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Use of Wolbachia in the Americas to Control Vectors Responsible for Diseases of Public Health Interest

PAHO position and data analysis

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Introduction

- ✓ In the Americas, *Aedes aegypti* is the vector of major urban arboviruses such as dengue. Approximately 500 million people are at risk of contracting such viruses. (Pan American Health Organization, 2023)
- ✓ Dengue has increased in the Region in the last four decades, rising from 1.5 million accumulated cases between 1980 and 1989, to 16.2 million accumulated cases between 2010 and 2019. (Pan American Health Organization, 2023)
- ✓ Although advances have been made in the development of dengue vaccines, their mass use as a public health measure is not yet viable. At present, there are also no specific drugs registered on the market to treat dengue infection. Vector control interventions therefore continue to be the main tool with which to protect at-risk populations.
- ✓ The global increase in disease burden resulting from these illnesses has led to the development of new technologies to make vector control more effective.
- ✓ These innovations have several properties for the biological control of arboviruses, with a variety of effects such as the suppression of natural wild *Aedes aegypti* populations (through the release of sterilized male mosquitoes, self-limiting genes, *Wolbachia*) or the interruption of transmission, replacing wild populations (through the release of female mosquitoes with *Wolbachia*).
- ✓ At its 13th meeting in December 2020, the World Health Organization (WHO) Vector Control Advisory Group (VCAG) concluded that studies conducted by the World Mosquito Program (WMP), using *Wolbachia wMel* strains to interrupt transmission, has produced evidence of public health value in tackling dengue. This technology reduces the ability of *A. aegypti* to transmit the dengue virus. (https://www.who.int/vector-control/vcag/meeting-reports/en/)
- ✓ The main evidence presented to VCAG were the results of a study (randomized controlled trial - cRCT), conducted in Yogyakarta, Indonesia, where dengue incidence and hospitalizations in areas with *Wolbachia* release were reduced by 77% and 86% respectively (Utarini, et al., 2021)
- ✓ Other non-randomized, controlled studies (conducted in non-endemic countries, such as Australia, and endemic countries, such as Indonesia, Brazil, and Vietnam) were presented, also showing a reduction in dengue transmission. (Ryan, et al., 2020)

- ✓ However, these new technologies face several challenges to large-scale implementation. These include the cost and complexity of infrastructure needed for (mass) production of mosquitoes in quantities needed to achieve the desired effect (replacement or suppression of *Aedes aegypti* populations), and the cost of sustained use of the technology in the long term. A robust advocacy and community involvement process is needed to prevent the population from rejecting this type of intervention due to lack of information or misinformation. There is also a need to harmonize the use of *Wolbachia* with other control methods, as well as complex surveillance and evaluation methods to confirm the effectiveness of the intervention.

Experiences and advances in the evaluation of *Wolbachia* in the Americas

- ✓ The Brazilian Ministry of Health, with the support of the FIOCRUZ consortium and World Mosquito Program (WMP), has been developing large-scale trials since 2017 to release female mosquitoes infected with the *Wolbachia Wmel* strain. Interventions have been carried out in the municipalities of Rio de Janeiro, Niterói, Belo Horizonte, Campo Grande, and Petrolina. (WMP, 2023)
- ✓ Overall, the results of these trials show that it is possible to establish the *Wolbachia wMel* strain among the wild mosquito population, and decrease the vector competence of wild species to transmit arboviruses. Supported by the use of mathematical modeling, it has been possible to estimate a reduction in the incidence of dengue and chikungunya. (Santos, et al., 2022) (Gesto, et al., 2021)
- ✓ A cRCT study is currently underway to gather the best evidence to demonstrate a reduction in the incidence of arboviruses in Belo Horizonte, Brazil, and results are expected in the next two years. (Collins, et al., 2022)
- ✓ In Colombia, study analysis began in 2015, and a protocol designed to evaluate the impact of *Wolbachia* use was published in 2019. Studies are currently underway in Bello, Medellín, Cali, Itagüí, and Sabaneta, with no results yet available. (WMP, 2023) (Velez, et al., 2019)
- ✓ Following the release of *Wolbachia* in Colombia, the WMP published a report claiming that using *Wolbachia* has a favorable cost-benefit ratio. (Shepard, et al., 2022)
- ✓ In Mexico, studies began in 2019, with the release of *Wolbachia*-infected mosquitoes in the municipality of La Paz, in the state of Baja California. Results are not yet available. (WMP, 2023)
- ✓ Non-WMP projects, supported and funded by the Mexican national and local governments, are being developed to breed and release mosquitoes infected with the *Wolbachia WAlbB* strain. Results and data are not yet available. (Martín-Park, et al., 2022)

