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BETWEEN INNOVATION AND UNCERTAINTY: A COMPREHENSIVE ANALYSIS OF THE RISKS ASSOCIATED WITH OX513A AND OX5034 GENETICALLY MODIFIED MOSQUITOES IN ARBOVIRUS CONTROL

ENTRE INOVAÇÃO E INCERTEZA: UMA ANÁLISE ABRANGENTE DOS RISCOS ASSOCIADOS AOS MOSQUITOS GENETICAMENTE MODIFICADOS OX513A E OX5034 NO CONTROLE DE ARBOVÍRUS

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ABSTRACT: The risks associated with genetically modified mosquitoes (GMOs) in combating arboviruses, specifically the strains of Aedes aegypti developed by Oxitec, have raised growing concerns due to potential dangers. With dengue becoming endemic in over 100 countries, the search for alternatives in vector control includes the use of GMOs. However, the introduction of these mosquitoes raises considerable concerns regarding potential risks to ecosystems and human health. Employing PRISMA guidelines, a database search identified 913 studies, of which only 4 were included after careful selection. The results highlight relevant findings, such as genomic instability in strains like OX513A and performance disparities between genetically modified mosquitoes and their wild counterparts. The review emphasizes the critical importance of dengue control in Brazil, considering factors like virus genetic variability and challenges in implementing control strategies, including the use of GMOs. Regulation of these organisms is conducted by CTNBio; however, the lack of consensus among various agencies raises doubts about the benefits of implementing these organisms. Given this landscape, the review underscores the ongoing need for monitoring the risks associated with genetically modified mosquitoes, encompassing not only biological implications but also environmental consequences. This approach is imperative for a comprehensive and informed assessment of the efficacy and safety of these organisms in the context of arbovirus control.

Keywords: Genetically modified mosquitoes. Arboviruses. Oxitec. OX513A. OX5034.

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RESUMO: Os riscos associados aos mosquitos geneticamente modificados (GMOs) no combate aos arbovírus, especificamente as cepas de Aedes aegypti desenvolvidas pela Oxitec, tem gerado crescente preocupação devido aos perigos associados. Com a dengue se tornando endêmica em mais de 100 países, a busca por alternativas no controle de vetores inclui a utilização de GMOs. Contudo, a introdução desses mosquitos suscita inquietações consideráveis em relação aos potenciais riscos para os ecossistemas e a saúde humana. Ao adotar as diretrizes PRISMA, uma pesquisa em bases de dados identificou 913 estudos, dos quais apenas 4 foram incluídos após uma seleção criteriosa. Os resultados destacam descobertas relevantes, como a instabilidade genômica em cepas como a OX513A e disparidades de desempenho entre mosquitos geneticamente modificados e suas contrapartes selvagens. A revisão sublinha a importância crucial do controle da dengue no Brasil, considerando fatores como a variabilidade genética do vírus e os desafios na implementação de estratégias de controle, incluindo o uso de GMOs. A regulação desses organismos é conduzida pela CTNBio; no entanto, a falta de consenso entre diversas agências levanta dúvidas sobre os benefícios da implementação desses organismos. Diante desse cenário, a revisão ressalta a necessidade contínua de monitoramento dos riscos associados aos mosquitos geneticamente modificados, abrangendo não apenas as implicações biológicas, mas também as consequências ambientais. Essa abordagem é crucial para uma avaliação abrangente e bem fundamentada da eficácia e segurança desses organismos no contexto do controle de arbovírus.

Palavras-chave: Mosquitos geneticamente modificados. Arbovírus. Oxitec. OX513A. OX5034.

INTRODUCTION

Arboviruses are characterized by their replication and transmission cycle associated with arthropods. These diseases represent great importance in countries where climate, environmental conditions and socioeconomic issues favor the establishment and reproduction of vectors (LOPES et al., 2014). Dengue is considered an endemic disease in more than 100 countries with predominance in Latin America, South-East Asia and Central Africa (COSTA et al., 2016). Approximately 100 million new cases are notified by the World Health Organization (WHO) annually. In that sense, alternative control interfaces for the vectors of these diseases have emerged and been implemented over the years, such as mechanical, chemical and biological control. Among them, appeared the Genetically Modified Mosquitoes (GE), otherwise known as transgenic mosquitoes (OLIVEIRA et al., 2011).

