Advancing 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

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*. Problem formulation, an initial step in environmental risk assessment (ERA), was performed for simulated field releases of the *dsxF*^{CRISPRh} transgene in West Africa.

Using problem formulation, eight potentially harmful effects from these simulated releases were identified and 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. 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). This analysis revealed that the efficacy of population suppression caused by the *dsxF*^{CRISPRh} transgene should itself directly affect most pathways (n=35).

To develop the next stages of this ERA, experts from Africa, Oceania, Europe and the USA from disciplines including risk assessment, biosafety regulation, modelling, population genetics, social science, ecology, entomology and vector control accepted invitations to participate in a series of six online workshops between April and May 2021. Participants considered how best to optimize problem formulation and subsequent stages of ERA for gene drive applications, which lead to the development of nine recommendations around issues of engagement, technical aspects of risk assessment and evaluating ecological risk.

Key words: gene drive, problem formulation, modelling, ecological risk, engagement.