GM mosquitoes in Burkina Faso

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Genetically modified (GM) mosquitoes were exported from Imperial College in London to Burkina Faso in November 2016. They are currently in "contained use" facilities in Bobo-Dioulasso, and they are being used in experiments by a research consortium called Target Malaria.[1] The project already received a permit from the National Biosafety Agency (under the Ministry of Higher Education, Scientific Research and Innovation, MESRSI) to import the GM mosquitoes into Burkina Faso for contained use experiments. The Institut de Recherche en Sciences de la Santé (IRSS) in Burkina Faso is a member of Target Malaria and will be making an application to release the GM mosquitoes into the environment in 2018; most likely in the village of Bana, west of Bobo-Dioulasso.[2]

About the Target Malaria project

Target Malaria is a consortium of research institutes that receives core funding from the Bill & Melinda Gates Foundation and the Open Philanthropy Project Fund, an advised fund of Silicon Valley Community Foundation. Individual laboratories also receive additional funding from a variety of sources to support each laboratory's work, including the United Kingdom government (the UK Department of Environment, Food and Rural Affairs and the Medical Research Council), the Wellcome Trust (a UK-based charity), the European Commission, the Ugandan Ministry of Health, and the Uganda National Council for Science and Technology (UNCST).[3]

Target Malaria also works in Mali and Uganda, but, to our knowledge, has not yet sent any GM mosquitoes to these countries.

Target Malaria's ultimate aim is to make open releases of "gene drive" mosquitoes, with the aim of reducing the population of *Anopheles gambiae* mosquitoes, which can transmit the parasite that causes malaria. The hope is that reducing the mosquito population will reduce the risk of malaria transmission and hence disease incidence. "Gene drive" is a way of trying to spread genetically engineered traits through a whole population of plants or animals (in this case, mosquitoes). In this project, the aim of the gene drive is to spread a genetic trait that biases the sex ratio of the mosquito population towards male mosquitoes, thus suppressing the mosquito population. However, the technology to do so does not yet exist and may not be successful. There have been many warnings, including from scientists working in the area of gene drive, that gene drive may be uncontrollable and could have unintended consequences, and civil society organisations have called for a moratorium on this technique.[4]

Target Malaria says it will take a phased approach to its ultimate aim of releasing gene drive mosquitoes, beginning with the first phase, the proposed release of 10,000 GM "male-sterile" (and non-gene drive) mosquitoes this year, followed by a second phase in which a second type of (non-gene drive) GM mosquito will be released into the open. This second phase is intended to bias the mosquito population to be male only so that matings of the GM mosquitoes with wild females will mainly produce male offspring. In the third and final phase, which involves either male bias or female infertility combined with gene drive, the gene drive mosquitoes will be released. It is unclear whether this third stage will ever be reached, let alone whether it can be effective. In the meantime, any release of GM mosquitoes will carry risks.

All three proposed phases involve releasing GM mosquitoes with traits that are intended to reduce the target population of *Anopheles gambiae* mosquitoes (known as "population suppression"). However, Target Malaria does not expect the phase one releases to actually reduce the *Anopheles gambiae* mosquito population. Whether phase three can do so, will depend on how well the gene drive works. However, there is already scientific evidence that gene drive is unlikely to work, because resistance to the gene drive will evolve, preventing some mosquitoes from inheriting the modified genes.[5,6,7,8] Thus, the benefits of the project overall are extremely speculative.

Potential impact of population suppression on malaria

The first proposed release of GM mosquitoes is not expected to make any difference to the number of wild mosquitoes that can bite and transmit disease (see further below). But even if releasing future versions of GM mosquitoes were to be successful at reducing the numbers of wild mosquitoes, how reducing the population of *Anopheles gambiae* mosquitoes will impact on the risk of malaria is not fully understood.

One complication is that several different *Anopheles* mosquito species can transmit malaria. Other relevant species in Burkina Faso include *Anopheles arabiensis* and *Anopheles funestus*.[9] Reducing only one species of mosquito could mean that mosquitoes from another malaria-transmitting species may move in to take its place, continuing disease transmission and perhaps being harder to eradicate. However, it is also possible that released GM *Anopheles gambiae* mosquitoes can mate with these other species and perhaps transfer the modified genetic trait to them.

Another issue is human immunity and timing of infection, which can lead to a "rebound effect". Where people have a high exposure to malaria, most are infected as children and build up some immunity before adulthood. Because primary malaria infections in adults cause more severe disease than in children, in the longer term, a reduction in mosquito numbers could – in theory – result in an increase in malaria in adults, if fewer people are infected while they are children.[10] If this happened, the long-term effect of future GM mosquito releases could be harmful to the local population.

