Review Article

Current vector control challenges in the fight against malaria in Brazil

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Abstract

In Brazil, malaria is an important public health problem first reported in 1560. Historically, fluctuations in malaria cases in Brazil are attributed to waves of economic development; construction of railroads, highways, and hydroelectric dams; and population displacement and land occupation policies. Vector control measures have been widely used with an important role in reducing malaria cases. In this review article, we reviewed the vector control measures established in the Brazilian territory and aspects associated with such measures for malaria. Although some vector control measures are routinely used in Brazil, many entomological and effectiveness information still need better evidence in endemic areas where *Plasmodium vivax* predominates. Herein, we outlined some of the needs and priorities for future research: a) update of the cartography of malaria vectors in Brazil, adding molecular techniques for the correct identification of species and complexes of species; b) evaluation of vector competence of anophelines in Brazil; c) strengthening of local entomology teams to perform vector control measures and interpret results; d) evaluation of vector control measures, especially use of insecticide-treated nets and long-lasting insecticidal nets, estimating their effectiveness, cost-benefit, and population acceptance; e) establishment of colonies of malaria vectors in Brazil, i.e., *Anopheles darlingi*, to understand parasite-vector interactions better; f) study of new vector control strategies with impacts on non-endophilic vectors; g) estimation of the impact of insecticide resistance in different geographical areas; and h) identification of the relative contribution of natural and artificial breeding sites in different epidemiological contexts for transmission.

Keywords: Vector control. *Anopheles*. Malaria.

INTRODUCTION

Malaria is an acute febrile infectious disease transmitted through the bites of infected female *Anopheles* mosquitoes. In 2017, approximately 219 million cases of malaria were reported in 91 countries, compared with 237 and 211 million cases in 2010 and 2015, respectively. The change in the endemicity pattern is attributed to the large-scale implementation of malaria control measures, such as adequate and early treatment of patients, use of insecticide-treated nets (ITNs), and insecticide indoor residual spraying (IRS). Despite such global reductions, the case incidence substantially increased in the Region of the Americas between 2014 and 2016[1].

Historically, fluctuations in malaria cases in Brazil are attributed to waves of economic development; construction of railroads, highways, and other large edifice-like hydroelectric

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power plants (HPPs); and population displacement and land occupation policies, especially in the Northern region[2-5]. Consequently, vector control measures were widely used with an important role in reducing the epidemiology of malaria. Indeed, the success in the extinction of *An. gambiae* in the Brazilian territory is a notable outcome of such a process[6-8]. In this article, we reviewed the vector control measures established in the Brazilian territory.

MALARIA AND VECTOR CONTROL IN BRAZIL: A BRIEF HISTORICAL OVERVIEW

After the colonial period, there was a substantial increase in malaria cases in the Amazon region, mainly owing to the great displacement of immunologically incompetent Northeastern migrants led by rubber extraction in the Amazon (1879-1912) and the expansion and construction of the Madeira-Mamoré Railroad (1907-1912)[3,9-13].

During the late 1930s, the Northeast Region of Brazil was invaded by *An. gambiae*, an important vector of malaria in sub-Saharan Africa later identified as *An. arabiensis*[6]. This vector was introduced accidentally in Natal, Rio Grande do Norte from Dakar (Senegal) and immediately spread to the immediate vicinity of the railway and canals near the Potengi river[7,9,13,14]. In 1931, 344 deaths were reported in Natal, and in 1938, it spread silently inwards, reaching less arid valleys of the Jaguaribe river in the state of Ceará[9,12,15,16]. This uncontrolled spread led to 150,000 cases of malaria and 14,000 deaths in 8 months in both states[9,17]. The Northeast Malaria Service was created in the following year, exclusively to fight against the malaria African vector[18]. Larvicides incorporated with Paris green (i.e., copper acetoarsenite, an inorganic compound usually used as a rodenticide and an insecticide) were deployed, and all houses were fumed with pyrethrum[9,19]. In 1940, the malaria African vector was eradicated in Brazil[13].

