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COMMENTARY

Population modification of *Anopheles* mosquitoes for malaria control: pathways to implementation

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While considerable progress has been made in combating malaria, largely due to mosquito control measures such as insecticides, the disease is still a major burden and the inability of existing approaches to remain efficacious is a major concern [1]. As such, there is an urgent need for novel tools to curb malaria. Over the years many studies have shown that mosquitoes can be engineered to reduce *Plasmodium* infection [2], offering promise for population modification approaches to control malaria. However, a stumbling block for this strategy was the successful development of a robust gene drive system that could spread desirable genes through field mosquito populations. It appears this hurdle can be overcome with the CRISPR-Cas9 system, which has been used to spread alleles into lab populations of *Anopheles* mosquitoes [3,4]. While challenges to gene drive strategies have been highlighted [5–7], in principle, the two major elements required for population modification (interfering with *Plasmodium* transmission and spreading genes that induce this phenotype through mosquito populations) have now been demonstrated [2–4]. Given that genetic control strategies for mosquito vectors are within our grasp, focus needs to shift towards considerations for implementing these strategies into the field.

In their manuscript, Carballar-Lejarazú and James [8] elegantly summarize the concepts and literature surrounding population modification strategies, highlight the next set of challenges for this technology, and perhaps most importantly, propose a framework to translate the latest research findings into effective control strategies suitable for implementation in the field. Specifically, they outline several possible routes whereby promising lab studies can be translated to vector control approaches. These routes take into consideration the scientific capacity of the disease endemic country utilizing the technology. Essentially, these approaches either transfer conceptual ideas, provide the DNA constructs for creating transgenic mosquitoes, or supply the altered mosquitoes themselves. Regardless of which approach is undertaken, ultimately it places the local authority in control of the intervention strategy, which is significant as it not only transfers ownership of the approach, but also empowers these countries to tailor the intervention to local ecological, political, demographical, and social factors. As approaches to engineer mosquitoes improve and become less technically demanding, countries deploying control strategies will become more autonomous and less reliant on other laboratories to generate resistant mosquito lines.

Importantly, a set of key parameters for evaluating each step in the developmental pipeline is provided, which outline both ideal and minimally essential outcomes. These parameters focus on safety and efficacy outcomes that are required for the strategy to continue down the pipeline towards implementation. The use of ideal and minimally essential outcomes recognizes the gap between theory and practice. It is important to carefully consider and transparently stipulate these thresholds prior to evaluation, as approaches that do not meet the more stringent ideal outcomes, but could still be useful in a particular context, can continue along the developmental pipeline as long as they fulfill the minimally essential criteria.

This work [8] should act as a primer to stimulate discussions regarding the development of genetic control strategies, specifically in regards to methods to deploy and evaluate approaches in disease endemic countries where they are sorely required. Looking forward, genetic intervention approaches in combination with traditional control strategies [9] could work synergistically to push malaria towards elimination..

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