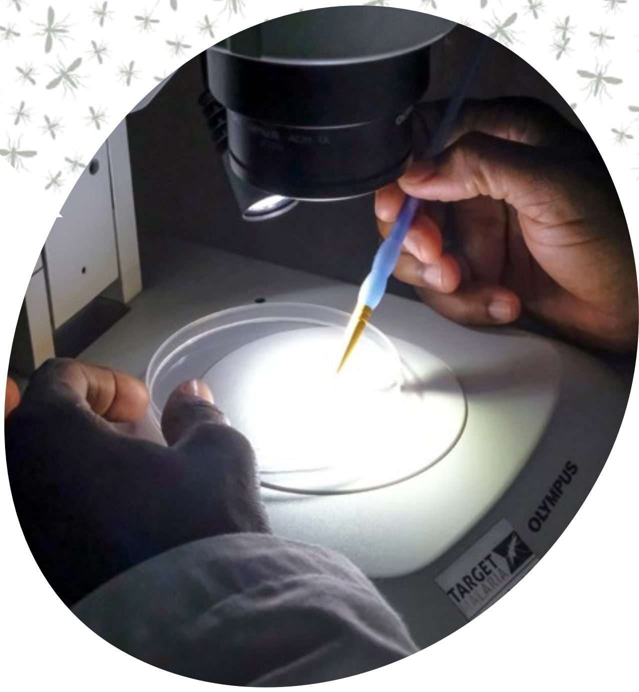
Potential human & environmental impacts of gene drive mosquito releases on other mosquito species



Target Malaria is working to develop and share novel genetic technologies to help control malaria in Sub-Saharan Africa. We aim to do so by developing and releasing genetically modified mosquitoes that carry a genetic trait that will result in the reduction of local malaria mosquito populations and which could complement existing methods of malaria control. Reducing the number of mosquitoes that can transmit the malaria parasite would result in fewer malaria infections.

Anopheles gambiae's role in malaria transmission

Malaria is exclusively transmitted by *Anopheles* mosquitoes. There are more than 400 different species of *Anopheles* mosquitoes in nature; but only around 30 to 40 are malaria vectors.[1] Amongst those, species in *Anopheles gambiae* complex are the most important vectors of human malaria in sub-Saharan Africa (notably *An. arabiensis, An. coluzzii* and *An. gambiae sensu strictu* (s.s)). These are the focus of Target Malaria's work.

Mosquitoes belonging to the *An. gambiae* complex are some of the most efficient vectors of human malaria because of their susceptibility to the *Plasmodium* parasite (the malaria parasite) and their preference for human blood and indoor-feeding. For example, in Burkina Faso, 50-100% of malaria transmission intensity is due to *Anopheles gambiae.*[2]

In addition to species in the *An. gambiae complex, An. funestus* is also an important vector of malaria in Africa. Though Target Malaria's current research does not tackle the issue of transmission by *An. funestus*, genetic control approaches are relevant to this species and could be developed in the future.

Ecological niches

All species live within an ecological community where they have roles, requirements, and interactions with other species; for example by eating dead insects or plant material, or being eaten by other insects, or through pollination. The combination of these needs and interactions is called a "niche". Multiple species often compete for the same limited resources, such as food or breeding sites, which can result in competitive displacement, where one species is prevented from occupying its full or preferred niche by another. In certain circumstances, following the removal of the displacing species, niche "expansion" can occur, where the displaced species is then able to expand its own niche.[3]

Since Target Malaria's approach is to reduce the population of *An. gambiae* to control malaria transmission, one of the important questions for the project is whether such a reduction would lead to the creation of an empty "niche" and if it could have a negative impact on the environment or on human health. For example, if another species occupies this niche, would it increase transmission of malaria or another disease? The findings from this research form part of the project's risk analysis and would be shared with regulatory authorities.

Niche displacement

In all malaria vector control programmes, such as those using insecticides, the common goal is to reduce the populations of *Anopheles mosquitoes* that carry malaria. Where *Anopheles* species already outcompete other species in their ecological niches and maintain their dominance even when reduced, there would not be any niche displacement. However, if the reduction is so extensive that it releases other species from competition, then another species could increase in number.

