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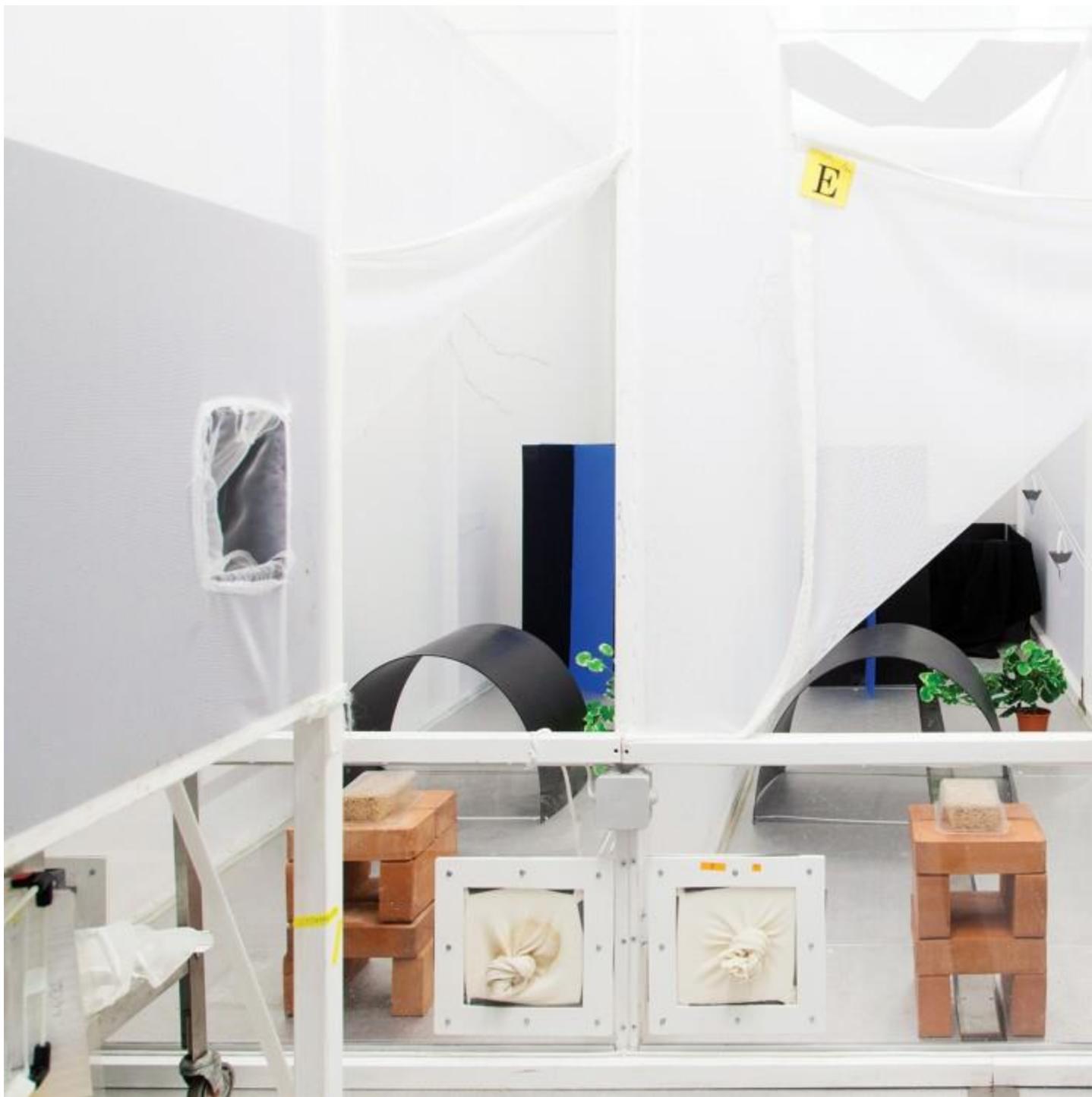


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Biomedicine

## The Extinction Invention

A genetic technology that can kill off mosquito species could eradicate malaria. But is it too risky to ever use?

- by [Antonio Regalado](#)
- April 13, 2016

Above: Room-size insect cages at the Polo d’Innovazione Genomica, in Perugia, Italy, mimic the outdoors. Here researchers can study the mating behavior of self-destructing mosquitoes.

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Malaria kills half a million people each year, mostly children in tropical Africa. The price tag for eradicating the disease is estimated at more than \$100 billion over 15 years. To do it, you’d need bed nets for everyone, tens of thousands of crates of antimalaria drugs, and millions of gallons of insecticides. But it would take more than stuff. You’d need things the poorest countries in the world don’t have, like strong governments, purchasing power, and functioning public health systems. So malaria keeps killing.