GE mosquitoes are organisms that display part of its genome altered for improved viability. In this sense, strains of *Aedes aegypti* mosquitoes were created with altered genetic stock by the British company Oxitec. Their main objective was to control populations of wild mosquitoes and, consequently, help in the fight against arboviruses related to these vectors, as is the case of dengue fever (SANTOS et al., 2018) (RUFATTO & CONTE, 2015). Meanwhile, the introduction of genetically modified mosquitoes as a measure to control arboviruses, raises great concern regarding the risks linked to the exposure of ecosystems and human health to exogenous constructs. In

addition, authors point out that the release of these organisms to eliminate the wild population of mosquitoes is not a good alternative for eliminating arboviruses (WALACE et al., 2013; CASTRO et al., 2022).

In regards to the implementation of the GE mosquitoes in Brazil, beyond inconsistent in the standardization process, the agencies responsible were based in the Cartagena Protocol for the assessment of biosecurity of the GE mosquitoes, due to the lack of specific law that evaluated the risk of these organisms in the country (SIMÕES et al., 2004). It is evident that there is no definite consensus involving the release of these transgenic mosquitoes, as well as the ethical issues and cost-effectiveness and analysis of the epidemiological profile of its use. With this in mind, the objective of this study is based on a systematic survey to assess the risks associated with these GMOs.

METHODS

Systematic review procedures

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), available at ‹https://www.prisma-statement.org/›.

A search was carried out in the electronic databases of Biblioteca Virtual em Saúde, PubMed Central (PMC) and Scientific Electronic Library Online (SciELO), using a combination of keywords related to constructs, biological effect and organism (Figure.1)

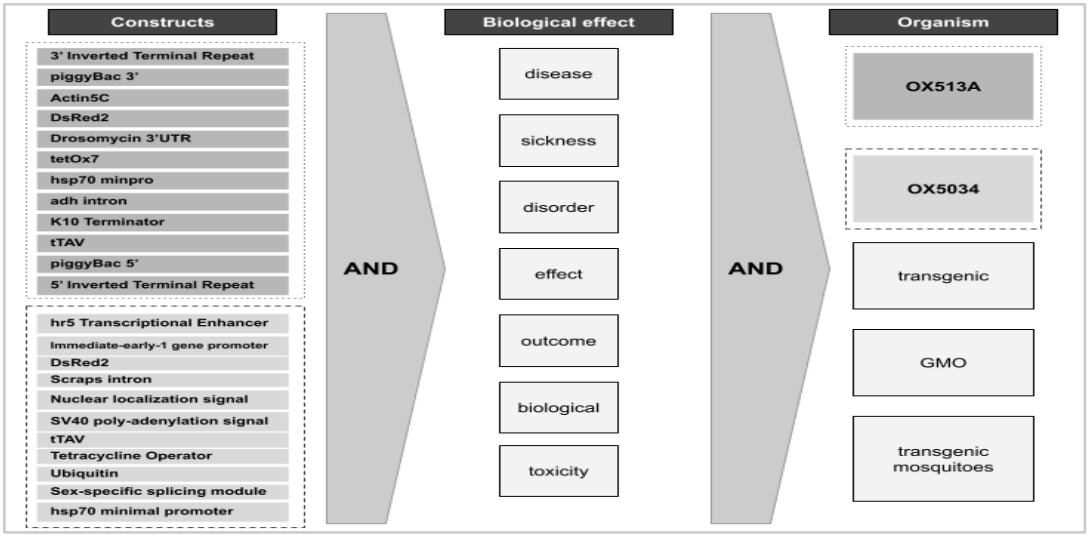

Figure 1. Scheme of the use of keywords in the search in the databases. The constructs highlighted in dotted and darker gray are related to OX513A, while those highlighted in dashed and lighter gray are related to OX5034. This differentiation is important, as each of the two types of mosquitoes received a different composition of constructs, implying a distinction throughout the searches.