Competition between animals typically occurs over food and breeding. Since resources for the adult stages of mosquitoes, mostly blood and nectar, are generally not limited, existing scientific research suggests that if competition occurs, it would likely be over the more limited resource of aquatic breeding habitats.[4] Therefore, the most likely species to expand into the vacant ecological niches of *Anopheles* would be the ones that have similar breeding habitat requirements but are being outcompeted, either behaviourally or physiologically. The most likely candidates are other *Anopheles* species or other mosquitoes, such as *Culex* due to their co-occurrence in larval breeding sites.[5]

Impact on disease vectors

Vector control has been a widespread practice for many centuries, and insecticides - whether as part of bed nets or as part of indoor residual spraying campaigns - have been one of the most effective tools in reducing malaria transmission since the 1940s.[6] As a result, it is possible to look at the impact of previous vector control campaigns on local ecosystems to identify the possible impacts that using a gene drive approach to control *An. gambiae* could have.[7]

In some areas, vector control campaigns using insecticides have resulted in localised elimination of the malaria vectors.[8] Studies carried out to evaluate the ecological impact of reductions or localised eradications of mosquitoes from the *An. gambiae* complex indicate that there are limited effects in terms of niche expansion and they also do not reveal increases in malaria infections from other malaria vectors[9].

These findings are not surprising. Theoretically, it would be possible for other disease vectors to move into the unoccupied niche left after the reduction of *An. gambiae* mosquitoes. However, only a limited number of species both have similar larval breeding requirements to *An. gambiae* species and are human disease vectors.
As a result, there are very few species, if any, that might increase in number following increase in number and present and increased risk to human health, following *An. gambiae* reduction.

For example, *An. gambiae* favours breeding sites that are transient, shallow, sunlit and rural; whereas species of *Aedes* (a mosquito species responsible for transmission of diseases such as dengue, yellow fever, chikungunya and zika, but not able to transmit malaria), live and breed predominantly in man-made water containers in urban areas or tree stumps in forested areas. As the environments in which these species exist are so different, reducing the population of *An. gambiae* is not expected to allow *Aedes* species to expand in numbers. It is, nevertheless, possible that these two species may already coexist to some extent.

Should niche displacement occur following the reduction of mosquitoes in the *An. gambiae* complex because of the use of gene drive technology (as of any other control intervention), the most likely scenario would be for the niche of *An. gambiae* to be occupied by another species of Anopheles, outside of the *An. gambiae* complex. These other Anopheles could be vectors of some of the same diseases as *Anopheles gambiae*, (mainly malaria and lymphatic filariasis; and to a much lesser extent some arboviral infections such as O'nyong-nyong). Even then, *An. gambiae* is such an effective vector of human diseases that any increase in a displaced species is unlikely to wholly reverse the gains made.

Therefore, reduction of *An. gambiae* and any niche expansion of another species of *Anopheles* is unlikely to increase malaria incidence.

Assessing possible risks tied to niche displacement

Identifying and minimizing any potential risks from our technology is of paramount importance to Target Malaria. Risk assessment identifies potential pathways to harm that could have adverse health or environmental effects, evaluates the likelihood and magnitude of such potential harms occurring and highlights any further areas of uncertainty.[10] The question of niche displacement is being studied as part of the project's efforts to identify possible risks linked to the use of a gene drive approach for malaria control in sub-Saharan Africa.

As part of this effort, Target Malaria Ghana is working to understand ecological interactions between *Anopheles* and other species in the field. As we know that the primary area of competition between species is the aquatic habitat, we are looking at the effects of small-scale controlled experimental removals from that environment.

These field studies are being combined with reviews of previously published literature involving entomological and epidemiological studies of insecticide-based vector control programmes targeting *Anopheles* species in Africa to search for any evidence of increases in either the numbers of other disease vectors or the transmission of diseases following previous vector control programmes.

The findings that result from these studies will be part of Target Malaria's risk assessment for its technology. They will be published in peer-reviewed literature and shared with regulatory authorities as part of any request for permission to carry out releases of Target Malaria modified mosquitoes.

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