

ORIGINAL ARTICLE

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SUMMARY

One of the biggest challenges currently for public health in Brazil and worldwide are vector-borne diseases, and current control measures are inefficient. Mosquitoes are among the vectors of various diseases, because they are hematophagous, females require blood in the ovulation period for reproduction and once contaminated, the mosquito can contain bacteria, protozoa and viruses that are allocated in their salivary glands, thus infecting the individual

directly into the bloodstream. *Aedes aegypti* is responsible for the diseases: dengue, zika, chikungunya and yellow fever. The forms of control for vector mosquitoes so far are ineffective, and with this several technologies have been developed as alternatives in the control and combat of the *Aedes aegypti* mosquito. With recent approvals for the release of genetically modified insects, there is a need for more detailed studies to assess their ecological potential and evolutionary effects. These effects can occur in two phases: a transient phase when the focal population changes in density, and a steady state phase when it reaches a new and constant density. With the innovations in vector control through genetically modified insects give us a new perspective in relation to genetic manipulation. This study aims to evaluate the potential effects of a rapid change in the density of the *Aedes aegypti* mosquito related to biological control through the genetically modified mosquito. So we wonder, can biotechnology be a solution to public health problems in the case of the *Aedes aegypti* mosquito or a problem? Since the transformation or modifications of these living beings in laboratories are new techniques that so far it is impossible to know what the long-term consequences will be.

Keywords: Genetic selection, transgenic animals, *Aedes aegypti*, mosquitoes, mosquito control.

INTRODUCTION

Mosquitoes have been intensely studied since the 19th century when they were first related to disease vectors for men and other vertebrates (WILKE; GOMES *et al.*, 2009). The genera *Culex*, *Anopheles* and *Aedes* are the vectors of three groups of human pathogens: malaria of the genus *Plasmodium*, filia of the genera *Wuchereria* and *Brugia* and numerous arboviruses, and the agents of dengue and yellow fever (TAIPE-LAGOS and NATAL, 2003).

In the national legislation, item I of Article 3 of the National Environment Policy (Federal Law N°. 6,938/81) defines the environment as “the set of conditions, laws, influences and interactions of a physical, chemical and biological order, which allows, shelters and governs life in all its forms” (FARIAS, 2017).

The processes of environmental degradation, which has been occurring mainly as a result of

anthropogenic activities, are altering the ecological balance and providing adequate habitats so that vectors of diseases such as mosquitoes can reproduce, develop and transmit diseases (KWEKA; KIMARO and MUNGA, 2016). The environmental disasters that have been caused by the disorderly exploitation of man by natural resources and by the development of the process of urbanization and industrialization have reached unimaginable proportions, endangering human health (BARBIERI, 1998). These serious environmental imbalances that have reached a global scale, highlighting the picture of destruction of nature, these situations of environmental transformations are what most favor the emergence of new diseases (SCHMIDT, 2007) (KWEKA; KIMARO and MUNGA, 2016). In an interview given at the Chino Ulysses Confalonieri Dialogue, a researcher at the Oswaldo Cruz Foundation stated that “deforestation has always been one of the main causes of tropical diseases in Brazil” (VEIGA, 2017). Studies have shown that environmental changes and ecological disorders, whether of natural cause or anthropogenic cause, can exert a marked influence on the emergence and proliferation of certain diseases (SACCARO JUNIOR; MATION and SAKOWSKI, 2015). Several mechanisms have already been suggested to explain how environmental imbalance has contributed to the increase of diseases caused by mosquitoes (SACCARO JUNIOR; MATION and SAKOWSKI, 2015).

National and international scientific literature shows that viruses and bacteria in nature await the ideal moment to reach humans. The gaps are created by man through decades of alteration and destruction of the environment, considering the space of time between the development of primitive human society to the present day, and the ways in which natural resources have been exploited by man, has influenced in the context of what has been happening today, since forests have given way to agriculture and urban centers of varying sizes (UJVARI, 2003).

