COMMENTARY

The Release of Genetically Engineered Mosquitoes in Burkina Faso: Bioeconomy of Science, Public Engagement and Trust in Medicine

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Malaria, which is transmitted by mosquitoes, continues to be responsible for a significant number of disease episodes and childhood deaths on the African continent. A variety of mosquito control strategies are currently in

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place, but since case numbers are rising again, and drug and insecticide tolerance slow down progress made, there has been a push for innovative strategies. In August 2018, the National Biosafety Agency of Burkina Faso granted approval for the release of a maximum of 10,000 male *Anopheles* mosquitoes in experimental trials conducted by the multi-country consortium Target Malaria. These mosquitoes are rendered infertile through genetic modification, namely through "re-programming" of endonucleases that "cut through essential genes," in this case, genes for fertility (Target Malaria 2019). The idea is that through the sterilization of male mosquitoes, the population of malaria-transmitting mosquitoes will be reduced, thereby decreasing the overall number of malaria infections.

However, Target Malaria admits that the more pertinent reason for these initial releases is to prepare for scientifically more ambitious releases of gene-drive mosquitoes that would be engineered to stop malaria transmission. These mosquitoes would then be labeled transgenic, as they are fertile and their genetic modification would be able to spread into wild populations. This solution is considered scientifically elegant by many, as it turns the disease vector into a "public health tool" (Beisel & Boëte 2013). However, in its elegance also lies its risk, as the genetic modification spreads and reproduces "naturally." These genetically-driven technologies are rapidly progressing, but at the moment they are not yet ready for field trials.

As of July 1, 2019, genetically sterilized mosquitoes have begun to be released in two small villages in northwest Burkina Faso. This intervention is the first of its kind on the African continent, although genetically engineered eggs have been imported since 2016 to laboratories of the *Institut de Recherche en Sciences de la Santé* (IRSS) in Bobo-Dioulasso. These mosquitoes were developed at Imperial College London. The consortium Target Malaria, which has developed the genetically modified (GM) mosquito and is tasked with their release, has been funded by the Bill and Melinda Gates Foundation since 2005 (USD35 million) and by the Open Philanthropy Project (funded mainly by contributions from the co-founder of Facebook and Asana) since 2017 (USD17.5 million) (Dunning 2017).

Regulatory approval was preceded by some small-scale protests, both internationally (e.g., The African Centre for Biodiversity 2018), and regionally, by the *Coalition pour la protection du patrimoine génétique africain* (COPAGEN) and *Terre à Vie*. This program was discussed at the UN conference of the Convention on Biological Diversity (CBD) in November 2018. The Convention was responsible for developing the Cartagena Protocol, an international treaty governing the movements of living engineered organisms, which came into force in 2003. At the 2018 conference, non-governmental organizations and activists tabled a proposal for a moratorium on the release of gene-drive organisms, which was ultimately rejected. While the planned release does not involve gene-drive organisms, it was nevertheless the trigger for the proposed moratorium. In response, over one hundred scientists signed an open letter opposing this initiative (Outreach Network for Gene Drive Research 2018).

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In this commentary we critically assess the current release of GM mosquitoes in Burkina Faso. While wholeheartedly supportive of innovative approaches to malaria control, we argue that the potential and risks of genetically-engineered mosquitoes need to be understood in relation to funding for other malaria control interventions and the underlying bioeconomy of science and ecological dynamics of malaria, as well as the public engagement process and broader dynamics of trust in medicine in Africa.

Science and the bioeconomy of transgenic mosquitoes

While the program in Burkina Faso is the first release of engineered malaria-transmitting *Anopheles* mosquitoes and the first to occur on the African continent, it is not the first release of GM mosquitoes. Engineered *Aedes aegypti* mosquitoes transmitting dengue and Zika were first released in 2009, when an Oxford-based biotechnology company (secretly) conducted experiments in the Cayman Islands. Further releases have occurred in Malaysia and Brazil. Since 2012, a biofactory in Juazeiro, Brazil, has produced transgenic *A. aegypti* with capacity of four million male mosquitoes per week (Reis-Castro & Hendrickx 2013:125). When the Zika epidemic struck the Americas, genetically sterilized mosquito control efforts were intensified further.