But what if, instead, you needed only a bucket full of mosquitoes?

I saw such an invention at Imperial College London. A student led me through a steel door, under a powerful gust of air, and into a humid room heated to 83 °F. Behind glass, mosquitoes clung to the sides of small cages covered in white netting. A warning sign read, “THIS CUBICLE HOUSES GENE DRIVE GM MOSQUITOES.” It went on to caution that the insects’ DNA contains a genetic element that has “a capacity to spread” at a “disproportionately high” rate.

A gene drive is an artificial “selfish” gene capable of forcing itself into 99 percent of an organism’s offspring instead of the usual half. And because this particular gene causes female mosquitoes to become sterile, within about 11 generations—or in about one year—its spread would doom any population of mosquitoes. If released into the field, the technology could bring about the extinction of malaria mosquitoes and, possibly, cease transmission of the disease.



*Anopheles gambiae* mosquitoes. The species spreads malaria in Africa.

The mosquitoes I saw were created as part of Target Malaria, a project led by Imperial College that has quietly expanded to involve 16 institutions and includes teams in Italy and three African countries, Mali, Burkina Faso, and Uganda, where secure mosquito facilities are currently being outfitted. Its work is funded by the health foundation of Microsoft billionaire Bill Gates, in Seattle. An official there said the foundation now considers gene drives “necessary” to end malaria and projects that the technology will be ready years before an effective vaccine. According to a business plan developed for the Gates Foundation, the self-annihilating mosquitoes could be unleashed in 2029.

The plan is to disperse *Anopheles gambiae* mosquitoes harboring selfish genes across sub-Saharan Africa. The gene drive could spread across a huge swath of territory, causing mosquitoes to disappear and blocking transmission of the parasite that causes malaria. “Malaria is a problem of poverty, of instability and lack of political will,” says Andrea Crisanti, the Italian parasitologist and genetic engineer who developed the insects at Imperial College. “We are asking the drive to do what we can’t do politically or economically.”

Beyond helping with malaria, conservationists think gene-drive technology could save Hawaii's disappearing native birds (from avian malaria) or maybe rid Australia of invasive, destructive toads that have been hopping westward across the continent. Why not also eliminate *Aedes aegypti*, the mosquito spreading dengue fever and Zika in the Americas?

## **Does any country, agency, or individual have the right to change nature in ways that could affect everyone?**

The technology creates risks that society has never before had to consider. Would removing mosquitoes upset ecosystems? Are we risking a genetic epidemic if the selfish DNA should jump the species barrier to affect other insects? Most perplexing: what country, agency, or individual has the right to change nature in ways that could affect the entire globe? "This is why I hate the malaria problem," says Kevin Esvelt, an MIT biologist who has been warning about the unprecedented dilemmas gene drives will create. "It makes the technology so tempting to use."

These questions need answers soon. Only 12 months ago, gene-drive technology was still a promising theory. Not anymore. Rapid-fire technical advances are occurring thanks to CRISPR, a new gene-editing technique. At Imperial's lab I peered through a microscope at an immature mosquito, called a pupa, a grisly creature that looks like a holiday ham with a lobster tail attached. Inside its body I could see fiery fluorescent spots where an artificial selfish gene was busy copying itself. The potentially ecosystem-altering transformations had been carried out mostly by a 27-year-old student named Andrew Hammond during a few months of late nights in the lab. "There are so many cool ways to build these," Hammond exulted. "There are so many easy things to do."

And that's just the problem. Officials in the United States and elsewhere worry that it might be a little too easy. The FBI is looking into whether gene drives could be misused, say, to create a designer plague. And this May, the U.S. National Academy of Sciences is expected to publish recommendations for "reducing ecological and other risks" ahead of any field test. Twenty-seven researchers wrote to *Science* with warnings against the accidental release of gene-drive organisms, something they fear would devastate public trust. Others have said the research ought to be classified, though it's too late for that.

## Despised species

Of the 3,500 species of mosquitoes, about 30 spread malaria, although three nearly indistinguishable subtypes of *Anopheles gambiae* do the most damage in Africa. The female mosquito's bite spreads the plasmodium parasite, which gives people fever and chills by exploding red blood cells. These three mosquitoes are the ones targeted by Imperial for elimination, Crisanti says, swinging his glasses by a tip and jumping up from his chair.

Crisanti acknowledges that gene-drive technology is generating tension. Pressure will mount to use the technique, given the health and social benefits that ending malaria could bring. On the other hand, there are as yet no agreed-upon regulations or procedures for developing a technology able to spread itself among wild organisms. "The gene drive is controversial for the potential to wipe out a species," he says. "So there should be a clear benefit."



