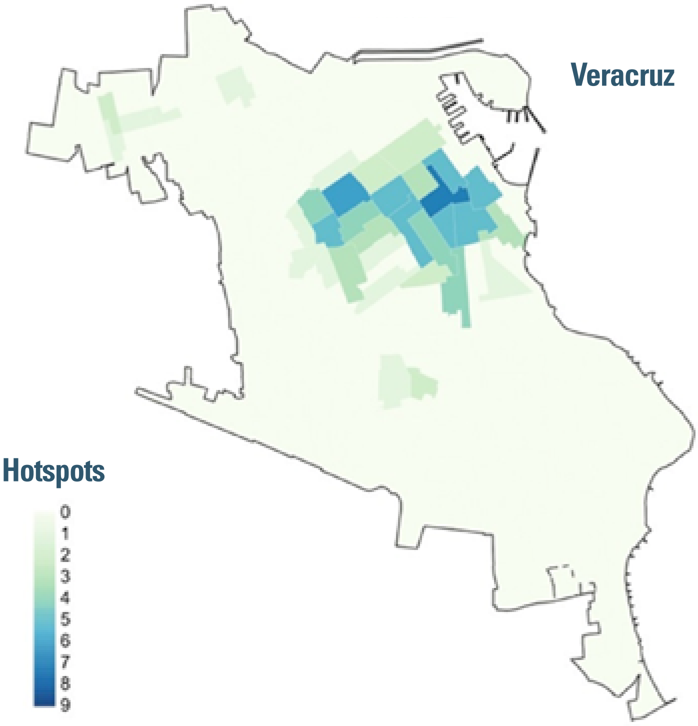
One example of a descriptive spatial analysis supported by geographic information systems (GIS) and statistical correlation analysis is the study conducted in Maracay, Venezuela, by Barrera *et al.* (2000) to locate hotspots by sector or neighborhood. Transmission persistence by neighborhood – that is, the maximum number of consecutive months that a neighborhood had cases of dengue – was considered a stratification variable. The cases were aggregated at the neighborhood level on spreadsheets and subsequently exported to a GIS for analysis and graphic representation. The result was the stratification of the urban area and the classification of neighborhoods by the prevalence and persistence of dengue between 1993 and 1998. Based on simple linear relationships (Pearson's correlation), the authors found that in the six-year period, the neighborhoods with higher numbers of dengue cases also had the highest number of dengue hemorrhagic fever cases (a positive and significant correlation between dengue and dengue hemorrhagic fever cases) and that the neighborhoods that had many cases in one year continued to have many cases in the other years (positive and significant correlation between the number of cases per year and the neighborhood). Using this analysis, 14 neighborhoods were found with cases during periods of 16-50 consecutive months and 41 neighborhoods with cases in periods of 6-15 consecutive months. This spatial pattern indicates that vector control measures could be prioritized in 4% or 16% of the total universe of neighborhoods (349 neighborhoods), depending on program capacity.

Specific examples of more complex spatial analyses for stratification within districts are two projects currently under way right now in Mexico and another in Brazil: the Mexican projects are based on the identification of transmission hotspots; and the Brazilian project, on the ArboAlvo proposal for characterizing vulnerability to arbovirus transmission.

The examples from Mexico explore the model for identifying hotspots by geocoding historical cases of dengue, calculating the proportion of cases reported in a specific geographical area in one year (e.g., intensity of transmission by census unit or neighborhood) and applying spatial statistics to determine which areas are hotspots in each period (usually, each year) (Bisanzio *et al.*, 2018). This study used the number of cases per census unit (known as the AGEB) to identify hotspots with a high number of cases, using the Getis-Ord Gi statistic. Using the dengue cases reported in the period 2008 2015 for this analysis, the authors estimated a measure of transmission persistence, using the sum of the years that each census unit was considered a hotspot. They found that the 30% of the city identified as a hotspot had more than 50% of the reported cases; this area coincided with the areas where the chikungunya and Zika epidemics had initially been reported (Bisanzio *et al.*, 2018).