The list of genetic constructs was obtained from the Biosafety Clearing-House website (https://bch.cbd.int/en/). To manage the references, JabRef v. 4.3.1 and EndNoteTM online were used.

Inclusion criteria

Studies containing evidence of biological effects caused by the insertion of constructs into the genome of mosquitoes, as well as studies published until December 2022 were included in this work. The accepted languages were English and Portuguese.

Exclusion criteria

Some studies were excluded for having (i) no relation with the effects of biological related to constructs; (ii) places where mosquitoes were not released; (iii) no connection to the hypothesis presented in this study (iv) inadequate statistical analyses; (v) duplicate data from the same author; (vi) duplicates; and (vii) publishing date not within the specified period.

Selection of studies

A systematic review was conducted blindly by three reviewers. In case of disagreement between the results, the inclusion decision was achieved by consensus among the reviewers.

RESULTS

Systematic review

A total of 913 studies were identified in the databases, of which 755 were retained after deleting duplicates. Of these, 643 were not related to the proposed objectives. After this step, 112 studies remained eligible for full text reading. In the final screening stage, 4 studies were included (Figure 3).

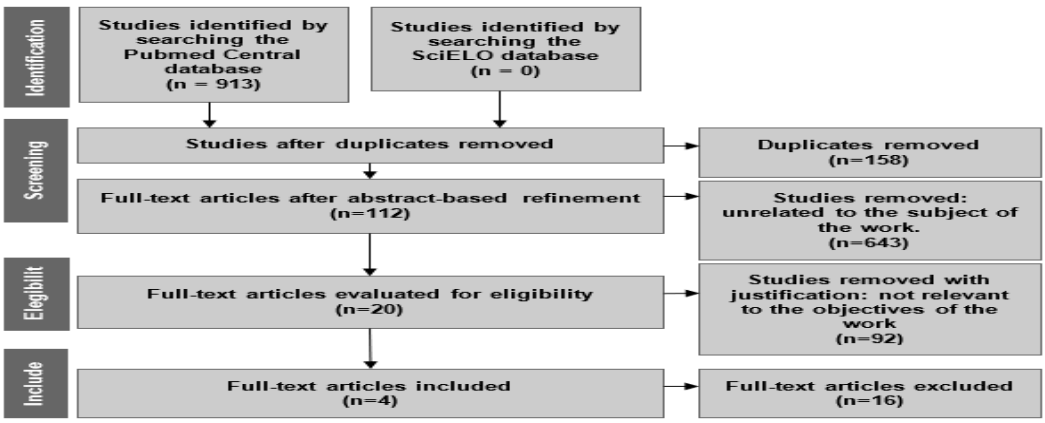

Figure 2. Flowchart representing the stages of selection of studies referring to the white literature in the systematic review

Based on the information from the selected studies, a table was constructed detailing the characteristics of each one **(Table 1).**