In view of the large number of cases reported in the 1940s, the National Malaria Service was created, but was quickly changed to the Malaria Eradication Campaign (CEM), which adopted the Global Malaria Eradication Program strategies of the World Health Organization (WHO)[12,20,21]. During this period, there was a significant and important impact on malaria transmission owing to the indoor application of dichlorodiphenyltrichloroethane (DDT) and the use of antimalarial drugs[12,22,23].

The CEM was suspended in 1970 owing to the reduction of cases, criticism of the public health administrative model, and concerns regarding DDT use[4]. Malaria control activities are coordinated by the Superintendence of Public Health Campaigns, also responsible for the provision of antimalarial drugs for appropriate use and mass treatment, technical supervision, and use of outdoor ultra-low volume nebulization impregnated curtains and new insecticides[3,4,21-23]. At the end of 1998, the Pan American Health Organization released an analysis of the epidemiological situation of malaria in the Americas, in line with the initiative adopted by the WHO known as Roll Back Malaria[24,25]. In October 1999, the actions to reduce malaria in Brazil were conducted through the Plan to Intensify Malaria Control in the Legal Amazon (PIACM)[24]. However, despite the advances, several problems have not yet been solved, and the incidence of malaria remained high[25]. In 2003, the PIACM was replaced by the National Malaria Control Plan (NMCP)[26] driven by objectives that aimed at reducing the morbidity, mortality, and severity of malaria along with stopping the transmission where possible.

MALARIA VECTORS IN BRAZIL: BIONOMICS AND BEHAVIORAL ASPECTS

The study of anopheline species in a region is important to direct vector control measures especially because the same species at the same site may change their habits over time, mainly as a result of environmental changes[27-30]. The main vectors in the Americas are widely distributed in diverse environments and present high variability in their behavioral patterns, even including intrapopulation[31]. In Brazil, 54 species of *Anopheles* mosquitoes are known, and the main vectors belong to two *Anopheles* subgenera: *Nyssorhynchus* and *Kerteszia*[32-34]. *An. darlingi*, *An. aquasalis*, and members of the *An. albitarsis* complex are the main transmitting species of malaria in the subgenus *Nyssorhynchus*[31,33,34]. Conversely, the subgenus *Kerteszia* is responsible for the transmission in the Atlantic Forest, notably *An. cruzii* and *An. bellator*[35,36].

An. darlingi is considered the primary vector of malaria in Brazil[29,32,37]. It is collected in greater quantity in peridomiciles[38]. The largest period of hematophagic activity occurs during the first 3 hours of the escotophase[39], varying from 18:00 to 21:00 or 17:00 to 20:00, depending on the type of locality, density of the *Anopheles* population, season of the year, distance between residences and forests, and presence of other hosts[29,35,40,41]. Large reservoirs of water where there are limited current and salinity are used as breeding grounds[35,42]. This species still bears uncertainties in relation to its biome and behavior, especially with regard to feeding habits, resting, and periodicity, which may be different according to locality[32-35,37-42]. Such differences in behavior can be explained by the high chromosomal polymorphism that allows the species to be able to explore different habitats, especially during the rainy season[43-45].

An. aquasalis is found along coastal areas, in some localities that are approximately 100 and 200 km from the coast, and in soils rich in sodium chloride, as is the case in some areas of the northeastern backlands or in regions where tidal invasion occurs, such as Belém, Pará[46-49]. Galvão et al.[47] pointed to the preferential zoophilic profile of *An. aquasalis* in Belém, Pará, where the climate is equatorial; conversely, *An. aquasalis* in the Northeast region, which has a semi-arid climate, presents anthropophilic habits[49-52].

The *albitarsis* complex brings together the most common *Anopheles* mosquitoes widely distributed in Brazil, including *An. oryzalimnetes*, *An. deaneorum*, *An. marajoara*, and *An. janconnae*[53-55]. The cryptic species belonging to this complex cannot be distinguished morphologically in the adult phase; however, several methodologies were used for identification, including allozymes and DNA-based techniques[53-59]. The members of the *albitarsis* complex have large distributions, as well as high behavioral variabilities[60]. Their preferred breeding sites are clean freshwater reservoirs, preferably in sunny or shaded fields and pastures. In most of the Brazilian territory, they present zoophilic and exophilic habits[60].

