Extinction on demand

The promise and peril of gene drives

A new genetic-engineering technology should be used with care

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Nov 8th 2018

"I THINK I got it," says Alekos Simoni with a grin, returning an electronic fly zapper called "The Executioner" to a nearby metal shelf. With a deft flick of his wrist he has done away with a genetically modified mosquito that was making a bid for freedom. There are many levels of containment to ensure such creatures do not leave this basement laboratory at Imperial College, London. But none, perhaps, quite so satisfying as The Executioner.

The extermination that the creatures in Mr Simoni's lab are designed to take part in is less viscerally gratifying—but far more consequential. The mosquitoes are being fitted with a piece of DNA called a gene drive. Unlike the genes introduced into run-of-the-mill genetically modified organisms, gene drives do not just sit still once inserted into a chromosome. They actively spread themselves, thereby reaching more and more of the population with each generation. If their effect is damaging, they could in principle wipe out whole species.

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To engineer an extinction is quite a step. But it is not unprecedented. In 1980 *Variola*, the smallpox virus, was exterminated from the wild. That marked the eradication of a disease which, from 1900 to 1980, killed around 300m people. If gene drives like those being worked on at Imperial and elsewhere were to condemn to a similar fate the mosquitoes that spread malaria, a second of humankind's great scourges might be consigned to history.

It need not stop with malaria. Gene drives can in principle be used against any creatures which reproduce sexually with short generations and aren't too rooted to a single spot. The insects that spread leishmaniasis, Chagas disease, dengue fever, chikungunya, trypanosomiasis and Zika could all be potential targets. So could creatures which harm only humankind's dominion, not people themselves. Biologists at the University of California, San Diego, have developed a gene-drive system for *Drosophila suzukii*, an Asian fruitfly which, as an invasive species, damages berry and fruit crops in America and Europe. Island Conservation, an international environmental NGO, thinks gene drives could offer a humane and effective way of reversing the damage done by invasive species such as rats and stoats to native ecosystems in New Zealand and Hawaii.

Needless to say, the enthusiasm is not universal. Other environmental groups worry that it will not prove possible to contain gene drives to a single place, and that species seen as invasive in one place might end up decimated in other places where they are blameless, or even beneficial. If drives are engineered into species that play a pivotal but previously unappreciated ecological role, or if they spread from a species of little ecological consequence to a close relative that matters more, they could have damaging and perhaps irreversible effects on ecosystems.

Such critics fear that the laudable aim of vastly reducing deaths from malaria—which the World Health Organisation puts at 445,000 a year, most of them children—will open the door to the use of gene drives for far less clear-cut benefits in ways that will entrench some interests, such as those of industrial farmers, at the expense of others. They also point to possible military applications: gene drives could in principle make creatures that used not to spread disease more dangerous.