The idea of releasing sterilized male mosquitoes in order to reduce insect populations is much older than genetic modification technology. Mosquitoes sterilized through irradiation have been released since the 1950s in efforts to control insect pests. Sterile insect technique (SIT) has been successfully used in eliminating screw-worm fly from the United States and Central America, in the control of the Mediterranean fruit fly, as well as during the Zika epidemic. Proponents of genetic sterilization often underline similarities to these initiatives; however, crucial differences exist. First, while the technology is commonly considered as "self-limiting" (since due to their infertility it is assumed genes cannot spread through the population), genetic sterilization is not 100 percent successful, and approximately 4 percent of the engineered mosquitoes have been found to be fertile and therefore capable of spreading into the wild population (Meghani & Boëte 2018).

Second, there is an insufficient number of peer-reviewed studies of these dynamics: "It is worrisome that, as of yet, there are no published peer-reviewed studies about the fitness of that subpopulation of GE insects or its progeny. Moreover, as of yet, there are no peer-reviewed published studies about the epidemiological efficacy of this mosquito that demonstrate that field trials resulted in lower incidence of disease in humans" (Meghani & Boëte 2018:2).

The issue of insufficient study is closely related to the economic dimensions of GM mosquitoes. The overwhelming majority of GM mosquitoes released to date are mosquitoes developed by the private biotechnology company Oxitech. Oxitech operates as a for-profit business—this means their scientific embedding is particular and not primarily focused on producing knowledge. It is for this reason that independent peer-reviewed ecological and epidemiological impact studies have not been done. The GM mosquito that

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will fly free in Burkina Faso is different, as it has been developed in a public university, and the research and implementation has been funded by philanthropic organizations. The consortium Target Malaria is therefore more closely aligned with scientific principles. For instance, the consortium commissioned an ecological impact assessment (Hayes et al. 2018), although this assessment was criticized for not including existing scientific and regulatory guidance (African Centre for Biodiversity et al. 2018:6ff). Partners of the consortium also started a USD3 million field study in Ghana on the ecological effects of reducing mosquitoes in the local environment. However, since the study team is also part of the Target Malaria consortium, the study cannot be considered fully independent and impartial. In any case, the current data on ecological dynamics of GM mosquitoes is limited to one review paper (Collins et al. 2019).

There is a second economic dimension pertaining to GM mosquitoes. The fact that this mosquito is self-limiting also means mosquitoes will need to be released regularly in order to sustain the diminishing effect on the overall local mosquito population. This means locking customers into regular payments for weekly releases in order to continue to suppress the wild population. Although the releases are funded by non-profit organizations, one might reasonably ask what are the long-term prospects of such technologies: will the BMGF and Open Philanthropy Project cover costs beyond the trial? Even if international organizations cover the initial phases, their support would not likely be long-term. Is the Burkinabè Ministry of Health able and willing to cover the ongoing (significant) costs of the procedure?

Here, it is relevant to remember that the program is not an experiment aimed to test and develop a future malaria control intervention, but rather to prepare for future trials of gene-drive mosquitoes. There is, of course, scientific merit to starting with less risky genetically-engineered organisms. However, from the perspective of the local population and national malaria control strategies, the benefits are less evident. On the one hand, African populations would be the long-term beneficiaries if a gene-drive technology were to offer a sustainable solution to mosquito-borne disease. It also makes scientific and operational sense to undertake interventions within many African contexts where the malaria burden is pronounced. On the other hand, conducting trials of high-end science, and of controversial and potentially non-reversible innovations in settings of poverty and with populations where many have had access to only basic education, is ethically challenging and requires careful public engagement.

How has the local population been informed, and are local populations in favor of the release?

The Target Malaria consortium employed an anthropologist for public engagement activities prior to field trials. While we found no engagement strategy on the corporation's website, and email inquiries remain unanswered, Target Malaria's Vimeo stream hosts two videos, in which two local residents provide statements in support of the project (https://vimeo.com/user26144953).

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In the first video, Komon Sanou, president of the Bana village development council, where mosquitoes are due to be released, shares his views on the project and gives insights into the engagement process that took place in the village. In the second video, Zerbo Madina, a resident in the laboratory neighborhood in Bobo-Dioulasso, emphasizes several times: "In a transparent way, they approached us to include us into their activities."

Two independent journalists who traveled to the area reported different experiences. Zahra Moloo documented how their team was first not allowed to enter the villages. When they persisted and spoke to some minority group farmers who lived on the Bana outskirts, they reported that they had heard of the activities taking place but had received no information from Target Malaria and no consent was asked of them. Moloo suggests that public engagement activities had only taken place in the center of the village and so had not included the entire village population, let alone surrounding communities. She analyzes the results of her investigative journalism as "cutting corners on consent" (Moloo 2019).