Item	Study design	Sample size group (n)	Outcome measures	Statistical methods	Experimental animals	Experimental procedures
Evans BR, et al. (2019)	Genomic copies of DENV-2 and ZIKVBR were quantified using a one-step qRT-PCR method.	OX513A Strain (25) | F1 Hybrids After 6 Months (57).	SNP chip for genotype analysis.	Utilization of the R package for ADMIXTURE analysis.	Females originating from the ROCK, OX513A, and Jacobina strains.	Isolated engorged females (ROCK, OX513A, Jacobina) were quantified for genomic copies using one-step qRT-PCR. Standard curve created using DENV-2.
Baeshen R, et al. (2014)	Molecular forms of all strains were determined using PCR/restriction fragment length polymorphism (RFLP) diagnostic techniques.	Strain 'Mopti 2003' | Renewed Strains | Transgenic Strains EE and EVida3 of Anopheles gambiae.	PCR/RFLP analysis	Dependent variables and body size were characterized using the logarithmic equation $\log(y) = \log(a) + b \log(x)$. Parte superior do formulário	Strain 'Mopti 2003' | Renewed Strains | Transgenic Strains EE and EVida3 of Anopheles gambiae. Parte superior do formulário	Mosquitoes maintained at 27°C, 70% humidity, 12-hour light/dark cycle. Larvae fed ground fish food. Adult density: 600-800 per enclosure, water, 5% glucose.
Bargielowski I, (2012)	Tetracycline-supplemented larval diets' impact on flight potential and energy reserves in WT, OX3604C, and tetracycline-dependent OX513A.	The study involved three lines: the Wild-type line (WT), the bi-sex lethal line (OX513A), and the female-specific flightless line (OX3604C).	Utilization of the Flight Mill system, measurement of wing length, and biochemical analyses.	The tukey's Honestly Significant Difference (HSD) test was employed for post-hoc analysis.	Wild-type strain (WT), Bi-sex lethal strain (OX513A), and Female-specific flightless strain (OX3604C).	Experiments conducted in a controlled insectary at 28±2°C, 65±10% humidity, 12-hour light/12-hour dark cycle.
Irvin N, (2004)	Assess fitness in transgenic Ae. aegypti by comparing demographic data with non-transformed lines to gauge competitiveness.	EGFP strain, pBacMOS strain, and Aedes aegypti strain.	Longevity of Adults, Fecundity of Females, Construction of Partial Life Tables, and Offspring Sex Ratio.	ANOVA in SAS, along with Tukey's Studentized Range Test for multiple comparisons. 5	Strain EGFP, pBacMOS, and Aedes aegypti.	Three transgenic Ae. aegypti lines derived from Orlando strain, consistently maintained at the University of California, Riverside. Parte superior do formulário

Table 1. Detailed caption highlighting specific and relevant information for each column, including details on the method, sample, and statistical analysis used in each study.

Genetically Modified Organisms (GMOs) have been the subject of extensive research to understand their biological effects and potential environmental consequences. A study conducted by Evans et al. (2019) revealed notable partial genome instability in OX513A strains, suggesting the possibility of vertical transmission. This finding underscores the importance of continuous monitoring and risk assessment over time. Baeshen et al. (2014) provided crucial insights by highlighting performance disparities between genetically modified OX513A strains and wild strains. These disparities may pose significant challenges in the effective implementation of this technology.

Additionally, Bargielowski et al. (2012) emphasized the need to consider the potential for flight and energy reserves in relation to tetracycline supplementation. This consideration highlights the complexity of the interaction between the environment and the performance of modified mosquitoes. Irvin et al.'s (2004) studies observed a reduction in demographic factors in transgenic strains of Aedes aegypti.

DISCUSSION

Dengue is one of the main infectious diseases in Brazil, representing a major public health problem in Brazil and in the world, occurring mainly in tropical and subtropical regions (ZANOTTO et al., 2018). The dynamics of transmission of serotypes of dengue virus depends on the interaction of many parameters, including genetic variability of influenza viruses, aspects of the ecology and Interaction vector-host, and are affected by host defense and the feeding behavior of the vector (WEARING, H, J et al., 2006). The influence of the temperature and rainfall variation on seasonality of *Aedes aegypti* as well as the *Aedes albopictus* that has been shown relatively more responsive to these factors (SERPAI et al., 2006) (CESAR et al., 2007). Among the abiotic elements involved in the spreading and survival, stand out the precipitation which provides the ideal environment for the eggs to hatch, heatstroke, and there are some correlations with the interference of humidity on this process of development (JÚNIOR, 2016).

In Brazil, dengue is present throughout the national territory, with more than three million cases reported between 1998 and 2007, making Brazil one of the countries most prone to the occurrence of the disease, especially for people living in tropical and subtropical regions (MACIEL, I, J. et al., 2009). In addition, more than seven million cases were reported between 2014 and 2021, with 52.4% belonging to the Southeast Region (MISTRO et al., 2022). On the international scene, dengue fever is unevenly distributed and has evolved differently depending on the region, with Southeast and South Asia being the most prominent, partly due to medical conditions; in addition to a marked increase in transmission in hyperendemic parts of the Americas (YANG et al., 2021).