The anophelines *An. cruzii* and *An. bellator* breed in bromeliads in the Atlantic Forest and have acrodendrophic habits, a behavioral characteristic of mosquitoes of the subgenus *Kerteszia*, especially *An. cruzii*; this refers to the preference of these vectors in practicing hematophagy in the crown of trees, occasionally descending to the ground, which results in the accomplishment of repasts in the two heights of the forest[42]. *An. cruzii* is restricted to the Brazilian coast, where it is a transmitter of the *Plasmodium vivax*, *P. simium*, and *P. brasilianum*, causing human and simian malaria[61-69]. It is found in peridomiciliary environments, with its 24-hour activity peaking in the crepuscular periods of the day[65,67,68]. *An. bellator* is found only on the coast and presents eclectic habits regarding hosts. It has preference in breeding in bromeliads exposed to the sun[70].

VECTOR CONTROL IN BRAZIL

Vector control is an essential component of malaria prevention[71]. In Brazil, it was initially performed through early management of mosquitoes with the use of Paris green and petroleum derivatives[5,7,9]. With the discovery of DDT, the focus of malaria control strategies shifted to managing the adult mosquito population. DDT spraying was officially conducted throughout the Amazon in 1960[12]. Indoor spraying of DDT was banned in Brazil in 1999 because of its ecotoxicological risks, and currently, several classes of insecticides have been used, with special emphasis on pyrethroids, etofenprox PM 20% and lambdacyalothrin CE 5%[72,73]. Further, different methods for vector control have been used in the field (**Figure 1**).

INTERVENTIONS BASED ON IRS

Aimed at adult mosquitoes, IRS consists of spraying the interior walls of houses with insecticides[71,74]. Once applied, the insecticide will form a film of small crystals on the surface, killing the vector when it rests on the wall before or after a meal of blood[75]. Some of the insecticides used in IRS are also capable of repelling mosquitoes, reducing the number of vectors entering the households. It has been the most widely used method in malaria vector control[75], with some official guidelines available[75-78].

Some researchers have evaluated the effectiveness of different IRS insecticides used in Brazil. Roberts and Alecrim[79] investigated the behavioral alterations in female *An. darlingi* mosquitoes after DDT spraying, observing that they stopped entering and leaving houses, with a reduction in the bite rate. However, IRS did not interfere with the persistence of malaria in the study area, probably owing to the sprayed houses presenting incomplete walls. In their field trial, Charlwood et al.[80] compared the effects of lambdacyalothrin (ICON) and DDT when used as residual sprays on the internal surfaces of houses. ICON killed more mosquitoes than did DDT. From the observed efficacy, prompt acceptance by the local population, and cost-effectiveness of ICON, the authors have suggested its use in antimalaria campaigns. Santos et al.[81] evaluated the residual effect of pyrethroids on *Anopheles* mortality. The insecticides used were a suspension of deltamethrin, pyrethroids, lambda-cyhalothrin, and etofenprox in wettable powder, which were sprayed onto the surface of local dwellings. The authors observed that the insecticides applied to wood and uneven surfaces were more stable and lasted longer. Based on the findings of the study by Santos et al.[81] the NMCP changed the insecticide from alpha-cypermethrin to etofenprox in 2013.

Etofenprox PM 20% is the insecticide used by the Ministry of Health for residual spraying in houses for vector control

FIGURE 1: Methods used for malaria vector control. **(A)** Use of an insecticide-treated bed net; **(B)** fogging; **(C)** indoor residual spraying; and **(D)** larval source management.

of malaria. This product has a residual effect for 4 months[81]; therefore, three annual application cycles are required. This insecticide is applied by municipalities quarterly by filling out a standardized worksheet with the following information: (i) number of properties to be worked on in each cycle and (ii) number of malaria cases in the same period of the previous year and updated inventory of the insecticide in the municipality (**Figure 2**). For the Indigenous Special Sanitary Districts (DSEIs), etofenprox PM 20% application is conducted by sending a request with the abovementioned data directly to the Ministry of Health (**Figure 3**).