Using the methodology of Bisanzio *et al.* (2018), it was found that other cities – in this case, Veracruz, Mexico – also have high clusters of transmission in specific areas (Figure 1; see annexes that detail the method).

Figure 1. **Example of stratification by DENV transmission hotspots, based on an analysis of confirmed cases over nine years in Veracruz, Mexico**



Note: *Analysis performed with area data (sociodemographic administrative units, called "AGEB"). The intensity of the color indicates the number of times per year that an area became a hotspot.*

Spatial analysis makes it possible to quantify transmission risk based on the epidemiological data. Another method is to calculate the vulnerability of an area to the transmission of DENV and other arboviruses, based on variables that are correlated with vector abundance or transmission risk, such as the distribution and density of human populations, socioeconomic status and the housing situation, the health infrastructure, climate, etc. This method includes several assumptions about the factors associated with transmission risk in a selected city and employs non-spatial multivariate analysis (main components, regression analyses) to delimit the space of variables associated with the highest risk of transmission. Although the analyses can be performed without epidemiological data, inclusion of the cases reported by area increases the validity of the predictions of multivariate analyses. One example of the calculation of spatial vulnerability is the ArboAlvo project, which is being evaluated in Brazil (see annexes, which contain more details).

Whatever the method, stratification should be a dynamic process that is periodically reviewed and evaluated. At the end of each year, the stratification should be reviewed and updated, considering the possibility that hotspots may shift to other areas of the city and determining whether preventive control is having an effect on historical transmission areas or whether demographic and entomological conditions have changed.

4.2. Timing of the interventions

The next level of decision-making is linked to the following questions: What action must be taken in the risk areas identified by the stratification, when, and for how long? The approach to these questions should involve anticipatory measures that include a two-phase vector control intervention package (Figure 2):

- Preventive measures during the interepidemic period.
- Early response measures in the phase prior to the high transmission period (early outbreak).

The purpose is to simultaneously implement comprehensive measures to prevent outbreaks in hotspots (high-risk areas), without ignoring the response measures for outbreak management (inside or outside those same risk areas) – that is, the intensification measures that the program adopts in the high-transmission stage of the disease (emergency response[10]).

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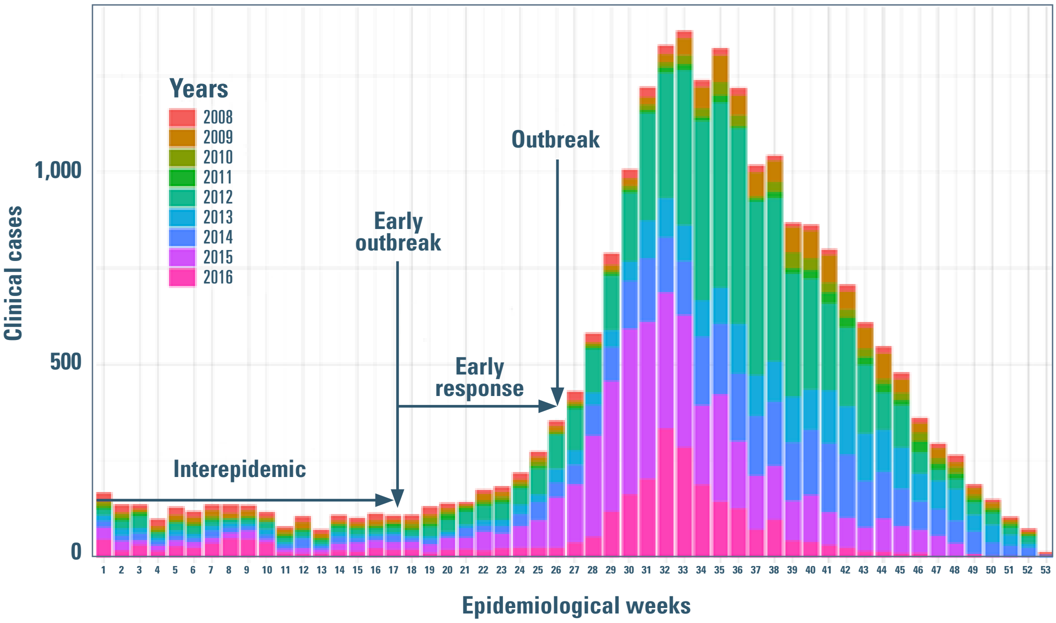
[10] Actividad Intense short-term activity aimed at a rapid reduction in the adult mosquito population to eliminate transmission in an epidemic or when an epidemic appears to be imminent.

