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Engineered mosquitoes to fight mosquito borne diseases: not a merely technical issue

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Malaria, dengue and other mosquito-borne diseases pose dramatic problems of public health, particularly in tropical and sub-tropical countries. Historically, vector control has been one of the most successfully strategies to eradicate some mosquito-borne diseases, as witnessed by malaria eradication in Mediterranean regions such as Italy and Greece. Vector control through insecticides has been used worldwide; unfortunately, it is losing effectiveness due to spread of resistances. Control of mosquito-borne diseases through field-releases of genetically engineered mosquitoes is an innovative and now feasible approach. Genetically modified mosquitoes have already been released into the wild in some regions, and protocols for this release are on hand in others. Local authorities are vigilant that transgenic insects in the field are safe for human and animal populations, and the public engagement in every control program is assuming a central role.

Keywords: malaria, mosquito, public engagement, transgenesis, vector-borne diseases

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Introduction

Numerous species of mosquitoes are vectors of human and animal pathogens responsible for malaria, dengue, yellow fever, chikungunya, filariasis and other diseases. They are a major global concern in public health, and integrated programs centered on vector control provide an effective barrier to their spreading.[1-3]

A paradigmatic example of a successful vector control is malaria eradication in Europe and North America. In the history of the Italian Public Health, malaria eradication is unanimously regarded as one of the major achievements. At the end of the 19th century, malaria was widespread in a large part of Italy. Malaria deaths numbered 15,000–20,000 per year, and the malaria cases amounted to 2 million, i.e., nearly 7% of the entire population.[4] The last outbreak occurred in Sicily in 1955, and the last sporadic cases were reported in 1962 in the same area.

A drastic reduction of malaria endemism (anticipatory of a complete eradication) was mainly determined by the approval of laws of strong social impact approved by the Italian Parliament in the first half of the 20th century. Two laws were particularly effective. They regulated the production and free distribution of quinine, and promoted actions to reduce the breeding sites of larvae of *malaria* vectors.

Political decisions resulting in substantial social and economic modifications were of key importance for malaria eradication also in other European and North-American countries.

An even more decisive factor for the success of malaria eradication in Italy, was the involvement of citizens and workers (a matter that cannot be taken for granted and needs ad hoc persuasive actions). In Sardinia, for example, even though few people had technical expertise, some people was recruited and trained as disinfectors, larva scouts, and sprayers while others were enrolled to perform supply, transport, and administrative services.[5]

This happened during the early stages of the eradication campaign, when citizens and workers got only general information about the eradication program. This inadequate information resulted in a scarce motivation among workers, and pushed for a more exhaustive circulation of information and a deeper consultation of municipal authorities and skilled workers.[5]

In this regard it should be emphasized that a fair and accurate information regarding specific programs to fight vector-borne diseases is essential for their implementation. On the contrary, lack or incomplete information may strongly affect program effectiveness. This is well represented by example of New Delhi, where a lack of proper communication on a sterile male release program for the eradication of *Aedes aegypti* turned out to be a complete failure because of a climate of suspicion based on false statements that have gone accrediting over time.[6]

Transgenic Mosquitoes and Malaria Control

To date, malaria control programs based on the use of drugs and insecticides, meet severe limitations due to resistance developed by parasites and vectors. New methodologies have been developed and some of them are being evaluated for their use in the field. In this context, particular attention has been attracted by methodologies that are based on genetic modifications either of mosquitoes, and the mosquito microbiota, and directed to block transmission. Obviously, these approaches raise several ethical implications that have to be properly addressed prior to their structural integration in malaria control programs.

People argue that much of the controversy on biotechnological applications and genetic engineering is a consequence of a general inability to properly deal/cope with ethical and social issues in a systematic way.

In 2005, Macer[7] stated that: "*The approach to genetically modify insects raises few intrinsic ethical issues; however, important environmental and human health concerns need to be assessed before release of any GM insects. The policy that each community adopts should be the product of open dialogue involving all sectors of society. It can be expected that this process will take years and not all communities will endorse genetic control approaches to insect vectors.*"

Nevertheless, field release of Genetically Modified (GM) mosquitoes directed to defeat dengue infection has already been performed in the Cayman Islands, Malaysia and, on a larger scale, Brazil.[8]

Ethical concerns about field release of GM mosquitoes touch a variety of aspects, some of which relate to technical problems. For example, "what about horizontal and cross/inter-species gene transfer?" Others problems reflect assessment of unpredictable risks. Some people are worried that genetic modifications may alter the mosquito blood feeding behavior. Other concerns invest more the philosophical and/or religious sphere. It is a diffused opinion that humans should in no way alter their ecosystem. Followers of some religions are prevented from killing insects. Other people consider any living organisms (insects included) not a tool in the hands of humans for "their own purposes."[9]

These doubts and concerns reflect different backgrounds relevant to experts in the field, government officials, members of institutions responsible for the control of public health, ordinary citizens with different degrees of education, and others.