From the change of the environment some living beings that had as habitat the forests, began to live in cities with man, among these beings we can find the mosquito, an insect that can be found in almost all parts of the world, being, however, the vector of malaria, yellow fever, dengue, chikungunya, zika and other serious diseases. For this, the mosquito needs some factors such as problems in the infrastructure of cities, lack of basic sanitation, which favor the proliferation and dissemination of the mosquito (NEVES; MELO *et al.*, 2005).

These pathologies have in common the *Aedes aegypti* mosquito, which is the transmitter of

diseases known as arboviruses and which presents with important epidemiological prominence (SANTOS; SILVA et al., 2017) (LOURENÇO and RODRIGUES, 2017). *Aedes aegypti* can be defined by its resistance and ability to adapt to different environments, it is a mosquito from Africa, from the Culicidae family, now distributed in almost all world territories, *Aedes aegypti* is considered by the European Agency for Disease Prevention and Control to be one of the most irradiated mosquito species on the planet (BRAGA and VALLE, 2007).

In the last century, during the 1950s and 1960s, several vector control programs were created in several countries, using chemical strategies without restriction of use such as DDT. And today these measures to control the *Aedes aegypti* mosquito have been less efficient than when used in the 1950s (WILKE; GOMES et al., 2009). Currently several strategies to control the population of the *Aedes aegypti* mosquito have been developed, such as risk mapping, natural compounds, Wolbachia, insecticide dispersing mosquitoes, sterile insect technique, transgenic mosquitoes and other (PAN-AMERICAN HEALTH ORGANIZATION, 2019) (ZARA; SANTOS et al., 2016). In the fight against the *Aedes aegypti* mosquito some types of basic control mechanisms can be used: mechanical, chemical and biological (HOY, 1985) (ZARA; SANTOS et al., 2016).

The genetic strategies that have been developed for vector control are possible to divide them into two stages. The first stage proposes to reduce or even eliminate mosquito species through the development of lethal genes, or capable of making insects sterile, in this technique insects do not require radiation sterilization (POST-PN-360, 2010) (DONOVAN, 2009). In the second stage involves the transformation or replacement of the population, through the introduction of an effector gene to reduce or block the transmission of the disease in the population of wild insects (ARAÚJO; CARVALHO et al., 2015), (ANDRADE; ARAGÃO et al., 2016).

A Oxford Insect Technology (Oxitec Ltd. Oxford, England), a company that focuses on the development of technology to combat the mosquito with the use of transgenic strains, has developed a lineage of *Aedes aegypti* for population control. Currently the OX513A lineage was the first that showed the best results in the laboratory, and received technical approval from the National Technical Commission of Biosafety (CTNBio) for commercial release in Brazil (ZARA; SANTOS et al., 2016) (POST-PN-360, 2010).

POPULATION SUPPRESSION OF INSECTS WITH DOMINANT LETHAL GENE

This is a method known as the RIDL system proposed by Thomas that consists of a mechanism in which a dominant lethal gene is associated with a specific promoter of females, such as the calf promoter (WILKE; GOMES *et al.*, 2009) (ALPHEY; BENEDICT *et al.*, 2010).

In this technique, the dominant lethal gene that was introduced into the mosquito can be disabled in the presence of tetracycline. During the separation of male and female mosquitoes, tetracycline is removed from the system, causing the death of all females (OLIVEIRA; CARVALHO and CAPURRO, 2011). The system is blocked when tetracycline exists inside the mosquito, because tTA has more affinity for tetracycline than tetO (ALPHEY, 2002). Thus, all ridl homozygous males released into the environment will copulate with wild females and all offspring will carry the transgene, in the absence of tetracycline in their diet these mosquitoes will die from toxicity caused by the high levels of tTA in cells (OLIVEIRA; CARVALHO and CAPURRO, 2011) (WILKE; GOMES *et al.*, 2009).