Thinking nothing's wrong

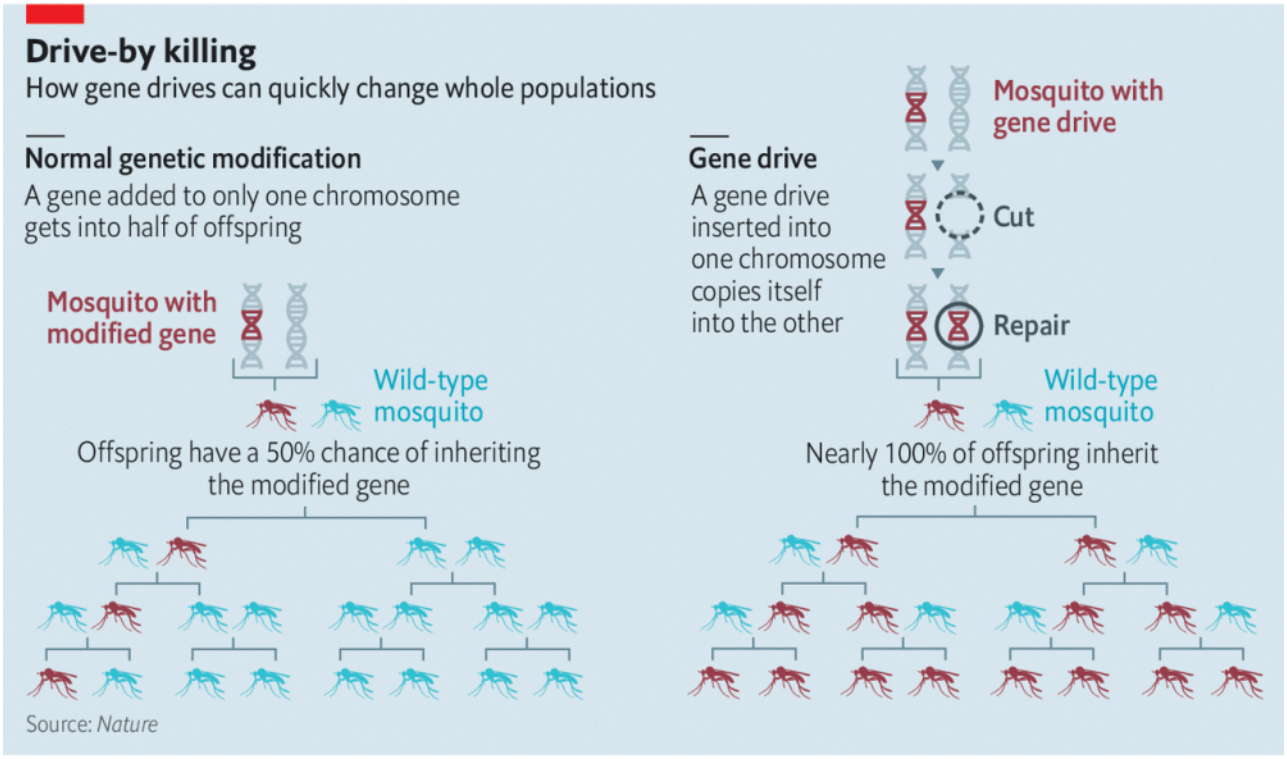
Although allegations of playing God are two a penny in debates about breakthrough technologies, with gene drives they do feel better-founded than usual. The ability to remove species by fiat—in effect, to get them to remove themselves—is, like the prospect of making new species from scratch, a power that goes beyond the past ambit of humankind.

Gene drives are, at heart, a particularly selfish sort of gene. Most animals have two copies of most of their genes, one on the set of chromosomes they got from their mother, one on those from their father. But they put only one version of each gene—either the maternal one or the paternal one, at random—into each of their own gametes (sperm or eggs). Some genes, though, seek to subvert this randomising in order to get into more than 50% of the gametes, and thus more than 50% of the next generation.

In 1960 George Craig, an American entomologist, suggested that such subversive genes might be a way of controlling the populations of disease-carrying mosquitoes, for example by making them more likely to have male offspring than female ones. In 2003 Austin Burt, at Imperial College, described how a gene drive

that could cut a place for itself in a chromosome and copy itself into the resulting gap could, in the right circumstances, drive a species to extinction.

A fascinating idea, but one hard to put into practice—until, in 2012, a powerful new gene-editing tool called CRISPR-Cas9 became available. Gene drives based on CRISPR-Cas9 could easily be engineered to target specific bits of the chromosome and insert themselves seamlessly into the gap, thus ensuring that every gamete gets a copy (see diagram). By 2016, gene drives had been created in yeast, fruitflies and two species of mosquito. In work published in the journal *Nature Biotechnology* in September, Andrea Crisanti, Mr Burt and colleagues at Imperial showed that one of their gene drives could drive a small, caged population of the mosquito *Anopheles gambiae* to extinction—the first time a gene drive had shown itself capable of doing this. The next step is to try this in a larger caged population.



The Economist

This drive disrupts a gene called *doublesex* that controls the differentiation of the sexes. Mosquitoes with one copy of the drive pass it on to all of their offspring. Females with two copies—which crop up more and more often as the gene spreads through the population—are sterile. Using sterile insects to control disease is not, in itself, a novel technique. Swamping a population of disease-spreading insects with individuals that cannot reproduce can be an effective way to limit numbers;

lots of the fertile wild ones breed fruitlessly with the sterile interlopers. What is new here is that a gene drive can actively spread sterility through a population.

Evolution can be expected to take a dim view of such an affront. Mutants which lack the DNA sequence that the drive targets, and which can thus escape its distorting effects, will be hugely favoured in the population that the drive is attacking. The cleverness of the Imperial scheme lies in choosing *doublesex* as its target. Without a functional copy of *doublesex*, mosquitoes cannot reproduce. Mutations which stop the gene drive from targeting it are also likely to stop the gene working properly—it is unusually sensitive to change. So a mosquito in which *doublesex* is sufficiently messed up by random mutation that the gene drive no longer has a target will be unable to reproduce anyway.