Public engagement and consensus are thus a strategic and pre-requisite to set-up an effective campaign of field-release GM mosquitoes. If a large public consensus will run together with political decisions, these interventions may become feasible and will not give rise to disputes as occurred in previous experiences.[10]

With more work preliminarily done to define risk assessment, it will be easier to properly inform public and representatives of government and institutions.

In this frame, simulation modelling appears to be particularly strategic. For example, the use of semi-field studies performed in large cages (also known as MalariaSphere) may be of great efficacy in evaluating dynamics of trans-gene spreading and monitoring phenomena of horizontal gene transfer (HGT). Some very useful studies, while investigating the feasibility of GM mosquitoes based approaches do not propose field release. One example refers to the study of Lavery and colleagues aimed to i) establish a field site for genetic control trials, among several potential sites characterized by proper dengue epidemiology and Ae. aegypti ecology and ii) test the interaction of genetically modified and local wild-type mosquitoes, using both laboratory cages and in large cage trials at the field site.[11] This type of approach is very useful to assess the relative fitness of GM mosquitoes and to monitor the spread of effector genes intended to block pathogen transmission and reduce/eliminate vector populations.

We have recently carried out a survey in Burkina Faso (West Africa) to assess the receptiveness to the use of GMOs and GM mosquitoes in particular.[12] Burkina Faso is one of the 48 African countries that have signed the Cartagena Protocol on Biosafety and adopted principles from the African Union's Model Law on Biosafety of 2001. Also in 2003 it introduced transgenic cotton in relation to a project that incorporated policies on public engagement.

Our survey has clearly pinpointed that the use of GM Mosquitoes would be welcome at the condition that the characteristics of the GM mosquitoes are properly specified and justified. On the other hand, some people appeared to be not totally aware of possible environmental negative aspects consequent to the release of GM Mosquitoes, as well as of how GM mosquitoes work once they are released in the wild.

The data that we have collected in Burkina Faso closely reflect those described by Marshall and collaborators[13] in relation to a study performed in Mali. The majority of the interviewed people were open to a release of GM mosquitoes for malaria control. However, they were eager to be previously ensured about safety and efficacy of the technology, and possibly trough preliminary trials.

In terms of public consultation and engagement, the Malaysian experience is a good reference study. It shows that a certain degree of dissatisfaction is inherent in this type of approaches, as pointed out also by Subramaniam and collaborators[14] in reporting that "*Our [Their] experience showed that despite executing a well-planned transparent public engagement process that was relevant for a release in an uninhabited site, there was still some dissatisfaction from some community groups.*"

One more important aspect is related on how researchers working with GM mosquitoes perceive the public involvement on their research. This issue has been properly addressed by Christophe Boete through a questionnaire monitored how scientists working on malaria and its vector mosquitoes perceive public opinion and how they evaluate public consultations on their research. Interestingly this study pinpointed that even if malaria researchers agree to interact with a non-scientific audience, they are reluctant "*to have their research project submitted in a jargon-free version to the evaluation and the prior-agreement by a group of non-specialists.*"[15]

In conclusion, as underlined by Alphey & Alphey [16] "*It's not just the genetics,*" and the use of GM mosquitoes, as any new technologies, should match public acceptance. Ethical, legal and social issues have to be addressed upstream any field release, so as it is mandatory to take in proper consideration normative, cultural and epidemiological characteristics of the region in which the field trail is going to be performed. In many cases, the commitment of local people involves communities with high levels of illiteracy and little knowledge of the modes of transmission of malaria and other mosquito-borne diseases. Nevertheless, this commitment has to be organized in such a way that these communities are convinced to be the major beneficiaries of the trial.

Given this context, the involvement of governmental officers and local scientists can be of enormous help to achieve a sustainable and effective epidemiological impact of the use of GM mosquitoes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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