While we have been unable to conduct our own fieldwork in these sites and therefore cannot judge the quality of the public engagement, the case raises questions about who may consent to such processes? A standard approach to consent would require conversations and agreements with the entire populations affected. And this reflects a draft decision on Synthetic Biology: "Where appropriate, the 'prior and informed consent', the 'free, prior and informed consent' or 'approval and involvement' of potentially affected indigenous peoples and local communities is sought or obtained, where applicable in accordance with national circumstances and legislation" (Convention on Biological Diversity 2018 Paragraph 9c). But how to demarcate and define who is "affected" and what is "local" in this trial is not clear-cut. Is it as far as the mosquitoes can fly? While the flying range of mosquitoes has been shown to be limited to a few kilometers, mosquitoes have been highly successful in the past in utilizing the wind or hitching rides on ships, cars, or trucks to extend their reach.

Target Malaria has advocated a restrictive position on who is affected: "According to the organization, 'it's not logistically possible to obtain consent from each and every person affected' by the release of genetically modified mosquitoes" (Moloo 2018). In this context, activists from COPAGEN (a West African agricultural organization) have outlined their position: "Burkina Faso, and Africa by extension, should not be considered as a laboratory nor should the African people be seen as guinea pigs. We say it insistently, we do not want GMOs in our fields and on our plates, we do not want mosquitoes genetically modified who supposedly fight against malaria. These are false solutions to real problems" (Sikeli 2018). The suspicion of being treated as "guinea pigs" has a history, as it relates directly to experiences of colonial abuse (see, for example, White 2000), and to ongoing abuses, for instance, the recently documented blood and sample theft during the West African Ebola epidemic (Freudenthal 2019). More recently, the sponsoring global philanthropic organizations, notably the Bill and Melinda Gates

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Foundation, have been characterized as actively pursuing an agenda of the Global South as "a laboratory of technological experimentation" (Fejerskov 2017). In this context, it is crucial to ask what effects global health initiatives and philanthropic organizations have on underlying social, political, and economic inequalities? It is important to note that the question of whether one argues pro or contra genetic approaches should not be seen as a general question for *or* against technological innovations, but rather as tied up in a complex societal entanglement of science, economy, and democracy in *specific* settings in an unequal world. Attention to specificity would mean carefully considering the level of public engagement. We suggest a standard public health approach of science communication that informs the public about facts, benefits, and risks would not do justice to the complexities. Furthermore, being sensitive to the setting requires a "lively ethic" based on an acknowledgment of vital difference, not similarity of actors and settings (Nading 2015). For instance, the local population is highly diverse in terms of economic background and educational level, to name just two important factors that would need to be taken into consideration.

It is no coincidence that COPAGEN is protesting GM mosquitoes in the Burkinabè health sector. COPAGEN was already active in the country, when Burkina Faso showcased genetically altered cotton in smallholder agriculture. Monsanto partnered with the Burkinabè government in 2003 and started to introduce Bt cotton to farmers from 2008. In the years that followed, Bt cotton proved to be increasingly popular, and by 2013 Monsanto's Bt cotton market share rose to 70 percent (Dowd-Uribe & Schnurr 2016). However, the quality of Bt cotton gradually worsened in comparison to the renowned quality of conventional cotton in Burkina Faso. Ultimately, Bt cotton was phased out in 2015. Given this history, it seems a curious choice to conduct the first GM mosquitoes field trials in the same region where Bt cotton was introduced and ultimately failed.

How does genetic engineering relate to other malaria control and elimination strategies?

In a press conference, COPAGEN stated that "the best way to fight against malaria remains to put in place a good sanitation policy for our habitats and our environment." This statement raises the question of how genetic engineering relates to other malaria control and elimination strategies? This is, of course, a complex story that cannot be told in its entirety in this short commentary, but two points are worth making. The first one is that malaria control can be read as a story of constantly adapting strategies against two biologically complex and actively shifting and mutating species—the *Anopheles* mosquito complex and the *Plasmodium* parasite (Beisel 2015). The mutability and adaptability of the mosquito has in recent years become a major concern, because genetic, ecological, and behavioral mutations in *Anopheles* mosquitoes have created high levels of insecticide resistance used in bed nets and in spraying interventions (Hemmingway et al. 2016).