Figure 2. **Example of historical case curve. The stages for anticipatory action are observed: the interepidemic period (preventive measures) and the early outbreak of the disease (early response measures).**



Note: *Prepared with case data (2008-2016) from Veracruz, Mexico.*

Depending on local program capacity, the anticipatory measures for outbreak containment could include the development of a package of more intensive interventions for implementation only in specific priority areas of the locale, such as identified hotspots.

Although innovative interventions are not proposed, there is confidence that the selected strategies and tools will be effective in containing transmission if they are implemented simultaneously and intensively in a timely manner with high coverage, if their duration is sustainable, and if they target high-risk areas during the initial stages of transmission (Gómez Dantés *et al.*,2011). The timeliness of the interventions, applied step by step based on the stage of transmission, is essential for controlling *A. aegypti* populations (Table 6).

Preventive measures (interepidemic). During this phase, priority is given to the control of immature mosquito habitats (preferably using environmental or biorational measures, rather than interventions with synthetic chemical insecticides) and targeted treatment around cases. The main activities include campaigns to educate the population and raise public awareness about ongoing public health measures (personal and residential protection). The elimination and control of immature mosquito habitats in the post-transmission period are aimed at decreasing vertical transmission of the infection and reducing the risk of its reemergence at the beginning of the year with new generations of vertically infected females.

Since the targeted areas will be those with well-defined boundaries (neighborhood, sector, or another spatial unit) with known universes (number of residents, dwellings, blocks, etc.), targeted action can be taken with prior planning to increase public awareness and social mobilization. To this end, the public can be informed about preventive measures and the campaign to eliminate solid waste through the media (radio and the press) and social marketing (placement of banners, flags, and posters and the distribution of leaflets, especially to closed dwellings).

There is real justification for anticipatory control of *A. aegypti.* The high rate of asymptomatic transmission (Ten Bosch *et al.*, 2018) hinders the initial detection of outbreaks, which means that the reaction to cases always follows the transmission wave. A mathematical model shows that interventions capable of reducing *A. aegypti* numbers for several months, such as residual household spraying, are more effective if they are applied in advance of the transmission season (Hladish *et al.,* 2018).

The problem with preventive control is that it cannot be implemented city-wide. Risk mapping, therefore, provides the geographical framework and justification for the use of high-quality control methods in areas with a higher probability of producing or aggregating cases during the transmission season. Focusing high-coverage preventive measures in hotspots not only represents an important paradigm shift in *A. aegypti* control, but a necessary step for reducing the local burden of disease.

Preventive measures in hotspots will improve integrated vector management (IVM), not only with classical control methods but with other effective strategies for reducing vector populations or contact between the vector and the human population (bednets, mosquito netting impregnated with long-lasting insecticides in the form of curtains or permanently installed in doors and windows, lethal ovitraps, etc.), including new technologies once their epidemiological impact is known (e.g., release of autocidal *Wolbachia*-infected or genetically modified mosquitoes).

Early response measures (early outbreak). These should consist of intensive actions that are both sustainable and feasible. When the early response measures should begin will depend on the historical case curve and the start of the outbreak (Figure 2).

The intervention package for the early response phase can include one or more of the following measures:

- Environmental management and legislation.
- Control of breeding sites and physical elimination, with health promotion and community participation (educational campaigns).
- Physical, chemical, or biorational treatment of habitats, targeting key containers (productive breeding sites).
- Targeted treatment around cases (100-300 m radius).
- ULV space spraying with extensive coverage.