Although the work performed by different authors in Amazonian communities showed the role of IRS, it is still necessary to evaluate the effectiveness and costs of this action more specifically, as it is mainly related to the reduction of the morbidity of malaria in the Amazon.

ITNS

Rapid coverage of the population at risk through free and/or subsidized distribution of ITNs has been recommended by the WHO as a primary intervention for malaria control based on evidence of efficacy and effectiveness that this intervention has demonstrated in Africa, Southeast Asia, and South America[82]. Currently, there are long-lasting insecticidal nets (LLINs) that have a shelf life of approximately 2-3 years in the field or should be effective for 20 laboratory washes, with pyrethroid insecticides incorporated in the fabric[83,84].

ITNs emerged in the 1990s as one of the great hopeful methods of controlling malaria worldwide. In Brazil, the Ministry of Health started to distribute ITNs freely in malaria-endemic areas in 2007[85]. Between 2012 and 2014, there was an increase in the number of protected individuals with this strategy; however, there were discontinuity and subsequent reduction in the following years. LLINs impregnated with deltamethrin have been used in the Amazon[38]; however, the results have been contradictory, and there is limited knowledge on the effectiveness of ITNs in affecting the morbidity and mortality of malaria. The biting behavior of *An. darlingi* mosquitoes can be the main reason why ITBN-based malaria control programs may fail in this region[38,82,86-89].

In Brazil, the first work with ITNs was performed by Xavier and Lima[86] and Cavalcante et al.[87] who demonstrated the efficiency of DDT and deltamethrin and the effective repellent effect for up to 120 days, persisting even longer in locations not exposed to sunlight. Santos et al.[40] showed that ITNs used in Costa Marques, Rondônia did not change the risk of *Plasmodium* infection and did not reduce the cases of malaria and the average parasitemia associated with infection as observed in other continents. Probably, the protection failure of nets may have been attributed to bites occurring before entering