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This could serve as an argument in favor of developing genetic mechanisms of malaria control. However, it also can be read as its starkest warning: no matter what humans have so far done in order to control mosquitoes, there has always been a reaction, a mutation, a comeback of sorts.

A wide-ranging WHO and Nigerian government insecticide experiment from 1969 to 1976 in Garki is illustrative (Molineaux & Gramiccia 1980). The aim of that project was to determine the viability of disrupting the malaria transmission cycle through the reduction of mosquito densities via spraying. The results were very influential in debates surrounding the end of the malaria eradication program of the 1950s and 1960s, and often served as justification for a malaria control paradigm in the decades after. While the authors of that study had set out to achieve eradication of malaria in sub-Saharan Africa, the experiments showed that interrupting transmission was not possible. Although the presence of mosquitoes was reduced significantly by 90 percent, not only did this not reduce the presence of the parasite in the populations' blood to a similar degree, but the mosquitoes returned to earlier levels within two years. This is mainly due to biology: *Anopheles* mosquitoes lay approximately fifty to two hundred eggs per oviposition, and thus population numbers can increase swiftly under ideal conditions. These two issues together provide a strong case for extreme caution vis-à-vis genetic engineering success and sustainability. Genetically sterilized mosquitoes would need to be released regularly and in significant numbers to have a sustained effect on local mosquito densities (let alone malaria transmission rates). Moreover, insofar as *Anopheles* mosquitoes are a complex genus comprising about ninety genetically distinct (sub)species, it is unclear if a genetic modification would work in more than one (sub)species. Furthermore, as insecticide resistance shows, mutations and adaptations render mosquitoes among the hardiest organisms to control. These issues indeed speak to an urgent need for improving basic health infrastructures and environmental sanitation in malaria control.[1]

Genetically engineered mosquitoes and trust in medicine?

We suggest that three core issues regarding the Burkina Faso field trials require further consideration. First, it remains unclear how scientifically and ecologically sound the releases are. The sterilization rate is not 100 percent, and there has been little systematic research into the biological and ecological effects of genetically sterilized mosquitoes despite the worldwide releases. The bioeconomy to which the mosquitoes are tied is mainly driven by business interests and not science nor the public good. Although this particular trial is philanthropically funded, the data we have on effects so far is limited. What makes the current trial particularly challenging is the fact that the genetically sterilized mosquitoes released do not have a significant immediate public health benefit but relate to potential future benefits that transgenic mosquitoes promise.

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Second, what might a genuinely democratic decision-making process look like in a context of biological and ecological uncertainties? Trials of this nature are ideally complemented by a public engagement strategy and an independent and impartial scientific team. In our current comparative research project on trust in biomedicine in Sierra Leone, Ghana, and Uganda, we find that transparency and a genuine, open, and comprehensive engagement with the public are crucial factors leading to public trust or distrust of medical interventions (Park & Akello 2017). Public health education is here only one small part, and indeed not the most important one, for fostering trust. Rather, public health education and engagement are best conducted in a way that enables stakeholders to assess the issue at hand by themselves and "open up" debates, rather than to "close them down" by transferring seemingly uncontested/able knowledge (Stirling 2008).

Finally, the priorities in malaria control measures are dynamic and must be routinely reevaluated. The *Anopheles* mosquito is a complex and highly adaptive species that has been successful at evading human control measures, including selective genetic mutations. Local activists raise an important question when they ask if the financial investments made would not be better spent investing in robust and adaptive health infrastructures across the continent. These reservations are situated at an uneasy nexus of global health initiatives, focused on single diseases and evidence-based medicine on the one hand, and decades of experience with failed investments in international development in infrastructures on the other hand. Crucial questions remain regarding the engagement of Burkina Faso—and Africa as a whole—with transgenic mosquito trials. International consortia developing cutting-edge scientific interventions can do better as they situate their research and field trials within settings with limited public health infrastructure and poor populations. Such matters are crucial, not only to avoid the inevitable comparisons with colonial-era experimentation on African populations, but also with a view to fostering trust and equitable collaboration in biomedical innovations for the greater public good.

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Note

1. Although, as Eric Carter has convincingly shown, the connections and conflicts between "magic bullet" approaches (such as DDT spraying) and more "holistic" ecological and infrastructural approaches to malaria control have never been straightforward, but remain ambiguous and slippery (Carter 2012).

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