At the Italian outpost of Target Malaria, female *Anopheles* mosquitoes take a blood meal. Three days later they will lay eggs.

A gene drive wouldn't necessarily doom these mosquito species to extinction. Pockets of mosquitoes might remain, or they could be maintained in a lab, should anyone want to bring them back. But eradication is a possible outcome, Crisanti says, in particular if release of the gene drive coincided with conditions like a dry spell or a cold snap. Species go extinct continually, of course, but I wondered: is it ethical to eliminate any part of nature on purpose? "Are you asking in a Darwinian way or a theological way?" Crisanti responded. "I think it's a species competition between us and the mosquito. And I don't think a species has the right to exist or not to exist." He says what species do have is "fitness"—they have adapted to flourish in their environmental niche. For species we hope to save, we might use gene drives to add beneficial genes, like

ones for disease resistance. For species we despise, we can add ones that make them unfit for survival.

## **Selfish genes**

Target Malaria is led by Austin Burt, an evolutionary theorist at Imperial College whose specialty is selfish genetic elements. These are parasitic genes, found in many species, that make extra copies of themselves. (One, called the P element, even managed to hitchhike its way into the genome of every fruit fly on Earth during the 20th century.) Burt was interested in a particular kind of selfish gene present in slime molds, called an endonuclease. These slash open DNA at very precise spots they recognize and then, by offering themselves as a repair template, can trick a cell into copying them. Burt concluded that the simplicity of this process left it “open to human artifice,” and in a 2003 paper he described how it could be turned into an extinction device.

The paradox Burt had to solve is how something very bad for mosquitoes could also be spread by them. One answer, he saw, was a selfish gene that is harmless if one copy is present but causes sterility if two copies are. (Like humans, mosquitoes have two sets of chromosomes, one from each parent.) Starting with a male mosquito with one copy, the selfish gene will ensure that it ends up in every one of his sperm, rather than just half. That way any offspring with a wild mosquito will also be carriers, as will all their offspring’s offspring. As a result, the gene will rocket through the population.

Eventually, it becomes likely that any mating pair of mosquitoes will both be carriers—and their offspring, with two copies, will be infertile. Quickly, the population will crash, reeling from the genetic poison. On my dog-eared copy of Burt’s paper, I underlined its concluding sentences: “Clearly, the technology described here is not to be used lightly. Given the suffering caused by some species, neither is it obviously one to be ignored.”

Burt is a retiring Canadian whom I located in an office that was largely empty, except for a computer. He served tea that no one drank and answered several of my most provocative formulations about the massive power of biotechnology by saying, “Um, yeah.” He did confide that he’d tried to patent his idea. But it was rejected because he had little experimental evidence at the time to prove it could work. “I wanted to believe I had invented something,” he says.

At the time, Crisanti's lab had just determined how to genetically engineer *Anopheles* mosquitoes—a prerequisite for Burt's ideas to work. They applied to the Gates Foundation for funding, and since then Gates has spent \$44 million on the project, easily the largest sum spent to date on gene-drive research.

Yet engineering a selfish gene that would perform as predicted by the equations on Burt's computer screen proved difficult. Crisanti's team tried adapting selfish genes from slime molds, but it was difficult to make them cut vastly different mosquito genes. By 2011, the team had a partial prototype but nothing able to spread widely in the wild.

Then, in March of 2015, two fly biologists in California, Ethan Bier and his student Valentino Gantz, announced they'd created a selfish gene that fulfilled Burt's prophecy. It spread through a population of lab flies, causing a genetic change that turned the insects yellow. Instead of struggling with slime molds, Bier and Gantz had used Cas9, the DNA-slicing molecule becoming famous for its role in the gene-editing technology called CRISPR. The virtue of Cas9 is that it's easily directed to snip open any DNA sequence you like. So they'd added Cas9 to the fruit fly genome and told it where to cut.

### **“It's a species competition between us and the mosquito.”**

This meant that with CRISPR, even a two-person team could, in theory, change an entire species. By last December, Crisanti's group and another, led by Bier and mosquito expert Anthony James, had both used CRISPR to build gene drives capable of spreading traits through mosquito populations in cages—and probably in the wild as well.

With more scientists working on gene drives, the chance of accidental release has become a concern. Had one of Bier's insects escaped into California's orchards, it could have turned all the flies yellow. In August, Burt, Bier, and 25 others wrote a letter to *Science* agreeing on the need for “stringent confinement strategies” to avoid a genetic spill and calling on scientists to refuse requests to share the organisms they have made until some kind of rules can be figured out.