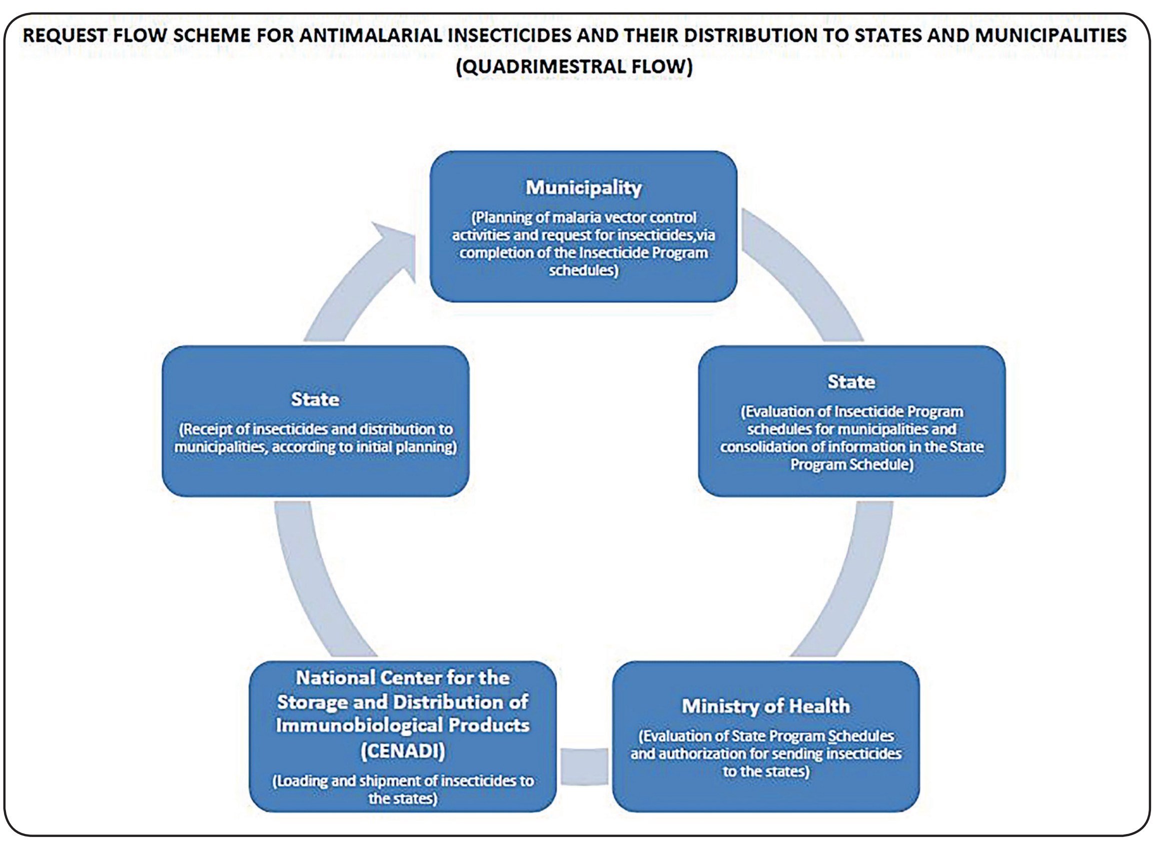

FIGURE 2: Flow chart presenting the distribution of vector control supplies in Brazil.

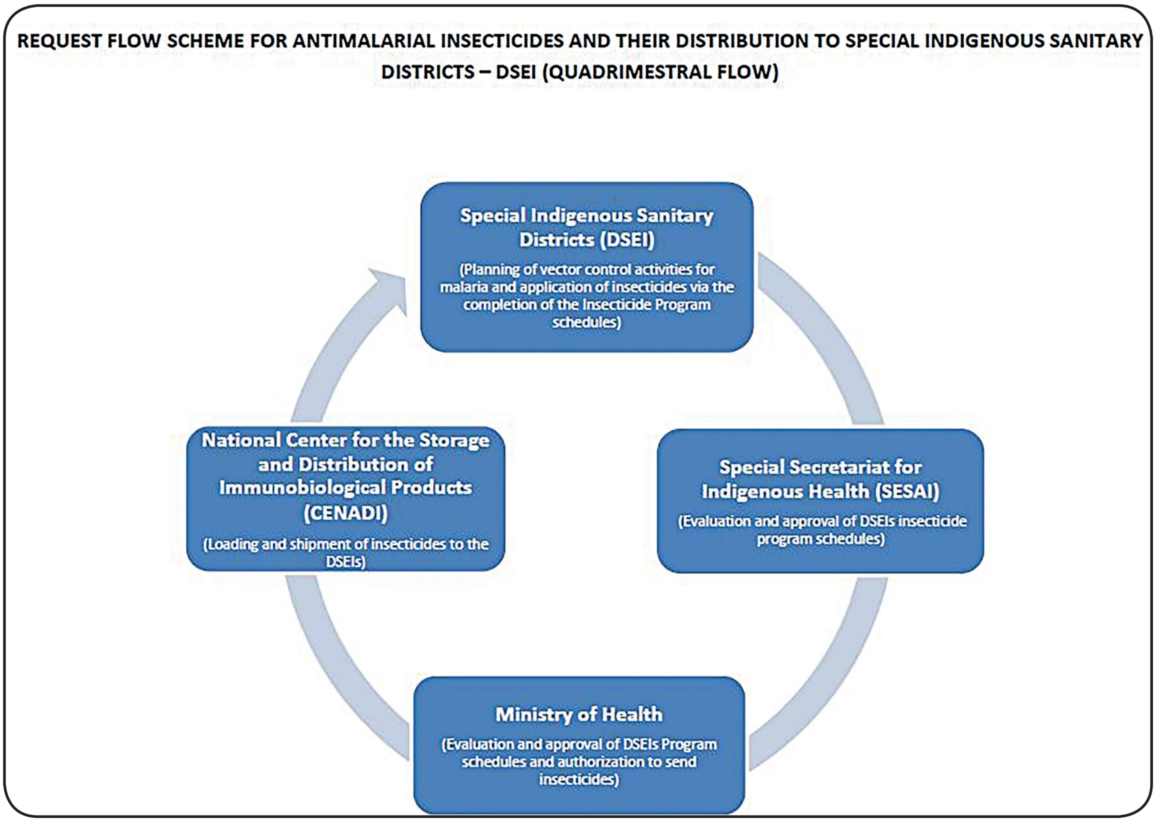

FIGURE 3: Flow chart presenting the distribution of vector control supplies in indigenous Brazilian areas.