The scientists at Imperial are part of Target Malaria, a research alliance supported by the Bill & Melinda Gates Foundation and the Open Philanthropy Project Fund to the tune of around $5m a year since it started in 2005. Target Malaria is already working in Burkina Faso, Mali and Uganda to prepare the way for a release of a gene drive. It would be introduced on top of a regime that includes bed nets, insecticide sprays and drugs for those infected (which kill the malaria parasites in the blood and thus stop them from hitching a lift in the next mosquito to stop by for a drink). With that amount of back-up, even a gene drive to which resistance evolves could break the cycle of malaria transmission definitively, wiping it out in the trial area. If that worked, the rest of Africa—home to 90% of the world's malaria cases—could soon follow suit.

Pay attention to your dreams

The Imperial team thinks that, scientifically, they might have drives able to make a difference in about three years. But the Gates Foundation is talking about 2026 as a possible date for trials that involve a release in the wild. Margret Engelhard, a biosafety expert at the German federal agency for nature conservation, points out some of the challenges ahead. These include evaluating the gene drives before release, predicting how the modified mosquitoes will behave in the wild and working out whether there will be knock-on effects on other species. Tilly Collins at the Centre for Environmental Policy at Imperial says that published ecological studies of *A. gambiae*—one of three mosquito species that carry malaria, and by far

the most important vector for the disease in Africa—have turned up nothing that preys on them to the exclusion of other foods. There is a vampire spider that lives around the shores of Lake Victoria that has a fondness for the females when full of human blood, but it will readily eat other mosquito species.

Work is under way to validate these findings in the field, and to discover whether the mosquito's larvae are similarly dispensable. At present, it looks unlikely that removing one or two of over 3,000 mosquito species will have any significant effect on the ecosystems in which they live.

What, though, of the risk that a drive might spread beyond its target species? In theory, because gene drives require their bearers to have offspring if they are to spread, they should stay in a single species; distinct species cannot, in general, reproduce through sex. However in the case of *doublesex* the target gene sequence is found across all 16 species of *Anopheles* analysed so far—this is the flipside of it being so resistant to mutation. And there is a small but measurable rate of hybridisation between some of those species. That probably would not allow a lot of spread: but the possibility needs examining.

The New Partnership for Africa's Development, an organ of the African Union, has recommended that the Union's member states support studies to verify the technology in African settings—including conducting a thorough investigation of the risks and looking for measures that may mitigate any negative impacts. Target Malaria is trying to get locals used to the idea of working with, and releasing, mosquitoes that have been genetically engineered by scientists. The next step will be the release, in Burkina Faso, of male mosquitoes genetically engineered to be sterile. That will help the scientists understand population dynamics, but with no gene drive to push the sterility into the population it will have no effect on malaria per se.

The Target Malaria gene-drive project carries the prospect of huge humanitarian gains. It is carefully designed, supported by deep-pocketed philanthropists and being carried out under a fair level of international scrutiny. It is gaining political support and inspiring a generation of researchers. It is hard to see it grinding to a halt in the absence of massive opposition, a currently unheralded alternative or profound technical failure. As Jim Thomas of the ETC Group, an NGO that opposes

gene drives, says, malaria is the "best possible use-case scenario" for the technology.

The worry of the ETC Group and its fellow travellers is that the use of gene drives against malaria will open the door to more troubling, slipshod and exploitative applications. Many may sound good: some of the $70m that Tata Trusts of Mumbai, a philanthropy group, has given to the University of California, San Diego,is for exploring ways of using gene drives to make crops more resistant to drought. If the technology were predictable, controllable and well-regulated, the potential for raised crop yields in the face of climate change, and perhaps reduced use of pesticides and herbicides, might be huge. But experience shows that few technologies make it into the world in a predictable, controllable and well-regulated form. Mr Thomas sees a raising of the stakes from a world in which businesses modify seeds crop by crop to one where they modify whole populations, indeed all of nature. "It is a pretty audacious switch," he says.