Imperial's mosquito lab in London is definitely no Fort Knox, with students coming and going. Instead, a key safety measure is its location far from the

current range of *Anopheles gambiae*. Any escaping mosquitoes—the students call them “fliers”—would probably get knocked senseless by dry air and cold as soon as they hit the lab hallways. And even if one somehow made it 200 yards onto Queen’s Lawn, it would find no other mosquito to mate with. The mosquitoes I saw in London, in any case, are not yet ready for release. They aren’t too healthy—it would be difficult for them to compete and reproduce in the wild. And in two of the cages the gene drive, which spread rapidly at first, began disappearing after a few generations of mosquitoes. The likely reason is resistance. One or more of the mosquitoes may have developed immunity to the drive, perhaps through a chance DNA mutation, and these mosquitoes’ offspring quickly multiplied.

“We have some problems to solve, but we have a lot of tricks in the cupboard,” says Tony Nolan, the scientific lieutenant of Crisanti’s lab. One idea is to combine several drives, targeting three different DNA sites at once. Mosquitoes might eventually evolve resistance to all three, but maybe not before they’re all dead.



On a monitor a mosquito larva glows with a fluorescent trace.

## Deploying the troops

The Gates Foundation has spent **\$36.7 billion** on education, public health, and vaccines since its inception in 2000. The fraction spent on gene drives barely registers, yet the technique has taken on a special allure in solving malaria, long one of Gates's top objectives. "If you were to invent the ideal way to tackle a problem in the developing world ... it would be a gene drive," says Fil Randazzo, a deputy director at the foundation.

If it works, it will be incredibly cheap, easy to distribute, and egalitarian, benefiting everyone, rich or poor. It will also keep working once released, avoiding a common problem: often, the most difficult part of eradicating a disease is the endgame, when attention wanders elsewhere and spending per case skyrockets. In a scenario Randazzo outlined for me, buckets of mosquitoes would be released every 50 kilometers or so, starting a chain reaction that, over two years, would flow through intervening forests and pasturelands and towns. The number of surviving mosquitoes would collapse, to less than 1 percent of normal levels. With the help of bed nets and sprays, bites would be at a minimum, breaking the cycle of malaria transmission. A campaign of drug treatment could then clear out the parasite's human reservoir—in some West African countries 25 percent of the population is infected.

The Gates Foundation has said it no longer believes that malaria can be wiped out without a gene drive. "You can't walk around with a bed net on you all the time. That's not going to eliminate malaria," says Randazzo. With a gene drive, "human behavior change is not required."

The Imperial team has begun building mathematical models of geography, climate, and other factors to get a handle on how a gene drive might act in the real world. In Burkina Faso, scientists have been releasing *Anopheles* doused with fluorescent dust in order to track them. Burt says he believes a drive could spread five to 20 kilometers a year from any release point, and that fewer than 500 mosquitoes could set off the reaction.



A lab worker carries out DNA tests at the Polo d'Innovazione Genomica, in Perugia, Italy, part of a network of laboratories financed by Bill Gates that are studying gene drives.