As with preventive control, there will be the possibility of implementing IVM in the initial phases of the outbreaks, combining classical control methods with new fastacting technologies (e.g., passive emitters of metofluthrin or transfluthrin, AGO traps). The important thing in this period is to determine whether the hotspots are contributing large numbers of cases to the outbreak and, if so, to propose rapid response strategies with high coverage to reduce the probability of their generalization to the rest of the city.

Table 6. Anticipatory vector control measures by stage of transmission and operational scenario in high risk areas

Scenario	Preventive (interepidemic period)	Early response
No transmission	• Environmental management and legislation. • Educational campaigns.	
Low transmission	• Environmental management and legislation. • Educational campaigns. • Targeted treatment around cases.	• Environmental management and legislation. • Educational campaigns. • Physical, chemical, or biorational treatment of habitats, targeting key containers. • Targeted treatment around cases.

Scenario	Preventive (interepidemic period)	Early response
Moderate transmission	• Environmental management and legislation. • Educational campaigns. • Targeted treatment around cases. • Preventive targeting of measures in hotspots.	• Environmental management and legislation. • Educational campaigns. • Physical, chemical, or biorational treatment of habitats, targeting key containers. • Targeted treatment around cases. • ULV space spraying with extensive coverage.
High transmission	• Environmental management and legislation. • Educational campaigns. • Physical, chemical, or biorational treatment of habitats, targeting key containers. • Targeted treatment around cases. • New technologies. • Preventive targeting of measures in hotspots.	• Environmental management and legislation. • Educational campaigns. • Physical, chemical, or biorational treatment of habitats, targeting key containers. • Targeted treatment around cases. • ULV space spraying with extensive coverage. • New technologies.
Epizootic	• Environmental management and legislation. • Educational campaigns.	• Environmental management and legislation. • Educational campaigns. • Targeted treatment around (human) cases. • ULV space spraying with extensive coverage.

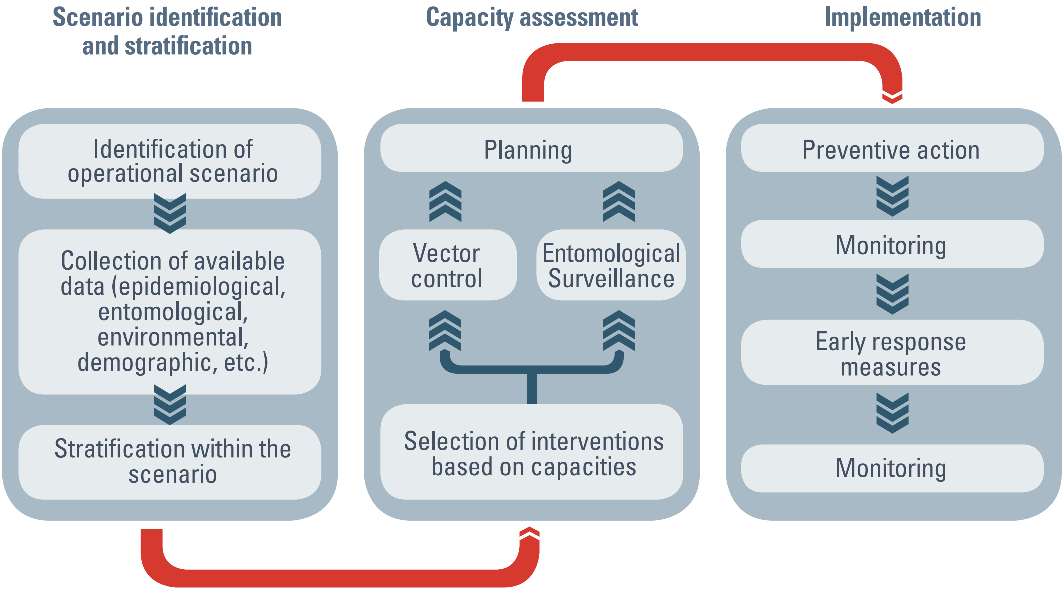
5 Final Considerations

In the current context of dengue and other arbovirus transmission by *A. aegypti,* risk stratification models are a useful tool for efficiently and effectively capitalizing on the resources of local vector control programs. This strategy is based on the premise that reducing the risk of transmission in hotspots will reduce transmission in adjacent areas – that is, that suppressing hotspots will significantly reduce the spread of cases to the rest of the areas in an urban context.

