

The double-edged sword effect of expanding *Wolbachia* deployment in dengue endemic settings

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Transmission of mosquito-borne arboviruses such as dengue (DENV), Zika (ZIKV), and chikungunya (CHIKV) has been on the rise globally in the past decade. Periodic arbovirus outbreaks in urban settings worldwide highlight that traditional methods of vector control such as targeting breeding sites and insecticide application have limited effectiveness in curbing infections.¹ Among the most promising approaches is the replacement of native *Aedes aegypti* populations highly susceptible to DENV, CHIKV, and ZIKV by a *Wolbachia*-transinfected strain with reduced vector competence to those arboviruses.² Thirteen countries across Latin America, Asia and Oceania have been receiving this program (<https://www.worldmosquitoprogram.org/en/global-progress>), and published data revealed remarkable 96% and 77% reductions in DENV incidence in Australia and Indonesia, respectively.^{3,4} Nonetheless, the epidemiological impact of *Wolbachia* is heterogeneous. In Brazil, limited introgression of *Wolbachia* into the native *Ae. aegypti* population fostered a modest reduction of dengue (38%) and chikungunya (10%) incidences.⁵

The scientific community was recently thrilled to hear that in response to successful field trials, the non-profit World Mosquito Program (WMP) has partnered with the Brazilian Ministry of Health to build for \$19 million a mosquito factory in that country, which is expected to produce five billion mosquitoes with *Wolbachia* per year for field releases starting in 2024.⁶ This is the biggest bio-factory in the world and will be probably used as a model for future *Wolbachia* deployments. Rearing a massive number of mosquitoes in a centralised factory for subsequent shipment and autonomous releases nationwide is, however, challenging. Data has shown the successful spread of *Wolbachia* depends on local characteristics, including fine-scale climate and environmental factors, the size of the native *Wolbachia*-free *Ae. aegypti* population, the absence of geographical barriers constraining mosquito dispersal, and mostly important, the need of a genetic match between native and released mosquitoes.⁷ Among the genetic traits required to support successful invasion

are those related to mosquito response to insecticides. A case example is the first wMel introgression in Brazil that almost collapsed, dropping from 65% to 10% frequency in the subsequent weeks after mosquito releases ceased. The underlying cause of this failure was a low frequency of pyrethroid-resistant genotypes in released mosquitoes compared to the native *Ae. aegypti* population, which was highly resistant to this class of insecticides. The domestic overuse of pyrethroids was selectively killing *Wolbachia*-infected mosquitoes and population invasion of *Wolbachia* was only achieved after creating a newly backcrossed mosquito line using local wild *Ae. aegypti* males, followed by continuous refreshing of the lab colony with males from the same population every two generations.⁸

A comprehensive study investigating knockdown resistance (*kdr*) revealed three different spatial clusters of *Ae. aegypti* in Brazil: (i) southeastern and north-western regions with high pyrethroid resistance, and (ii) northeastern and (iii) southern clusters with low to intermediate levels of pyrethroid resistance.⁹ Additionally, microsatellite analysis has shown that Brazilian *Ae. aegypti* populations are genetically distinct across at least three main geographical areas—central-western, northern, and coastal Brazil.¹⁰ Therefore, considering local pyrethroid resistance and microsatellite data, there are at least five distinct genetic clusters of *Ae. aegypti* (Fig. 1).

We can use Brazil as a showcase to foresee and avoid a double-edged sword effect associated with *Wolbachia* releases. Insecticide resistance of native *Ae. aegypti* populations is spread worldwide (<http://aedes.irmapper.com>), and positive results should boost *Wolbachia* deployment in other dengue endemic settings around the world. *Aedes aegypti* populations are heterogeneous and nationwide releases of a *Wolbachia* strain whose genetic backcross belong to a specific locality would produce an unsought homogenization of vector populations. *Aedes aegypti* homogenisation at large geographic scales could impose additional undesirable consequences in the long-term by promoting genetic hitchhiking of traits such as higher vector competence, lower susceptibility to repellents and insecticides, or more avid host-seeking and biting behaviour. Available data has shown that ensuring adherence to local characteristics, specially a matching genetic between native and released mosquitoes, is critical to enhance the likelihood of achieving a faster introgression in the field,