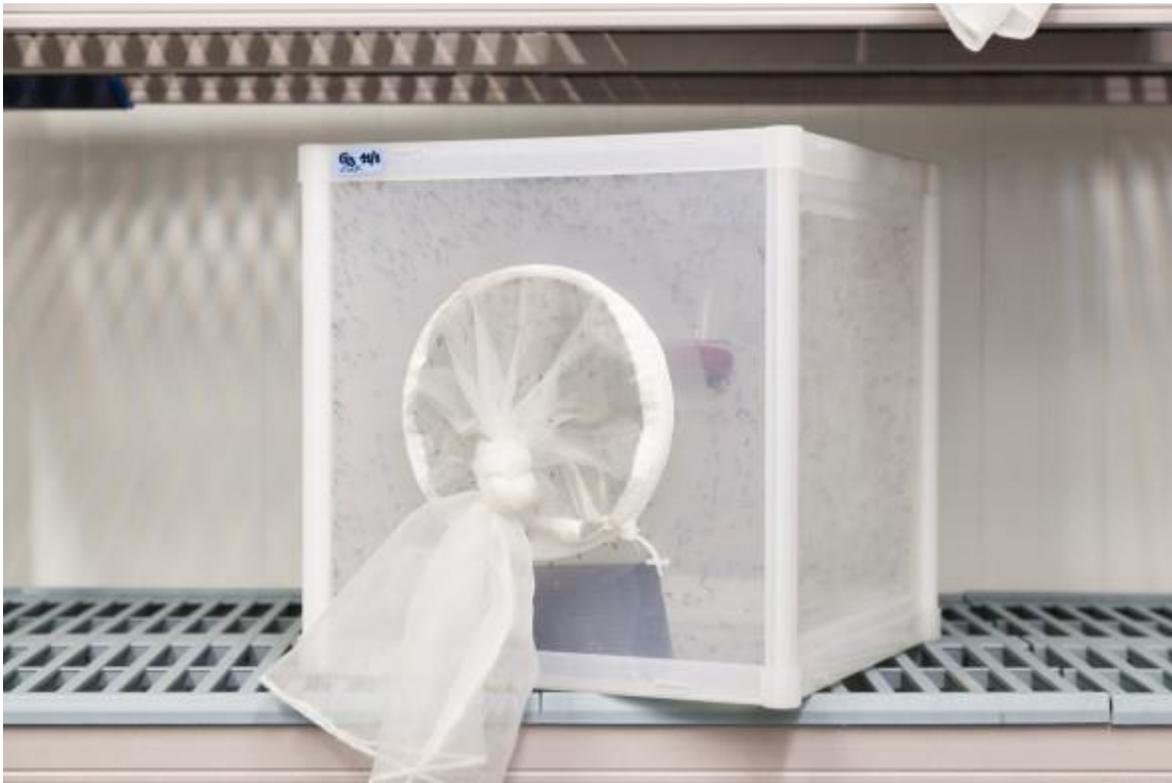
Some scientists told me they believe the malaria project is doomed. What if different mosquitoes end up transmitting the disease instead? Guy Reeves, an evolutionary biologist at Germany's Max Planck Institute, predicts that resistant insects will be the main problem, saying they'll cause the technology to fizzle. "We can't go for the shiny new thing every time," says Reeves, who thinks insects based on Burt's theories "will never prove sufficiently predictable to use with any confidence."

This March, around 75 policy experts and scientists, including Burt, attended a three-day closed-door symposium on gene drives in North Carolina. People who were there say concern was palpable about the prospect of genetic changes that can spread widely, across borders. MIT's Esvelt, who attended, says the

problem with the malaria idea is that it “will have an effect on everyone” in Africa but that getting everyone there to agree to the technology will be impossible. “I think Gates has every intention of pushing this forward,” he says. “And the question is, how can you do it ethically?”

Randazzo says Gates’s organization is committed to handing over the gene-drive technology “to the African people” and letting them decide. Efforts in this direction are well advanced. Starting in 2012, Target Malaria started developing ground operations in a handful of African countries, training scientists, refitting insect labs, and sending teams to brief local communities.

The plan resembles a military campaign, complete with drills, maneuvers, and blank charges. It includes the staged introduction of genetically modified mosquitoes that lack a gene drive. Although these won’t help with malaria, local scientists can train with them and create a regulatory path for the real thing. An application to import Africa’s first genetically modified mosquitoes is already pending in Burkina Faso.



Small

netted cages are used to hold mosquitoes for study.

But the real gene-drive insects will remain in Europe until African countries have accepted the technology and its consequences. The reason is that in a tropical location, unlike London, a lab mishap that lets mosquitoes escape could have irreversible consequences. “We won’t import them to Africa until it’s accepted, because we don’t think we could guarantee 100 percent it will be contained,” says Delphine Thizy, the political scientist who manages Target Malaria’s engagement teams.

Will people in Africa want this technology? I spoke to a Kenyan entomologist, Richard Mukabana, who worked on the ground campaign in communities around Lake Victoria. Using posters and diagrams, the teams visited rural areas to explain the idea, often to people who are illiterate. One cartoon used to convey what’s going on shows a blond scientist holding a mosquito cage next to a British flag. The objective of the ground work is to establish a “social license to operate”—a type of agreement, says Mukabana, that’s not written down or tacked to a wall but will have to exist if a gene drive is ever to be released.

Not even most scientists yet know what a gene drive is, or how one works. And describing it to people in the Luo dialect (the language President Obama’s father spoke) is challenging, since the language lacks a word for DNA. Mukabana borrowed words from English and Swahili and used “blood” as a synonym for genes.

Mukabana told me that when people in communities where children are dying from malaria hear that the disease could be eliminated, they’re for it. And if there’s a defender of mosquitoes around Lake Victoria, he didn’t meet one. “People won’t bother with mosquitoes going extinct,” he says.

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I am the senior editor for biomedicine for *MIT Technology Review*. I look for stories about how technology is changing medicine and biomedical research. Before joining *MIT Technology Review* in July 2011, I lived in São Paulo, Brazil, ... [More](#)

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