POPULATION REPLACEMENT STRATEGIES

These strategies involve the permanent replacement of a wild population of insects by GM varieties that have been altered in order to make them less capable of transmitting diseases (TERENIUS; MARINOTTI *et al.*, 2008). “This tuning is based on the hypothesis that an increase in frequency in a vector population of a gene that interferes with a pathogen will result in the reduction or elimination of transmission of this pathogen” (COLLINS and JAMES, 1996).

This approach consists in the creation of a transgenic insect that is capable of killing, or preventing the replication or dissemination of a specific pathogen, that is, capable of dying once it is infected by the microorganism (TERENIUS; MARINOTTI *et al.*, 2008).

This would happen during the transformation of the cells of a mosquito with a microorganism, which transcribes an inverted-repeated RNA (RNAi) derived from the genome. We can cite as an example the dengue virus type 2, this virus is able to generate a double-tape RNA, which in turn will activate the interference RNA pathway (RNAi), which is able to inhibit the viral

cycle preventing the replication of the virus in the mosquito (ADELMAN; SANCHEZ-VARGAS *et al.*, 2002).

In all cases of the creation of GM mosquitoes for release into the environment, it is essential to use sexing technologies, where only males can be released, since they do not feed on blood, such as females, reducing the risk of bites and transmission of diseases (WISE DE VALDEZ; NIMMO *et al.*, 2011).

For David the release of insect GMs should be considered an ecological disturbance whose adverse effects can occur in two phases: in the first occurs a transient phase during which the population of insects including the GMs insects released changes rapidly in density, in the second is the phase of steady state during which the population stabilizes at a constant density (DAVID; KASER *et al.*, 2013).

TRANSITIONAL PHASE

In this phase we can evaluate the evolutionary effects resulting from the transient changes of the gene flow. This gene flow is all the mechanisms that result from the exchange of information and the movement of genes from one population to another, which can occur in gametes or segments of extracellular DNA between populations of the same species, however, some cases of interspecific genetic exchange (WHITTEMORE and SCHAAL, 1991) (SLATKIN, 1985) are known. Where an advantageous gene can act positively by spreading easily in a growing population, when this happens for a long period, one can have the formation of a new species, due to the reduced influence of genetic drift, some of these changes can also move to the steady state phase (GOULD and SCHLIEKELMAN, 2004). Although gene flow between populations and subspecies may be desired in the case of release of transgenic insects carrying a dominant lethal gene (RIDL), it is necessary to take into account the importance of the effects of gene flow that may be disastrous (GOULD and SCHLIEKELMAN, 2004).

“For Prakash the introduction of a gene into different cells may result in different results, and the general pattern of gene expression can be changed by the introduction of a single gene” (PRAKASH; VERMA *et al.*, 2011).

It is also necessary to take into account the impacts of hybridization, the mixture can have several effects, ranging from decreased fitness to heterosis (FACON; CRESPIAN *et al.*, 2011).

According to David, a mixture was observed in several species of insects, such as *apis mellifera carnica* and *Apis mellifera linguist* hybridized with native populations of *Apis mellifera* in northwestern Europe and the introduction of African *Drosophila melanogaster* in American populations. (DAVID; KASER *et al.*, 2013)

Hybridization may imply new genetic advantages for the mixed individual (FACON; CRESPIAN *et al.*, 2011). We can find in the literature several examples of intraspecific genetic flow between transgenic organisms, mainly in relation to transgenic cultures. Although some researchers claim that there is a difference between genetically modified crops and insect pests in their physiology and purpose, it should be taken into account that transgenic crops can offer us a lot of valuable information about the various types of possible effects among transgenic organisms. Numerous studies have shown us that intraspecific flow of the manipulated gene can occur between varieties GMs and non-GMs of various cultures. We can cite as an example, Mexico, where they were found in a corn plantation, transgenes of Bt corn cultivars (MERCER and WAINWRIGHT, 2008). Transient interspecific gene flow can occur through mating, hybridization, and introgression between GMs and non-GMs organisms. If this hybridization occurs in a natural system, it can produce many ecological consequences, which can result in strong negative impacts for native species (KENIS; AUGER-ROZENBERG *et al.*, 2009).

