TARGET MALARIA

A Vector Control Research Alliance

Making lab and field progress towards the development of gene drive mosquitoes for malaria control in Africa

- Dr. Mamadou Coulibaly

Principal Investigator, Target Malaria Mali

- VCWG RBM Meeting

Target Malaria: who we are

- A not-for-profit research consortium, including:
  - Scientists from a wide range of disciplines i.e. molecular biologists, medical entomologists, population biologists, modellers and social scientists
  - Risk, regulatory, project management, communications, and stakeholder engagement experts
  - Teams from Africa, Europe, and North America
- A vision: To develop and share new, cost-effective and sustainable genetic technologies to modify mosquitoes and reduce malaria transmission
- Values: Excellence, co-development, evidence-driven, open & accountable

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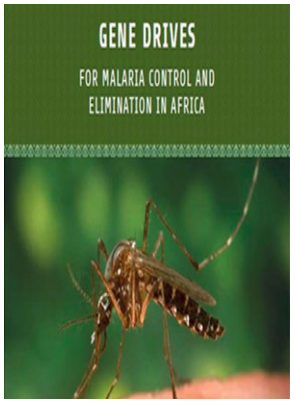
International support to innovation in vector control – AU and WHO

- Gene drive research is encouraged by the African Union (AUDA-NEPAD, 2018)



- Oct- 2020 WHO position statement encouraging research on innovative vector control tools including genetically modified mosquitoes

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Recent Progress

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Small scale release of non gene drive genetically modified mosquitoes

- July 1, 2019 in the Village of Bana in Burkina Faso
- Permission from the National Biosafety Agency and from the Ministry of Environment
- Agreement from the community of Bana after several years of engagement
- The release had two main learning objectives:
  - to estimate the daily survival rate of male mosquitoes of the sterile male strain,
  - to understand the nature of their dispersal in and away from the release village.
- It also aimed at building a dialogue with the authorities and affected communities about genetic approaches to malaria control.

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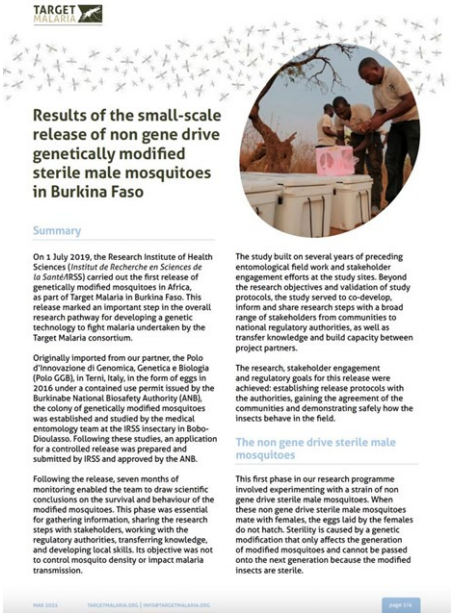
Results from the release of non gene drive genetically modified mosquitoes

- 20-day daily recapture and 7 months of monitoring
- Recaptured in swarms (important for reproduction)
- Recaptured inside homes for shelter
- Did not disperse beyond the release village boundaries and less mobile than wild-type
- Did not survive as long as their released non-modified siblings.
- Complete disappearance
- Scientific publications coming up (on entomology, laboratory and stakeholder engagement

Next step: import of non gene drive genetically modified male bias mosquitoes by Burkina Faso and Uganda after regulatory approvals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Results of the small-scale release of non gene drive genetically modified sterile male mosquitoes in Burkina Faso

Summary

On 1 July 2019, the Research Institute of Health Sciences (*Institut de Recherche en Sciences de la Santé*/IRSS) carried out the first release of genetically modified mosquitoes in Africa, as part of Target Malaria in Burkina Faso. This release marked an important step in the overall research pathway for developing a genetic technology to fight malaria undertaken by the Target Malaria consortium.

Originally imported from our partner, the Polo d'Innovazione di Genomica, Genetica e Biologia (Polo GGB), in Terni, Italy, in the form of eggs in 2016 under a contained use permit issued by the Burkinabe National Biosafety Authority (ANB), the colony of genetically modified mosquitoes was established and studied by the medical entomology team at the IRSS insectary in Bobo-Dioulasso. Following these studies, an application for a controlled release was prepared and submitted by IRSS and approved by the ANB.