and after leaving the mosquito net, to the more frequent exits during the night, and to the exophilic and endophilic behaviors of the main vector species in the region. These authors also showed that ITNs significantly decreased the number of *Anopheles* mosquitoes captured; however, impregnated and non-impregnated ITNs showed similar actions on the peridomiciliar density of mosquitoes. Still in Brazil, Galardo and Galardo[88] conducted a study in Mazagão, Amapá, evaluating the residual effect of ITNs impregnated with alpha-cypermethrin and observing an 80% reduction in malaria cases in the municipality. In 2012, approximately 150,000 LLINs were installed in nine municipalities in the state of Rondônia; Vieira et al.[89] evaluated the use of LLINs in nine cities and compared the outcomes with those in cities where LLINs were not used. However, no significant differences were observed in the annual parasite incidence 1 year after LLIN installation.

OTHER VECTOR CONTROL MEASURES

Space and aerial spraying

A spatial spray (fog) is a liquid insecticide dispersed into the air in the form of hundreds of millions of tiny droplets less than 50 µm in diameter[90]. Currently, neither space spraying nor aerial spraying has a WHO policy recommendation for use in malaria vector control[91]. Fogging might be justified for control of certain exophilic and exophagic vectors and during malaria epidemics, especially in camps for internally displaced individuals, where infective mosquitoes must be eliminated rapidly[26,92]. This will be important in vector control only in epidemiological emergencies and should never be used as a routine activity[92]. In Brazil, thermal fogging was selectively and exceptionally used in specific areas depending on entomological and epidemiological conditions, including areas of mining or those with lack of vegetation, as was the case in the Belo Monte site[93]. Measures, such as thermal fogging, are widely used in the Amazon for malaria control; however, they may be only slightly effective if not performed according to the mosquitoes' blood feeding activity[94]. Further, there is no evidence of the impact of nebulization or spatial spraying of insecticides on malaria transmission.

Lambdacyalothrin CE 5% is the insecticide currently used in Brazil for thermonebulization in malaria control, recommended only in epidemic situations; its application is not a routine activity of the malaria program. The application follows the same flow for municipalities and the *Departamento de Saúde Especial Indígenas* (DSEIs), but without the use of programming worksheets (**Figure 2**).

Larval source management (LSM)

LSM targets the immature, aquatic stages of mosquitos (i.e., larvae and pupae), thereby reducing the abundance of adult vectors[95]. The use of bacterial entomopathogens, such as *Bacillus sphaericus* and *B. thuringiensis israelensis* (Bti), is an alternative to conventional control measures against *Anopheles* larvae[96,97]. Bti is a bacterium that produces proteins, such as δ-endotoxins, which are toxic to larvae of several insects[98,99]. Rodrigues et al.[100,101] analyzed the larvicidal activity of *B. sphaericus* against larvae of anophelines in Amazonian conditions. They showed that the third larval instar of *An. nuneztovari* and the second and third larval instars of *An. darlingi* proved to be the least susceptible, while *An. braziliensis* was the most susceptible.

Galardo et al.[102] evaluated an intervention for malaria vector control using VectoLex(r) CG (granular formulation of *B. sphaericus* 2362 strain) at a mining site in Calçoene, Amapá. The VectoLex(r) reduced immature *An. darlingi* infestation levels during the entire study period and reduced adult mosquito populations during the rainy season.

Additionally, there are insect growth regulators, which prevent emergence of adults from the pupal stage. The most common compounds are diflubenzuron, methoprene, novaluron, and pyriproxyfen[95].