PAHO/WHO cooperation to meet countries' needs and demands for technical cooperation

In order to meet countries' needs for greater understanding of the benefits and challenges associated with the use of these new vector control technologies, PAHO has taken the following actions:

- ✓ In 2017, PAHO created an external (and independent) expert assessment panel, with the aim of advising and supporting countries in the development of pilot tests for these new technologies.
- ✓ In 2019, it prepared and published the document *Evaluation of Innovative Strategies for Aedes aegypti Control: Challenges for their Introduction and Impact Assessment.* (Pan American Health Organization, 2019)
- ✓ In its role as secretariat, and at the request of Brazil and Colombia, in 2019 and 2020 the external assessment panel convened by PAHO provided independent assessments of pilot projects on *Wolbachia* use sponsored by the World Mosquito Program (WMP) and its partners.
- ✓ The entomological results observed in Colombia and Brazil suggest, in general, that *Wolbachia* was established in wild *Aedes aegypti* populations at different times across the different release sites and, at the time of evaluation, there were no definitive epidemiological results to verify the impact in terms of reducing dengue transmission.
- ✓ The design and promotion of a new operating model for *Aedes aegypti* control, based on stratification of transmission risk, facilitated the reorganization of conventional control tools, and the incorporation of new technologies, within the framework of the Integrated Vector Management (IVM) strategy. Initiatives using this new methodology have been implemented in municipalities in Mexico and Brazil since 2018, in order to document its technical value and cost benefit. (Pan American Health Organization, 2019)
- ✓ In May 2023, support was provided to the Brazilian Ministry of Health for a training workshop for the health workforce, aimed at identifying dengue risk areas. This exercise has allowed the country to identify 42 priority municipalities eligible to receive innovative interventions for *Aedes aegypti* control, including *Wolbachia*.
- ✓ Virtual cooperation spaces (VCSs) on the Health Information Platform for the Americas (PLISA) were promoted for integrated analysis of information to strengthen the decision-making process on the use of new technologies and to monitor their outcomes.

PAHO/WHO position on the use of *Wolbachia* as a public health measure

- ✓ The documented experiences in the Americas on the incorporation of new technologies allow us to conclude that progress has been made in the development of mosquito breeding techniques, their distribution on a wider scale, and information/dissemination mechanisms to promote community involvement.
- ✓ In the near future, the Region has the potential to deploy other initiatives for producing mosquitoes infected with *Wolbachia* strains, e.g., those headed by the Mexican Government and by the United States Center for Disease Control and Prevention (CDC). This will reduce costs and expand the supply and access of technology to more countries.

- ✓ In line with the position of the Vector Control Advisory Group (VCAG), which considers the currently available data sufficient to begin developing the implementation guide for this tool, PAHO will prepare an operational technical guidance document for Member States, considering the advantages and limitations of its use in the Region. PAHO will also continue to promote and support additional studies with the most thorough evidence, aimed at evaluating the impact of *Wolbachia* in reducing the incidence of arboviruses, the interaction of *Wolbachia* with other vector control resources, and the most appropriate strategies for communicating with and engaging the population.
- ✓ PAHO reiterates the need for countries to adopt the integrated vector management (IVM) strategy as a model for incorporating new technologies. This will enable its optimized use alongside other available control tools and will increase its effectiveness.

Opportunities and challenges in the use of *Wolbachia* to control dengue and other arboviruses.

Opportunities	**Challenges**
Biological control	Difficulties in scaling production to meet the needs of all countries
Environmentally acceptable	Cost of infrastructure for mass production
Specific species for *Aedes aegypti* mosquitoes	Location of production plants near release areas
Sustainable, especially when adopting the wild *Aedes aegypti* population replacement strategy	High environmental temperatures may reduce the ability of *Wolbachia* to establish itself in wild *Aedes aegypti* populations.
Depending on the strategy adopted, wild mosquito populations may be eliminated and dengue transmission may be reduced.	Development of rapid, low-cost methods to monitor wild *Aedes aegypti* populations.
Can be incorporated into the set of existing interventions within the Integrated Vector Management (IVM) framework	Development of effective methods and roles for community participation

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