ECOLOGICAL INTERACTIONS

Biology has been showing us every day, various types of ecological interactions between living beings that can be considered harmonic or disharmonious. A transgenic organism can assume one of many ecological functions, such as consumer, competitor or disease vector. This type of change can occur during the transitional phase, and can lead to various ecological effects. If a change in the population density of an insect is affected due to the release of insect GMs, it may lead to an increase in the predator population due to prey availability (ROYAMA, 1984), even if a release of GMs insects does not necessarily cause changes in biomass, the increase in the population of an insect can have unwanted

consequences if a large number of agents is released to complement a naturally occurring population, this may increase the population of its predators (SNYDER and EVANS, 2006).

STATIONARY PHASE

If we take into account that the release of GMs insects has been successful, the local insect population should have a new steady state density after the transient changes in density. During this state it is possible to identify evolutionary and ecological effects that arose during this phase (DAVID; KASER *et al.*, 2013).

For Myers, evolution is not predictable, despite our inability to predict the products of evolution, we can predict significant estimates about evolutionary processes, as they will be affected by the exhaustion of biological diversity (MYERS and KNOLL, 2001).

“For David as a community adjusts to the altered focal population density, changes in the frequency of certain species interactions can result in new selection pressures in short terms” (DAVID; KASER *et al.*, 2013).

Several cases of rapid evolution have already been documented after species invasions, we have as an example in Australia the bedbug *Leptocoris tagalicus*, which evolved developing oral parts of 5 to 10% longer, in a period of 30 to 40 years, allowing it to feed on the seeds of an invasive vine *Cardiospermum grandiflorum* (CARROLL; LOYE *et al.*, 2005), it should be taken into account that a rapid evolution can happen in a species of insect released for the suppression of the local species, these extinctions can have great evolutionary consequences (ANDERSON; KELLY *et al.*, 2011).

GM insects can alter the evolution of virulence and transmission of a vectorized pathogen, first strains competing within a host can affect virulence and second individual strains transmitted between hosts can lead to a potential exchange between these two levels. Selection that acts on the parasite's virulence is more complicated when a host can simultaneously harbor several different strains or genotypes of a parasite. In which there is a dominance hierarchy, so that only the most virulent strain in a host is transmitted (MAY and NOWAK, 1995).

ECOLOGICAL INTERACTIONS

As stated earlier, living beings keep among themselves various types of ecological interactions, when there is a long-term reduction of a species of insects can have consequences for other interacting species (PRAKASH; VERMA *et al.*, 2011). These consequences can be easily observed when a species is removed or excised, generating an indirect effect on the ecosystem. It is necessary to identify them, before any specific release of transgenic insects, more for this is necessary, solid ecological information about community interactions and ecosystem functions of local species. The big problem is that this information rarely exists, but should not be interpreted as the absence of possible indirect effects (DAVID; KASER *et al.*, 2013).

We can cite as an example a study by Crawford that shows that amphibian populations worldwide are experiencing an unprecedented decline, this decline has been attributed to a fungal pathogen, *batrachochytrium dendrobatidis* (CRAWFORD; LIPS and BERMINGHAM, 2010). This recent decline in amphibians shows us an example of how reducing the species population can affect ecosystem processes (DAVID; KASER *et al.*, 2013). Few studies to date have evaluated the role of tadpoles and their importance in maintaining sediment bioturbation in water, their removal from aquatic systems decreases sediment resuspension that leads to increased biomass and diatomaceous diseases, generating a reduced availability of algae used by other species as food, affecting the abundance and diversity of basal resources as well as influenced by the dynamics of the food network of other primary consumers (RANVESTEL; LIPS *et al.*, 2004).