INSECTICIDE RESISTANCE

Insecticide resistance is the ability of insects to survive exposure to a standard dose of insecticide, owing to physiological or behavioral adaptation[103]. The molecular basis of insecticide resistance has been justified by the existence of mutations in insecticide target site genes and alterations in related metabolic pathways, including primarily the detoxification activity[104]. Behavioral resistance results from sub-lethal exposure to the active ingredient of insecticides and involves behavioral changes, resulting in avoidance and reduced contact with lethal doses of an insecticide[105]. Although the mechanisms of resistance to insecticides are known, the impact of resistance on the ability of malaria control interventions to reduce disease transmission is poorly understood[106].

Through the Global Plan for Insecticide Resistance Management in Malaria Vectors created by the WHO[107], the basis of any national vector control strategy was constructed, which includes a system based on epidemiological and entomological monitoring and monitoring of resistance to insecticides used, based on bioassays using WHO paper bioassays[104] or CDC bottle bioassays[108]. Ecological, epidemiological, and susceptibility information will help determine the proper use of insecticides to mitigate or delay the development of resistance.

Galardo et al.[109] evaluated the susceptibility of anophelines from Amapá to pyrethroids used by the NMCP, and no resistance was recorded for *An. darlingi*; however, *An. marajoara* requires attention. Silva et al.[110] evaluated the susceptibility profile of pyrethroid insecticides on *An. darlingi* and *An. marajoara* larvae. In this study, loss of susceptibility was observed in the populations of Manaus and Iranduba, possibly owing to the selection effect of the insecticides on the specific resistance alleles. Resistant mosquito populations may also appear owing to the long-term use of a single insecticide for malaria control vectors.

OFFICIAL RECOMMENDATIONS FROM THE BRAZILIAN MALARIA CONTROL PROGRAM

Two guidelines for malaria control are available from the Ministry of Health for professionals[77] and local management[26]. Through the Guide to Local Management of Malaria Control[26], the Ministry of Health establishes important recommendations on the methodologies for controlling anopheline malaria vectors in the country. According to this guide, vector control should follow the principles of selective and integrated control, with community participation and adjusted to the eco-epidemiological situations of each municipality. For this, the central axis of the vector control is the timely use of epidemiological information and the consolidation of a work routine in entomology with robust data on the parameters that must be monitored to support decision-making[26].

A careful and systematic analysis of the effect of control actions on malaria behavior depends essentially on the adequate completion and use of the information from the Malaria Epidemiological Surveillance System (Sivep-Malária)[26]. After identification of the priority areas, previously collected and updated local characterization information will help select the localities needing IRS and/or use of LLINs and those where control measures for breeding sites are necessary. In addition, adequate training and good maintenance of equipment avoid risks to human and environmental health, as well as economic losses[26].

IDENTIFYING RESEARCH PRIORITIES IN VECTOR CONTROL

In the national meeting on malaria research that took place in Recife, Pernambuco, in 2018, some gaps were identified for malaria vector control in Brazil. Considering such, some of the needs and priorities for future research and interventions include as follows:

- Update of the cartography of malaria vectors in Brazil, adding molecular techniques for the correct identification of species and complexes of species;
- Evaluation of vector competence of anopheline species in Brazil;
- Strengthening of local entomology teams to perform vector control measures and interpret results;
- Evaluation of vector control measures, especially the use of ITNs and LLINs, through community trials, estimating their effectiveness, cost-benefit, and population acceptance;
- Establishment of colonies of malaria-transmitting vectors in Brazil, with emphasis on *An. darlingi*, to understand parasite-vector interactions better;
- Study of new vector control strategies with impact on non-endophilic vectors;
- Estimation of the impact of insecticide resistance in different geographical areas, considering the insecticides indicated by the NMCP;
- Identification of the relative contribution of natural and artificial breeding sites in different epidemiological contexts for transmission

FINAL REMARKS

Vector control is an essential component of malaria prevention. In summary, incorporating vector control interventions, such as use of ITNs and IRS, is suggested for malaria elimination. Further confirmation from interventional studies is crucial to provide additional evidence for updating the malaria elimination policies in the territory. Vector control surveys are needed to address responses to changes in the NMCP guidelines, especially in the context of changes to eliminate malaria transmission in Brazil.

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