The proposed stratification process involves the following steps (Figure 3):

- cataloguing locations under the different operational scenarios, based on epidemiological, entomological, and demographic variables;
- selection of the risk stratification model, based on the availability and quality of the information obtained and the technical capacities identified;
- selection of the package of entomological-epidemiological control and surveillance interventions, following evaluation and planning of the available resources and technical capacities for implementation;
- design and planning of intervention strategies for the risk strata defined;
- implementation of anticipatory interventions (preventive measures in the interepidemic phase and early response activities for early outbreaks);
- monitoring of the impact on entomological and epidemiological indicators.

Figure 3. Risk stratification process



Note: *Insecticide resistance monitoring is included in* ***entomological surveillance.***

When selecting the package of interventions for effective *A. aegypti* control, methods with the following characteristics should be considered:

- An effective control agent (insecticide, depredator, trap, modified males, etc.), giving preference to those that guarantee a longer-lasting (residual) effect. Efficacy refers to the ability of the control agent to achieve the desired effect. For example, if an insecticide is used that *A. aegypti* is resistant to (low efficacy), it should be understood that its "efficacy" – ability to achieve control of the mosquito in nature and to prevent and control epidemics – will not be significant.
- Efficient methods for the distribution or application of the agent that cover the entire area infested with *A. aegypti*. This requires proper calibration of equipment, training, field supervision, and coverage to guarantee effective application of the agent. The use of an effective control agent, combined with proper application, should eliminate more than 80% of the *A. aegypti* population. For example, if the control method requires home visits and half the dwellings cannot be treated, a significant impact on the local *A. aegypti* population will be hard to obtain. Similarly, if space spraying is done with equipment mounted on trucks or airplanes and the insecticide is 100% effective but the insecticide droplets do not penetrate the mosquito's resting places, efficient distribution of the control agent to guarantee efficacy would not be achieved.

- Determination of how often to apply the control agent.
- The combination of several control agents and application systems. There is a consensus on the difficulty of controlling *A. aegypti* with a single tool or control technique. Combining control agents could lower program costs.
- Community confidence and acceptance.
- Close collaboration with communities through a mixed approach – that is, one in which the vector control program provides people with the tools they need to sustainably collaborate in the reduction of *A. aegypti*.
- Evaluation of the sustainability of the control strategy. Preference should be given to control strategies that keep *A. aegypti* populations at sustained low levels and whose application is equally sustainable and not episodic (reactive to epidemics).

Regardless of the methods selected for the entomological surveillance system, before implementation (planning phase), it is highly recommended that a baseline study be conducted that includes:

- An entomological assessment to identify the key breeding sites (productive and cryptic) for better selection of control measures and to use this information for a preventive approach.
- Monitoring of changes in the patterns of *A. aegypti* resistance to the control agent. For effective application of larvicides, bioassays should be performed before these products are introduced in programs or used on a large scale to detect any change that would suggest resistance. As with adulticides, resistance studies should be conducted to aid in selecting the most effective product and prevent the development of resistance to the insecticide in use or other products with similar modes of action. The recommendation is to prepare a plan for rotating control agents to impede the emergence of resistance.

Intervention impact assessment should include specific and precise indicators of mosquito density at all stages of development (egg, larva, pupa, and adult). Assessments of the effects of *A. aegypti* control measures should include:

- The percentage reduction in the *A. aegypti* population [(1 *A. aegypti* density after/*A. aegypti* density before) × 100] or [(1 –density in the *A. aegypti* control area/density in an area without control) × 100].
- Duration of the reduction.

