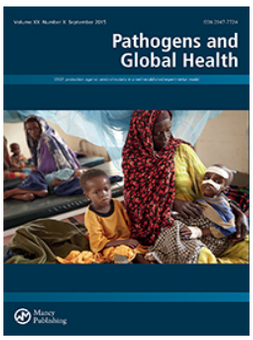

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Pathogens and Global Health

ISSN: 2047-7724 (Print) 2047-7732 (Online) Journal homepage: http://www.tandfonline.com/loi/ypgh20

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To cite this article: Robyn Raban & Omar S. Akbari (2018): Gene drives may be the next step towards sustainable control of malaria, Pathogens and Global Health, DOI: 10.1080/20477724.2017.1453587

To link to this article: https://doi.org/10.1080/20477724.2017.1453587

Published online: 23 Mar 2018.

PATHOGENS AND GLOBAL HEALTH, 2018
https://doi.org/10.1080/20477724.2017.1453587

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COMMENTARY

Gene drives may be the next step towards sustainable control of malaria

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Invited commentary on 'Gene drives to fight malaria: current state and future directions.'

A recent review by Hammond and Galizi [1] discusses the technical progress and challenges of using gene drive based technologies for malaria control. They begin by outlining the progress toward engineering a number of drive systems with molecular mechanisms inspired from naturally occuring selfish genetic elements including: transposable elements, heritable microorganisms, genetic underdominance, Maternal Effect Dominant Embryonic Arrest (MEDEA), meiotic drives, and the natural 'genetic scissors' known as homing endonucleases. While progress has been made for some of these drive systems in mosquitoes, CRISPR/Cas9 homing-based drive technologies, which have led the recent homing-based gene drive renaissance, are the primary focus of this review. Notably, there is proof-of-principle for these homing-based systems for both the population suppression or replacement in two distinct malaria vectors [2,3] displaying near complete transmission bias in confined laboratory experiments, however drive resistance did evolve rather quickly. The authors address resistance and off-target effects of gene drive technology with emphasis on their mitigation. The mitigation strategies include combinatorial gene drives to thwart drive specific resistance, and multiple methods to prevent target site resistance. Similar concerns are a challenge to all gene drive systems [4], and many of these drive methods may benefit from advancements in these CRISPR technologies [5]. Certainly, with the increased application of Cas9 technologies and the diversity of emerging bacterial endonuclease tools, there will be increased need to explore and mitigate potential resistance and off-target effects associated with these technologies.

Furthermore, the authors discuss laboratory containment and confinement practices for responsible development of these drive technologies. These considerations may be particularly important for malaria control, as stable reproductive isolation cannot be assumed for many malaria vectors [6–12]. Under these circumstances, ascertaining the stability and predictability of these drive systems is vital. The authors address the need to evaluate different containment and confinement strategies and transition them into large cage trials to evaluate vector behavior and fitness, validate modeling predictions and evaluate resistance mechanisms in semi-field conditions. Drive recall and reversal strategies and their use in conjunction with containment strategies, such as buffers zone, are also described as potential methods to reduce the risk of gene drive escape. The ethical considerations of implementing gene drive technologies in the field are also discussed and the costs and benefits of these systems are highlighted. As this review emphasizes, homing-based gene drives are a promising tool for malaria control; however, rigorous, responsible evaluation and regulation of these gene drive technologies is tantamount to the acceptance and sustainable implementation of these technologies in malaria prevention programs.

Disclosure statement

No Conflicts are declared.

Funding

These authors are supported in part by NIH [grant numbers 5K22AI113060, 1R21AI123937] and a Defense Advanced Research Project Agency (DARPA) Safe Genes Program [grant number HR0011-17-2-0047] to O.S.A.

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