Control for the eradication of dengue is permeated by advances, setbacks and difficulties and is a social problem in countries where large epidemics occur. The cost of dengue from a social point of view in Brazil is estimated at US$468 million (MARTELLI et al., 2015). The general increase in urbanization contributes to the persistence of dengue in Latin American countries, insufficient political commitment and inadequate funding are factors linked to the ineffectiveness of available preventive and control measures (CONYER et al., 2009). Vector control strategies for these diseases have emerged and been implemented over the years, such as biological, mechanical and chemical control. Among them, transgenics, also known as genetically modified mosquitoes, emerged (OLIVEIRA, CARVALHO, CAPURRO, 2011). The generation of mutant strains of *Aedes aegypti* developed by the British company Oxford Insect Technologies (Oxitec), which main objective and purpose is to reduce wild mosquito populations and, consequently, combat arboviruses transmitted by this vector, mainly dengue (SANTOS, 2018) (RUFATTO & CONTE, 2015).

The National Technical Biosafety Commission (CTNBio) in accordance with Law No. 11,105, of March 24, 2005 and Decree No. 5,591, of November 22, 2015, aims to provide technical support with regard to the biosafety of Genetically Modified - GMOs, related to the protection of the health of living beings and environmental preservation (BRASIL, 2005). The technology was regulated by CTNBio's technical opinion N 3964/2014 for experimental commercialization, which aimed to identify the possible impacts on health and the environment, with the following main points highlighted: i) assessing the risk in the use of technology; ii) verifying, through experimental evaluation, the risk of releasing transgenic mosquitoes; iii) releasing the technology for experimental research purposes. It also emphasizes other criteria, such as evaluating the effectiveness of technology in reducing the number of dengue cases, which are the sole responsibility of the Ministry of Health and the Environment (CTNBio, 2014). The lack of consensus on technology implementation between CTNBio and the other ministries responsible for the GMO registration and inspection process masks the real benefits and implications of implementing such an organization. For ANVISA, transgenic mosquitoes are objects of study in Brazil. Therefore, these organisms are marketed only upon the final opinion of CTNBIO for experimental research, without specific evaluation of the effectiveness criteria and possible impacts of use (ANVISA, 2016).

The introduction of GMOs as a control measure for arboviruses raises serious concerns regarding the risks of exposure to exogenous constructs in the environment, ecosystem and human health (WALACE, 2013). Some biological effects of transgenics, such as partial genome instability after gene introgression and possible vertical transmission in a population of native mosquitoes exposed to transgenic mosquitoes, have been reported, as pointed out by Evans et al. (2019).

Depending on the conditions, mosquitoes crossed in the laboratory can show significant physiological changes in relation to mosquitoes in the habitat. (BAESHEN et al. 2014). The genetically modified OX513A strains have low performance compared to wild strains, which poses a greater disadvantage to the implementation of this technology (BARGIELOWSKI et al., 2012). After the introgression of suppressor genes into the transgenic strains of *A. aegypti*, some demographic factors related to these organisms are reduced in relation to other non-modified strains (IRVIN et al., 2004).

CONCLUSION

In summary, the analysis of risks associated with GMOs, specifically OX513A and OX5034, raises concerns about potential environmental and human health impacts. The review highlights issues such as partial genomic instability and performance disparities of GMO mosquitoes compared to wild mosquitoes. The importance of dengue control in Brazil is of utmost significance; however, the implementation of these GMO mosquitoes lacks consensus among regulatory agencies, casting doubt on their effectiveness. Ethical considerations, cost-effectiveness, and the epidemiological profile also contribute to the complexity of the decision. In this scenario, the need for continuous monitoring of the risks associated with these GMO mosquitoes is crucial. This monitoring should extend beyond biological implications, encompassing environmental consequences to ensure an accurate assessment of the efficacy and safety of these organisms in arbovirus control.

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