When standardizing a control protocol, more than one measurement of *A. aegypti* abundance or density should be used. For example, if the aim is to reduce *A. aegypti* with a larvicide, in addition to measuring the reduction in larvae or pupae, the variation in the number of adults should also be measured as an independent method. The monitoring of *A. aegypti* females is ideal, since they are the mosquitoes that transmit the viruses. These entomological indicators should be continuously monitored (weekly-monthly) year round in the risk area. The evaluation and validation of control protocols should demonstrate their effectiveness in preventing and controlling arboviral diseases such as dengue, chikungunya, and Zika fever. The indicator of success will be comparatively lower densities in a sentinel area (an area without control).

Assuming that anticipatory control measures in hotspots can reduce the risk of exposure and transmission, contain epidemics, and lower incidence, epidemiological evidence of the impact of this strategy must be generated. This evidence can be constructed with the results of different studies in the different scenarios of the Region of the Americas. For example, a comparison of historical epidemiological data (before and after the intervention, treated and untreated areas, etc.), properly obtained and analyzed, could help generate evidence of its impact.

Finally, the significant potential of combining new technologies with the available control methods is recognized. Combining new technologies with other vector control measures will require the development of protocols for their simultaneous or sequential application and subsequent evaluation. It should be noted that work is under way on pilot studies of these new strategies and that they are not yet part of routine control programs.

6 Annexes

Annex I. Transmission hotspot model

The objective is to determine the existence of spatial and temporal variability that could help to detect the presence of hotspots – that is, areas that disproportionately contribute to transmission and where outbreaks are most likely to begin.

Sources of information. The different sources of information available at the local level are used:

1) databases from the local epidemiological surveillance of local or national health systems, containing the records of confirmed cases and their respective data (addresses of incident cases or households) in a particular period (preferably > 5 years);
2) local sociodemographic and socioeconomic databases at different spatial scales (state or province, village, housing section, neighborhood, block, sector, or some other socioeconomic or administrative unit);
3) if necessary, other databases – for example, on adult mosquito surveillance, entomovirological surveillance, or entomological surveillance with ovitraps.

For analyses in cities or smaller localities, the basic area in which data will be aggregated (neighborhood, census block) should be defined. It should be borne in mind that a very large area will imply a loss of statistical power and less possibility of obtaining high coverage with control measures.

Geocoding. Geocoding is used to convert epidemiological data (addresses of incident cases or households) and entomological data (adult mosquitoes positive for arboviruses and/or number of adult mosquitoes or dwellings) to spatial data, converting the addresses where mosquitoes are collected or the address of the case into geographical coordinates (latitude and longitude). In this step, a variety of free geographic information tools are used, and the sensitivity and specificity of each tool are confirmed, using 100 cases with their addresses and geographical coordinates provided by a GPS. The best tool for geocoding the data is used.

Aggregation of epidemiological data. Once the epidemiological information is geographically coded, a case count is conducted on both the previously identified operational scale (e.g., basic census area) and the temporal scale (cases from different years). The proportion of reported cases in a year that occur in a given spatial and temporal scale is interpreted as a measure of the intensity and persistence of transmission.

DENV, CHIKV, and ZIKV transmission hotspots. Spatial analysis tests (such as the Getis-Ord statistic) are performed to identify the areas that contribute a disproportionate number of cases of each virus (hotspots) during each available year. To address the spatial and temporal persistence of hotspots, they are calculated between years, at different times of the year (rainy and dry season), and between epidemic and nonepidemic years (Bisanzio *et al*., 2018).

Furthermore, to include the human mobility factor, two approaches are used to identify the hotspots:

1) hotspots in groups of children (up to age 11), since this is the age group with the least mobility;
2) hotspots with two adjacency matrixes (the adjacency of neighboring areas and the inverse distance of the weighted weights).

The first assumes that the risk is distributed throughout the matrix or area. The second assumes that the risk is an inverse function of the distance (1/Euclidean distance) between each area and each case's area of residence.

Spatial concordance of hotspots. The number of times a specific area was a hotspot is quantified (years, rainy or dry season, etc., depending on how the data are analyzed), and the result is used as a measure of transmission persistence by area.