Following the release, seven months of monitoring enabled the team to draw scientific conclusions on the survival and behaviour of the modified mosquitoes. This phase was essential for gathering information, sharing the research steps with stakeholders, working with the regulatory authorities, transferring knowledge, and developing local skills. Its objective was not to control mosquito density or impact malaria transmission.

The study built on several years of preceding entomological field work and stakeholder engagement efforts at the study sites. Beyond the research objectives and validation of study protocols, the study served to co-develop, inform and share research steps with a broad range of stakeholders from communities to national regulatory authorities, as well as transfer knowledge and build capacity between project partners.

The research, stakeholder engagement and regulatory goals for this release were achieved: establishing release protocols with the authorities, gaining the agreement of the communities and demonstrating safely how the insects behave in the field.

The non gene drive sterile male mosquitoes

This first phase in our research programme involved experimenting with a strain of non gene drive sterile male mosquitoes. When these non gene drive sterile male mosquitoes mate with females, the eggs laid by the females do not hatch. Sterility is caused by a genetic modification that only affects the generation of modified mosquitoes and cannot be passed onto the next generation because the modified insects are sterile.

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Important progress in risk assessment

- Systematic identification of plausible pathways to potential harm
- Building on the results of a series of NEPAD workshops with African regulators and other workshops organized by FNIH
- Based on simulated release of the *doublesex* gene drive mosquito strain in West Africa
- Uses “problem formulation”, a rigorous scientific analysis
- Initial step in Environmental Risk Assessments
- Identified 46 potential pathways to harm to 4 “protection goals”: human health, animal health, biodiversity and water quality.
- Most common potential harms: increased human or animal disease transmission
- Will inform the next stages of an environmental risk assessment, a critical component of a regulatory dossier

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Malaria Journal

RESEARCH Open Access

Systematic identification of plausible pathways to potential harm via problem formulation for investigational releases of a population suppression gene drive to control the human malaria vector *Anopheles gambiae* in West Africa

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Abstract

Background: Population suppression gene drive has been proposed as a strategy for malaria vector control. A CRISPR-Cas9-based transgene homing at the *doublesex* locus ($dsxF^{CRISPRh}$) has recently been shown to increase rapidly in frequency in, and suppress, caged laboratory populations of the malaria mosquito vector *Anopheles gambiae*. Here, problem formulation, an initial step in environmental risk assessment (ERA), was performed for simulated field releases of the $dsxF^{CRISPRh}$ transgene in West Africa.

Methods: Building on consultative workshops in Africa that previously identified relevant environmental and health protection goals for ERA of gene drive in malaria vector control, 8 potentially harmful effects from these simulated releases were identified. These were stratified into 46 plausible pathways describing the causal chain of events that would be required for potential harms to occur. Risk hypotheses to interrogate critical steps in each pathway, and an analysis plan involving experiments, modelling and literature review to test each of those risk hypotheses, were developed.

Results: Most potential harms involved increased human (n = 13) or animal (n = 13) disease transmission, emphasizing the importance to subsequent stages of ERA of data on vectorial capacity comparing transgenics to non-transgenics. Although some of the pathways (n = 14) were based on known anatomical alterations in $dsxF^{CRISPRh}$ homozygotes, many could also be applicable to field releases of a range of other transgenic strains of mosquito (n = 18). In addition to population suppression of target organisms being an accepted outcome for existing vector control programmes, these investigations also revealed that the efficacy of population suppression caused by the $dsxF^{CRISPRh}$ transgene should itself directly affect most pathways (n = 35).

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Developing a first candidate gene drive mosquito QFS2 – *doublesex* gene

- Targets 2 locations in the *doublesex* gene with CRISPR-Cas9
- Homozygous females completely sterile and cannot bite
- Heterozygous females fertile and low fitness cost
- Successful population suppression in small cages at Imperial College London (Crisanti Lab)
- Testing in large cages at PoloGGB in Italy ongoing to verify population suppression in closer to nature conditions
- Based on previous *doublesex* strain with single target (Kyrou et al 2018)
- Potential candidate for the first Target Malaria gene drive

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Capacity building in Africa

- Training
- Infrastructures

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For more information

- Website https://targetmalaria.org/
- Twitter @TargetMalaria 

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