In ecological systems all living beings interact with other organisms and their environment (PRAKASH; VERMA *et al.*, 2011). This is one of the reasons that make the biological system so difficult to study, are these possibilities of different interactions with organisms and with the environment that makes it so complex (JUNIOR, 2013). We have to take into account that the ecological system can be influenced by hysteresis which is the inability of a system to return to its original state from an alternative state (BEISNER; HAYDON and CUDDINGTON, 2003). Hysteresis can make it difficult to restore native vegetation in an invaded habitat, such as the removal of invasive plants can increase the number of exotic plants rather than increase the number of native plants in a habitat. The same may happen with the release of GMs insects that may induce an undesirable steady state phase making a reversal impossible (DAVID;

KASER *et al.*, 2013).

“For David the evolutionary effects of the transient phase may persist in the steady state phase, and several new effects may also occur” (DAVID; KASER *et al.*, 2013). According to Tsetsarkin, the exchange of vectors has already been observed in mosquitoes, the chikungunya virus has undergone adaptive mutations to switch to the vector *Aedes albopictus* of other species of *Aedes* (TSETSARKIN and WEAVER, 2011). Some factors may influence the ability of the vector: as the useful life of the vector, frequency of contact between mosquitoes and hosts and the general susceptibility or resistance capacity of the vector to the mosquito, these factors can evolve in other vectors, the declines in habitats, may favor the emergence of new species to colonize the spaces due to competitive release (COHUET; HARRIS *et al.*, 2010). The reduction in a population can influence the predator population (DAVID; KASER *et al.*, 2013), mosquitoes generally represent a significant part of the diet of various bats, spiders and generalist fish, reducing mosquitoes could reduce the population of these predators (REISKIND and WUND, 2009). “This can cause cascading community effects, disruption of food networks and potential loss of diversity in the affected community” (DAVID; KASER *et al.*, 2013).

DISCUSSION

Science and technology are present in all sectors of contemporary life, as well as promoting profound social, cultural and economic transformations (BRAGA and VALLE, 2007) (ROMERO-VIVAS; WHEELER and FALCONA, 2002). In this scenario biology has presented a prominent position in the area of science, mainly in the areas of Molecular Biology and Genetics with transgenic organisms. For this reason, it is of great importance that people be called to reflect and give an opinion on the ethical, moral and social benefits, risks and implications arising from the biotechnologies generated by the research. However, one of the major problems is that the information that people receive does not allow them to appropriate scientific knowledge in order to understand, question them and use them as an instrument of thought, it is possible to verify that there are often intuitive conceptions, strongly influenced by the media, usually devoid of scientific knowledge (ORTEGA; CAPRONI and ROZZATTI, 2011) (PEDRANCINI; CORAZZA-NUNES *et al.*, 2007).

For good or evil, “the trajectory is clear”, the introduction of a gene that reduces the fertility of mosquitoes or their ability to transmit a pathogen can be controlled? That’s a question that needs to be answered. If something goes wrong, who will take responsibility? How can the damage be repaired? Who should have the authority to introduce this technology into nature? We’re talking about eliminating a species or changing its behavior.

In The Science magazine in April 2015 an alert was given by Valentino Gantz and Ethan Bier of the University of California, San Diego. In one of their research, scientists modified a gene, called yellow, of a male of *Drosophila melanogaster* and performed the crossing of a modified male exempt with a wild female. The mutation that occurred because of this gene altered the staining of the flies, which became clearer. As the allele was recessive, the females generated from this crossing should be wild, but the male allele altered the female allele, and all descendants presented a yellow coloration, eliminating any variation that existed in the insect, or rather, all were the same. If these individuals were released into the environment, all wild insects of the species *Drosophila melanogaster* would now have this allele, the problem is that it is not known whether this change occurred in one of the regions of the genome or inserted into an unwanted region of the genome (GANTZ and BIER, 2015).