Including this information using a GIS makes it possible to visually verify the extent of the risk area. A more formal validation of the patterns be can conducted by comparing the distribution of dengue hotspots with those of Zika and chikungunya (Bisanzio *et al.*, 2018) or with the presence of adult *A. aegypti* that are positive for each virus (when it exists) and the address of the cases of neonatal microcephaly (when there are any). For the binary epidemiological and entomological data, a highly significant percentage of positive cases or positive pools in the hotspots would serve as external validation of their influence on transmission.

Hotspots and risk factors for their appearance. In order to determine whether dengue, chikungunya, and Zika hotspots are areas with a great abundance of mosquitoes (collected by eggs, pupae, or adults), negative binomial logistic regression analyses can be performed using abundance as an independent variable and the house's location in a hotspot as the dependent (binary) variable. Other census variables, such as the number of members in the household, the type of dwelling, the quality of public services, etc., can be used for areas with no entomological data or to buttress models that include entomology (Bisanzio *et al.*, 2018).

Annex 2. ArboAlvo Model: Proposed methodology for the stratification of dengue, chikungunya, and Zika risk areas in endemic Brazilian cities

The objective of the ArboAlvo Project is to develop a methodological proposal for stratifying risk areas for the transmission of arboviral disease, with sociodemographic, environmental, entomological, and epidemiological parameters, in four endemic cities of Brazil: Natal, Rio Grande do Norte, and Recife, Pernambuco, in the country's Northeastern region; Belo Horizonte, Minas Gerais, in the Southeast region; and Campo Grande, Mato Grosso do Sul, in the Center-West region. These cities were selected because of their history of endemic DENV transmission, the quality and completeness of their databases, and the existence of legally defined neighborhood boundaries.

In order to characterize social vulnerability to arboviral diseases in these cities, indicators are generated for health infrastructure, housing and environmental conditions, density of the poor population, and demographics. In order to characterize the territorial receptivity to *A. aegypti,* indicators are constructed that refer to the dimensions of climate (nocturnal/diurnal surface temperatures and rainfall) and land use (urban sprawl, occupied territorial area, growth of towns, verticalization of housing, altimetry by neighborhood and vegetation).

The characterization of *Aedes* infestation is evaluated by its frequency, intensity, and persistence in time and space and is performed primarily with data on egg-laying ordinarily produced by local programs and data from larval surveys of the Larval Index Rapid Assay for *A. aegypti* (LIRA).

The DENV, CHIKV, and ZIKV cases reported to the information system for the notification of reportable diseases (SINAN) are used for epidemiological characterization.

Characterizing the epidemics has made it possible to identify neighborhoods with characteristics of epidemic persistence, as well as neighborhoods where the epidemic processes began. This requires the generation of epidemiological indicators (to characterize the spatial and temporal dynamic of the epidemics of arboviral disease), diagnostic indicators (to characterize the accessibility and availability of health services), and symptomatologic indicators (to characterize the cases with greater severity and deaths).

The project uses fairly complex analytical models, such as the analysis of principal components, to create a few sociodemographic indicators that condense the information contained in other indicators obtained at the neighborhood scale. Missing climate data are obtained using time series techniques. The positivity and egg density indexes are calculated from egg counts in ovitraps.

Once the databases of each technical component of the project (environmental, sociodemographic, entomological, and epidemiological) have been processed and analyzed on an exploratory basis, the spatial-temporal models are adjusted to explain the epidemiological counts in terms of the entomological indexes, sociodemographic indicators, and environmental variables. The spatial-temporal models are also adjusted to explain the egg counts in relation to sociodemographic and environmental variables. These models are designed to serve as predictive instruments to guide activities for arboviral disease prevention and control.

A key strategy for ArboAlvo's implementation and development is to strengthen local capacities by training staff (in the municipal health services involved) in the technologies and tools used in the project. The project still faces the challenge of developing communication and mobilization strategies targeted to the population, which is a key actor for the guarantee of community-based interventions.

7

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