Can gene drive wipe out all mosquitoes?

Anopheles stephensi mosquito | Photo Credit: HANDOUT

In scientific research, periodically, blockbuster applications with the potential to prevent and cure diseases of mankind as never before take the community by storm. Gene therapy, stem cell therapy and synthetic biology are some such examples. Although, backed by strong scientific evidence, applications get entangled with too many technical, ethical and environmental issues to even realise modest success.

Gene drive technology to wipe out insects and pests is the latest addition in this category. It can potentially eliminate mosquitoes that cause malaria, dengue, Zika, chikungunya, yellow fever, West Nile, sleeping sickness, Lyme and others. It also has potential to eliminate pests infecting crops in agriculture. Elimination of the mosquito vector, starting with the malaria vector, has more than topical interest in India with Tata Trusts donating $70 million (Rs 458 crore) over the next 5 years in setting up The Tata Institute of Genetics and Society at the University of California San Diego in the US (UCSD) and mentoring its branch at the Institute for Stem Cell Biology and Regenerative Medicine (InStem) in Bengaluru. Half the grant is said to be for use in India for research and training of scientists at UCSD.

The idea itself is not new. Barbara McClintock got the Nobel Prize for discovering the jumping genes in maize. Transposons or jumping genes are DNA elements that move from one location to another in the genome. The P element discovered in *Drosophila,* apparently not present before the 1950s, has now spread to all fruit flies. Propagation of a genetic modification to block sexual reproduction in mosquitoes can eliminate this pest. In gene drives, the inheritance bias for an altered gene can be pushed to 100% unlike the 50% inheritance seen in Mendelian division. In 10 generations, the gene drive can increase the frequency by a relative 1,024-fold. The idea was born at the Imperial college, London, based on the homing endonucleases of yeasts and algae. The endonuclease gene gets inserted into the target DNA sequence that will prevent further cleavage, but the enzyme will cut the homologous chromosome that does not contain the endonuclease gene. The endonuclease gene containing chromosome will now act as a template giving rise to a replica, thus facilitating 100% inheritance of this gene. This concept has received a fillip with the availability of precise gene editing mechanism using CRISPR-Cas9 system. Imperial college and other groups including those at the University of California (UCSD); Wyss Institute, Harvard University; Broad Institute, MIT are all in the fray, extending the studies to *Anopheles gambiae* (African malaria vector) and *Anopheles stephensi* (major vector in India).

Rapid expansion of the mutated gene introduced into the germ line has been shown in caged mosquito populations. Will it work in the wild? The idea is to release such altered populations in sufficient numbers even periodically so that they can mate with the wild types and render the entire population vulnerable.

The biggest challenge is to prevent emergence of resistance over a period of time to the nuclease. Interference with fertility genes to prevent reproduction may actually impose a large selection pressure for resistance development in the mosquito. This has turned out to be true in a recent experimental study, where after an initial increase in gene drive, nuclease-resistant mutants started to emerge. Alternate strategies to target the receptor for the parasite in the mosquito (yet to be discovered) or a gene drive carrying an antimalarial peptide/single chain antibody to kill the parasite are contemplated. At UCSD, researchers have successfully followed the latter strategy in *A. stephensi*. Use of multiple drives to prevent resistance development has been suggested as another option.

As expected there has been a huge backlash from ecologists and environmentalists. The concerns have ranged from consequences due to inadvertent escape in experimental studies, breakdown of species barriers, emergence of new disease-transmitting vectors and the unknown ecological and environmental consequences of eliminating an insect species. Altered male mosquitoes released in Florida to contain Zika virus were not self-propagating. The challenge is to halt the gene drive when required, so that application can be restricted to limited geography.

The arguments are all reminiscent of the concerns expressed with GM crops, which are actually not self-propagating. In India, where even Bt brinjal is considered as an environmental risk, gene drive, even if technically feasible after years of research, may be made to hibernate for ever.

Of course, as Bangladesh has benefited by picking up our Bt brinjal clone, Africa may benefit employing the gene drive to contain malaria, thanks to Gates Foundation!

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The Ig Nobel Prizes show that scientists too have a sense of satire, sarcasm, humour and yet appreciation.

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