Gene drive for malaria vector control – from lab to application

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Why Malaria?
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African Experts
Using Insects To Do The Work
- Genetic Control

**Population suppression**
Elimination or reduction of a wild vector population

**Population replacement**
Replace a pathogen-susceptible vector population with pathogen-resistant insects

Released insects do the hard job of finding difficult to reach insect niches
Species-specific
Non-toxic

Suppression and replacement strategies can be combined
Two strategies of using nucleases

Driving Y chromosome

Based upon naturally-occurring driving Y in *Aedes*

Will gradually convert a population so it is almost all males

Gene knock-out by homing

Target gene

Germline promoter

Nuclease will cause population-wide knock-out of target gene (fertility or viability)

Both approach can suppress mosquito population
Gene drive testing hurdles

- Stakeholder Engagement
- Risk Assessment
- Science Bench
- Regulatory
- Science Field

Legal and ethical issues
Technical challenges
Safety Issues

« Safety deficiency is the one aspect that might not be easily remedied. One can gather more baseline data, one can lobby for political support and build capacity etc. but if we cannot provide a plan that people consider safe, the effort is really dead ».

Mark Benedict

Consequences of the release of gene-drive should be ascertained on a case by case basis (WHO 2014)
Built on three pillars

Science
Regulatory
Stakeholder engagement
Pathway for testing each phase

Sterile male – self limiting
- Genetically modified
- NO gene drive
- Learning phase
- No impact on malaria mosquito numbers

Self limiting – male bias
- Genetically modified
- Only persists for a few generations
- NO gene drive
- Currently only available for the male bias option

Self sustaining male bias &/or female fertility
- Genetically modified
- With drive
- Potential long-term and sustainable impact on malaria-mosquito numbers

- Contained laboratory experiments in London
- Large Cage experiments in Italy
- Safety Studies - off continent
- Contained laboratory experiments in Africa
- Small scale open field releases in Africa
Insectary readiness: Toward GMM importation

Burkina Faso
Factors were measured against general lab practice, specific TM policies or SOPs, national requirements on containment facilities to the degree these are known, or international practices when other guidance is not available.
Sterile male eggs importation
Contained use studies in Burkina Faso

- Establish colony and introgression into ‘local’ wildtype population (An.coluzzii = Ac(DSM)2)
- Insecticide Resistance testing
- Analysis of sexual sterility
- Life history
- Mating competitiveness
Stakeholder Engagement Challenges
Civil society

- Burkina Faso has a very active civil society
- Constitution-modification (2014)
- Removal of the president (2014)
- Protest against military coup (2015)
  - Collapse of the military coup

Social and political landscape analysis

- Map of different group of civil society
- Determine groups leaders
- Determine intervention fields of groups
- Determine pro GMO groups
- Determine Anti GMO groups
- Analyze impacts of civil society actions in national debates
Intentional bad Communication to create Psychosis

- Target Malaria will release Monster-Mosquitoes that will eat all the wild mosquitoes. Who is next after wild mosquitoes are all eaten?

- Target Malaria will release male mosquitoes to induce sterility in female mosquitoes. What will happen to our wives when they get bitten by these sterile mosquitoes?

- Target Malaria mosquitoes have brought Dengue to Burkina Faso. You can expect worse. How about HIV?
Field site
This is where the real work is happening, but most likely the real troublemaker will be coming from outside.

Reinforce the SE work at both level but protect your sites from an outside intoxication.
The Pyramidal Structure of Stakeholder Engagement

NATIONAL
- Government Authorities
- Civil Society

REGIONAL (HAUTS-BASSINS)
- Administrative Authorities
- Governor
- Municipalities
- Préfecture
- Health Authorities (DRS-District)

STUDY SITES
Stakeholder Engagement Strategy

Step by step progression

An inclusive engagement

Full transparency to build trust
Ministries and Parliament
Municipalities
Traditional and Religious Authorities
Journalists
NGOs
Villages
Other studies/information for deliberate release dossier

- Molecular characterization – single copy
- Genetic stability – 140 generations
- Mendelian inheritance confirmed
- Tissue specificity of expression – only in testes
- Bioinformatics on toxicity and allergenicity potential of introduced proteins
- Interspecific crosses

- Detailed information on release site
- Non-target /valued and charismatic species habitat analysis
- Stakeholder engagement and socio-economic impact assessment

Next Step: Small scale field release of sterile males
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