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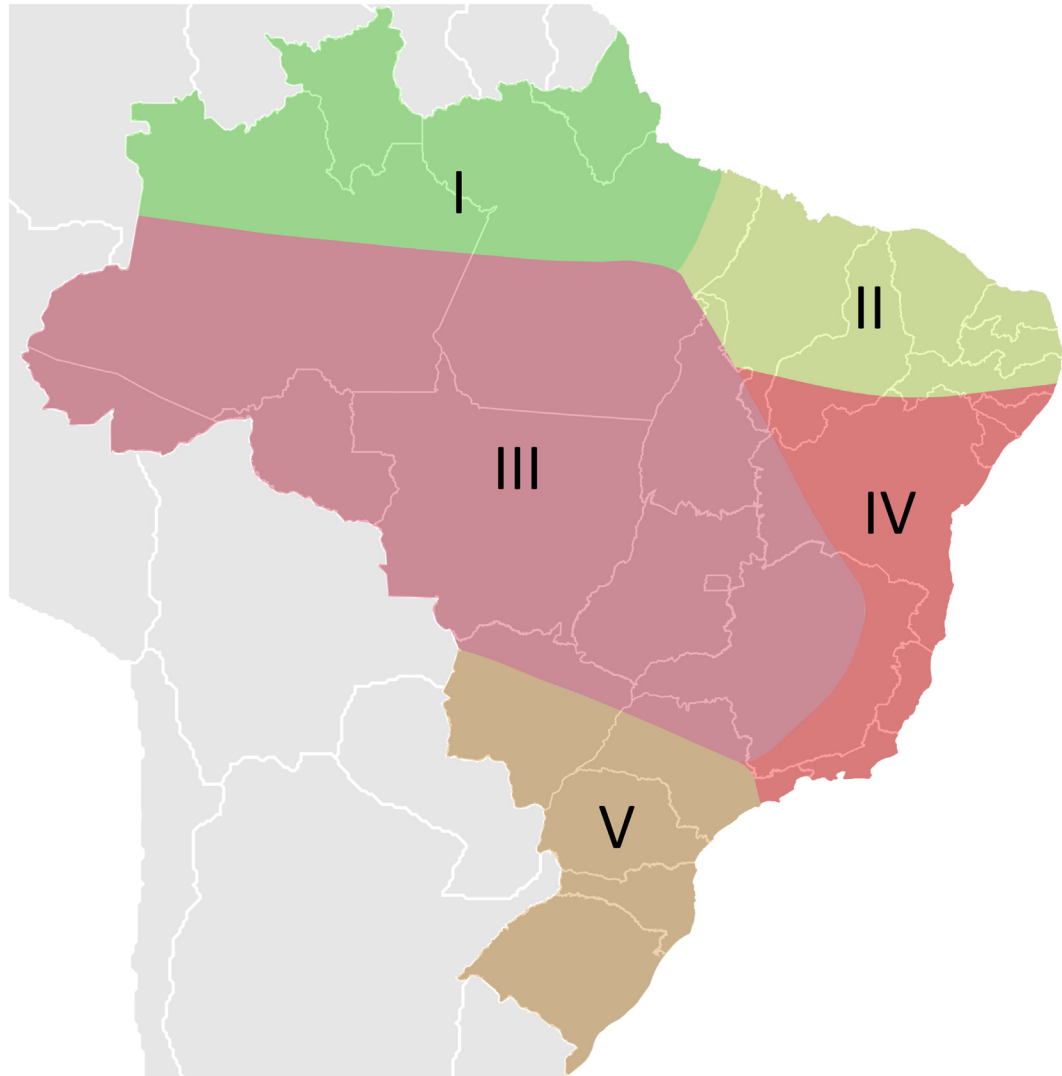


Fig. 1: Approximate geographic distribution of the five genetic clusters of Brazilian *Aedes aegypti* populations based on 12 microsatellite loci and *kdr* indices previously published.^{9,10} Reddish colours represent populations (III and IV) with a higher frequency of resistant *kdr* alleles and yellowish/greenish colours (I, II and V) harbour mosquito populations less resistant to pyrethroids. Clusters III and V are genetically similar, as well as II and IV, based on microsatellite data, while cluster I is genetically more distant from the others.¹⁰

realizing cost and time savings over the globe. Probably there are a myriad of yet undiscovered traits beyond insecticide resistance that may influence vector local adaptation and would affect the success of released strains. Therefore, neglecting the genetic diversity in favour of centralising the rearing of mosquitoes with *Wolbachia* for nationwide releases could represent a drawback for future releases. Long-term studies regarding the consequences of releasing mosquitoes with homogenous genotypes in diverse ecological and epidemiological scenarios remain a critical research priority, essential for informed decision-making and sustainable management of mosquito-borne diseases.

Contributors

MGP, GAG, MRD, and RMF conceptualized and contributed to the literature review. MGP and RMF wrote the original draft. GAG and MRD critically revised the comment.

Editor note

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Declaration of interests

We declare no conflicts of interests.

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