For Stewart, microorganisms that have been genetically improved have the ability to reproduce and establish themselves as a persistent population that can have subtle and long-term effects on biological communities and natural ecosystems (STEWART JR; RICHARDS and HALFHILL, 2000). DNA modifications may not be limited only to the characteristics of the replaced gene. It is important to take certain care to ensure that when these GM mosquitoes are released into the wild, they do not harm the environment or human health (ANDERSSON; BARTSCH *et al.*, 2006). We can highlight some environmental risks that are likely to occur by the use of Mosquito GMs in the field, because it is of great importance to highlight that each gene can control several different characteristics in a single organism.

Genetic contamination can be seen as a reality, when we introduce gm mosquitoes into a habitat, these mosquitoes can cross with wild or sexually compatible relatives. These new characteristics may disappear or confer a selective advantage to the recipient, altering the relationship and ecological behavior of native species.

The impacts of the ecosystem or the effects of changes on a single species can extend far

beyond the ecosystem. Unique impacts are always associated with the risk of damage and destruction of the ecosystem.

The lack of means makes it impossible to monitor these mosquitoes GMs introduced into the environment, with the emergence of some problems, it will be practically impossible to eliminate them.

The horizontal transfer of recombinant genes to other microorganisms is a worrying risk related to mosquitoes GMs, the acquisition of foreign genes by organisms is one of several environmental situations. This can occur especially in response to the change of an environment, providing other organisms, especially prokaryotes, which obtained a significant proportion of their genetic diversity through the acquisition of genes sequences of different organisms (OCHMAN; LAWRENCE and GROISMAN , 2000) (MARTIN, 1999), this may confer a new characteristic in another organism, which can be a source of potential damage to people's health or the environment (BENNETT; LIVESEY *et al.*, 2004). It would be a big mistake to assume that recombinant genes in one organism do not spread to other organisms.

The long-term effects of the impact of horizontal transfer of recombinant genes can be relatively strong, this can take thousands of generations for a receiving organism to become the dominant form in a population. In addition, other factors can help. As the appropriate time of biotic or abiotic environmental conditions and additional changes in the receiving organism, may delay adverse effects (NIELSEN and TOWNSEND , 2004). Several scientific evidence has emerged in recent years on genetically modified organisms, showing that there are several clear risks to human health and the environment. When genetic engineers create a transgenic organism they have no way to determine the specific location that will insert the gene. The gene ends up at a random location in the genetic material, and its position is usually not identified (CRAIG; TEPFER *et al.*, 2009) (LABRA; SAVINI *et al.*, 2001).

CONCLUSION

Researchers have been developing genetic modification techniques at an incredible rate and thereby allowing genes to be found that can control a particular characteristics of an

organism. By disparating these genes from the original source and transferring them directly to the cells of an animal, plant, bacteria or virus, offering an exciting possibility for advancement in global pest and disease management, however, the introduction of these genetically modified beings into the environment can bring environmental and ecological consequences. It is of great importance to rigorously evaluate the possible associated risks, providing means and structures to identify possible ecological effects on the evolution of resistance, immunity and transient changes in the interactions of genetically modified insect species. The use of genetically modified organisms is of great importance to meet the growing demands existing on our planet, we are living in a time of anxiety where we want to solve problems, on the one hand we are comforted by threats to health and the human environment, on the other hand, we see new alternatives to change the way things are, so we need vital monitoring and detection methods to assess and manage the risks of using genetically modified organisms. The spread of these transgenic mosquitoes, whose effects, particularly on biodiversity components are difficult to estimate and worse, can be irreversible, causing exposure of species to new pathogens or toxic agents, elimination of non-domesticated species, generation of superpests or genetic pollution among others. Given that these transformations or modifications of living beings in laboratories are new techniques and that so far it is impossible to know what the long-term consequences will be. And faced with the challenge of finding new alternatives to control a pathogen, scientists have been forgetting one thing, life will always find a way to adapt.

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