About the GM mosquitoes proposed for release in phase one in 2018

The GM mosquitoes proposed for release this year are *Anopheles gambiae* mosquitoes, which have been genetically modified to be male-sterile by a construct that incorporates the I-PpoI Homing Endonuclease Gene (HEG). Target Malaria reports that these GM mosquitoes have shown 100% infertility: stating that, to date, all eggs laid by females that have mated with these GM male mosquitoes have been infertile.[11] Two scientific papers have been published about these GM mosquitoes, including some trials of population suppression conducted in cages in the United States.[12,13]

As part of the "contained use" experiments that have taken place so far, the laboratory in Burkina Faso has mated the imported GM mosquitoes with local wild mosquitoes. The proposal to release 10,000 of these male-sterile GM mosquitoes is a training exercise for the researchers; Target Malaria says that the mosquitoes will not be used for malaria control. This is because repeated large releases would be needed to seek to suppress the wild population of mosquitoes, which, even if successful, would be prohibitively expensive.[14] The same report also notes that, in Bobo-Dioulasso, *Anopheles arabiensis* (not *Anopheles gambiae*) has become the major malaria vector.

Therefore, the proposed releases in 2018 are not intended or expected to provide any direct benefit to the local population in terms of malaria control. Conducting experiments with no potential benefit may be regarded as a waste of time and money, and is unethical.

Lack of a transboundary notification?

Under European Union (EU) law, Imperial College should provide a publicly available environmental risk assessment that meets European standards before exporting GM insect eggs for open release to foreign countries. This legal requirement arises because GM insect eggs are live genetically modified organisms (living modified organisms or LMOs) covered by the Cartagena Protocol on Biosafety (CPB) to the Convention on Biological Diversity, to which the UK and Burkina Faso are both Parties. The relevant legal requirements for export are implemented in the UK through the European Regulation (EC) 1946/2003 on transboundary movement of genetically modified organisms.[15] This Regulation requires that the environmental risk assessment (ERA) provided by the exporter meets the EU standards on risk assessment contained in EU Directive 2001/18/EC[16].

For GMOs that are not plants, a list of issues that must be covered in the risk assessment by the exporter is included in Annex II, D.1 of the Directive. Guidance published by the European Food Safety Authority (EFSA) outlines the issues and evidence that Imperial College would need to provide in the ERA.[17] Pages 73 to 107 of the EFSA guidance provide details on the following specific areas of risk of GM insects:

- Persistence and invasiveness of GM insects, including vertical gene transfer (VGT);
- Horizontal gene transfer;
- Pathogens, infections and diseases;
- Interactions of GM insects with target organisms;
- Interactions of GM insects with non-target organisms (NTOs);
- Environmental impacts of the specific techniques used for the management of GM insects; and
- Impacts of GM insects on human and animal health.

Regulation (EC) 1946/2003 is important because it requires the exporter (in this case, Imperial College) to provide a comprehensive, publicly available risk assessment that meets EU standards, for GMOs intended for release into the environment. However, it appears that Imperial College may argue that it is not required to make a transboundary notification that includes such a risk assessment for the proposed release of male-sterile GM mosquitoes in Burkina Faso, because the GM mosquitoes were exported for an initial period of contained use (for which a notification is not required) before release. This interpretation would make a nonsense of the Cartagena Protocol and the legal requirements that follow from it, because GMOs exported for contained use could subsequently be released into the environment without meeting the requisite risk assessment standards.

Other risk assessment requirements and regulation

Burkina Faso has adopted a law and regulations covering genetically modified organisms (GMOs).[18] The law requires a risk assessment to be conducted before any open release of GMOs. However, there is no specific national guidance on how to conduct a risk assessment for GM mosquitoes, or what public consultation is required.

EFSA's risk assessment guidance is directly relevant to any export of GM mosquitoes from the UK, since Regulation (EC) 1946/2003 requires the exporter (i.e. Imperial College) to meet EU standards. However, other guidance also exists. Under the CPB, the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management has produced guidance on the risk assessment of genetically modified mosquitoes.[19] In addition, relevant academic papers that discuss the risk assessment of GM insects, including GM mosquitoes, include Reeves et al. (2012)[20] and David et al. (2013)[21].

To date, Target Malaria has published only a risk assessment related to the "contained use" of the GM mosquitoes, as required by the law in Burkina Faso. However, it has stated that it will also publish a risk assessment for the proposed open releases, conducted by the Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO). Whether or not there is a published risk assessment by the exporter (Imperial College) that meets EU standards, as required by the implementation of the transboundary notification requirements in EU law, remains to be seen.

Public engagement and fully informed consent

The World Medical Association's Declaration of Helsinki outlines the internationally agreed ethical principles for medical research involving human subjects.[22] It includes requirements that:

> "*17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.*
> *Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.*"

And:

> "*26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study…*"

Although Target Malaria says it is engaging local populations and obtaining their consent, consent must be fully informed to meet ethical requirements. This cannot be the case until a comprehensive risk assessment has been published and opened for public consultation. Further, the benefits of any trial should outweigh the risk. This does not appear to be the case with this proposal, since Target Malaria acknowledges that there are no benefits to the proposed GM mosquito release.

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