In a report published in 2016, America's National Academies of Science highlighted the possibility of drives introduced for agricultural reasons damaging people's welfare. Excoriated as "pigweed" in the United States, related species of the plant are cultivated for food in Mexico, South America, India and China. American farmers might like a gene drive to eradicate pigweed, which has become resistant to the herbicide glyphosate, which is widely used in conjunction with today's genetically modified crops. But they would not necessarily bear the risks, or liability, of a release that went on to do damage to food crops in other countries.

There are also worries about how gene drives might be used to create a weapon. Humans are an unlikely target; a weapon that acts over generations seems ill-suited to war or terror, and the idea that future generations will not have their genomes sequenced in a way that shows up such attacks feels far-fetched. But they might conceivably be used to make small and rapidly reproducing insect and rodent species more objectionable or pathogenic. The need to find ways to guard against such attacks is one of the reasons that the Pentagon's Defence Advanced Research Projects Agency (DARPA) gives for its work on gene drives. Renee Wegrzyn, programme manager for DARPA's "Safe Genes" project, says the work is to prevent "technological surprise", whether in the form of an unintended consequence or nefarious use. One of the academic teams she funds has made progress in

developing anti-CRISPR enzyme systems that one day might be able to inhibit a drive's operation.

Many groups are working on ways of making gene drives more controllable and less risky. One option is to create "immunising" drives that could spread resistance to a drive gone rogue. Another is to limit the drive's power to spread. Current gene drives are self-driving: the cutting mechanism and the thing that gets spread are one and the same. But that is not the way things have to be. In the "daisy chain" drive designed by Kevin Esvelt of the Massachusetts Institute of Technology, gene drives are linked up in sequence, with the first creating the space for the second to copy itself into, the second creating the space for the third, and so on, until you finally get to the gene that you want to drive through the population. Because the upstream drives do not copy and spread themselves, they drop away, generation by generation, until only the last gene remains.

Think of it like the stages of a rocket launching a satellite—or warhead. Each stage gets the gene of interest further into the population before falling away. But once the last stage has burned out, the payload just goes where gravity takes it, powerless to push itself further. Such a self-limiting system might have a big effect over the short term, but vanish in the long term. These developments make it easier to imagine gene drives being used with minimal risk. But it is still the case that without care some gene drives might have the potential to trigger irreversible ecological shifts before countermeasures could be deployed. That is clear from decades of work on invasive species that are released either deliberately or accidentally. And because the effects of each drive will be unique, depending on the design of the drive, the gene or genes that it targets, the population it is introduced into and the ecosystem in which that population sits, the technology calls for a sort of joined-up regulation that does not yet exist. In 2014 Kenneth Oye of MIT and his colleagues pointed out in the journal *Science* the many gaps in America's patchwork of regulatory frameworks relevant to gene drives.


0—30
30—65
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90—150
Andrea Ucini

Oversight needs not just to bring together a range of government agencies; it requires co-operation between governments, too. The Cartagena Protocol on Biosafety, which entered into force under the UN Convention on Biological Diversity (CBD) in 2003, provides controls on the transfer of genetically modified organisms. But how it applies to gene drives is unclear—and besides, America has never ratified the convention. An attempt to ban gene-drive research through the CBD, which was backed by the ETC Group and other NGOs, failed at the convention's biennial meeting in Cancún in 2016.

A less ambitious call for restraint in field tests is likely to suffer the same fate later this month in Egypt. At present there is no consensus on what level and distribution of risk humankind is willing to accept from such technologies, nor what loss of wildness it is willing to accept. Like the reintroduction of vanished species advocated by the rewilding movement, gene-drive technology will provide new arenas for the fight between those who wish to defend nature and those who wish to tame it.

There is still time for such debate. The Gates Foundation does not expect to be ready for field trials for at least eight years. And the debate may be more fruitful if research continues to open up new options for better-designed interventions. If gene-drive research had been banned under the CBD two years ago, various self-limiting exotica currently under development might not have been dreamt up.

For malaria, at least so far, the case for moving towards tests in the field is a strong one. That does not mean that other uses will be as compelling down the line, or that there is no need for vigilance. And none of this will, in practice, be as neat as a swipe with an electronic tennis racquet. But for millions of Africans living with the burden of malaria, the idea of never needing to fear the bite of another mosquito could change the world.

This article appeared in the Briefing section of the print edition under the headline "Extinction on demand"

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Nov 8th 2018