Mosquitoes Are Deadly, So Why Not Kill Them All?

Zika virus's spread adds urgency to gene editing that could allow scientists to program the insects to die off, but it is fraught with quandaries

Guilherme Trivellato of Oxitec releases on Feb. 1 in Piracicaba, Brazil, some Aedes aegypti mosquitoes genetically modified to produce offspring that don't survive or reproduce. The species spreads at least four viruses that cause major diseases, including Zika.

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By BETSY MCKAY

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The death toll from diseases carried by mosquitoes is so huge that scientists are working on a radical idea. Why not eradicate them?

Mosquitoes kill more humans than any other animal and were linked to roughly 500,000 deaths in 2015, mostly from malaria. For more than a century, humans have used bed nets, screens and insecticides as weapons, but mosquitoes keep coming back. They are now carrying viruses like Zika and dengue to new parts of the world.

Powerful new gene-editing technologies could allow scientists to program mosquito populations to gradually shrink and die off. Some efforts have gained enough momentum that the possibility of mosquito-species eradication seems tantalizingly real.

"I think it is our moral duty to eliminate this mosquito," entomologist Zach Adelman says about Aedes aegypti, a species carried afar over centuries by ships from sub-Saharan Africa. It derived from a forest dweller and adapted to thrive among humans, to whom the mosquito spreads at least four viruses that cause major diseases.

Prof. Adelman, a virologist and associate professor of entomology at Texas A&M University, is working to program Aedes aegypti mosquitoes to develop as males.

Eventually, the mosquitoes would run out of mates, crashing the species' population in places it invaded and "cleaning up a global mess," he says. Female mosquitoes are the only ones that bite people and transmit viruses.

A technician separates genetically modified mosquito larvae used to fight the spread of disease. Other efforts include breeding bacteria-infected mosquitoes at a laboratory in Guangzhou, China. Mosquitoes are fed from a bag of blood.PHOTOS: PAULO FRIDMAN/BLOOMBERG NEWS; BOBBY YIP/REUTERS; ANDRE PENNER/ASSOCIATED PRESS

Purposely engineering a species into extinction—or just diminishing it—is fraught with quandaries. Scientists must weigh the potential impact of removing a species on the environment and food chain. It will take years more research, testing and regulatory scrutiny before most genetically altered mosquitoes can be released into the wild. And the strategy might not work.

Wiping a species off the face of the earth is "an unfortunate thing to have to do," says Gregory Kaebnick, a research scholar at the Hastings Center, a bioethics research institute in Garrison, N.Y.

He says humans shouldn't force a species into extinction to meet their own preferences. "We ought to try not to do it," says Mr. Kaebnick. One justification, he says, would be to avert a serious public-health threat.

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Mosquitoes have an ugly track record of spreading everything from the Zika virus to dengue fever to malaria. Could they be killed off? Here's a short look at a controversial question.

Out of more than 3,600 mosquito species, only a few dozen transmit viruses and parasites that can sicken or kill humans. Even the killer mosquitoes pollinate plants and are food sources for other animals, though usually not the only staple, entomologists say.

For decades, agricultural officials have used a “sterile insect technique” to eliminate pests that are dangerous to crops or humans. Insects are sterilized with radiation and then released into the wild.

Insects that mate with the sterilized ones produce no offspring, and the populations die off within a few generations. The technique was used to rid the U.S. and a few other countries of the New World screwworm fly, and it is now being used to battle fruit flies.

ENLARGE

Imperial College London researchers are refining a system under development for the past several years to drive a self-destructive genetic trait into the Anopheles gambiae mosquito, the major carrier of malaria in sub-Saharan Africa. The trait could eventually shrink the malaria carrier’s population. Malaria kills an estimated 438,000 people a year.

Aedes aegypti is high on the hit list of more scientists now that Zika has spread from Brazil to Miami , spawning an epidemic that has left hundreds of babies with devastating birth defects.

The same type of mosquito caused dengue to proliferate from Southeast Asia through tropical regions world-wide during the last quarter of the 20th century. The dengue virus infects an estimated 390 million people a year, killing thousands of them.

Aedes aegypti also is a carrier of chikungunya, a crippling disease that causes lasting joint pain, and yellow fever. In southern Africa, officials are struggling to contain a large outbreak of yellow fever, which can lead to fatal liver disease.

“Aedes aegypti is literally probably the most dangerous animal in the world,” says Omar Akbari, a molecular biologist and assistant professor of entomology at the University of California, Riverside. His conclusion is based on the number of infections to which the mosquito is linked.

Many entomologists say eradicating Aedes aegypti would have a minimal impact on the environment. Such mosquitoes thrive around humans, breeding in water that collects in tires, pipes and plastic containers. Humans are their only source of food.

Zika-carrying mosquitoes aren’t very appealing to other animals as a food source, entomologists say. “They’re so tiny a bat would have to eat thousands of them to equal a couple of moths,” says

Michael Doyle, an entomologist and former executive director of the Florida Keys Mosquito Control District, which battled a dengue outbreak several years ago.

Weapons used against the spreading Zika virus include sprays to kill adult mosquitoes in Duarte, Calif., street-cleaning machines in Miami Beach, Fla., and fumigating a Singapore residence.PHOTOS: PATRICK T. FALLON FOR THE WALL STREET JOURNAL; CRISTOBAL HERRERA/EUROPEAN PRESSPHOTO AGENCY; WONG MAYE-E/ASSOCIATED PRESS

Genetic-engineering technologies used by mosquito-fighting scientists include a new tool known as Crispr/Cas9.

With Crispr/Cas9, scientists can use an enzyme to snip DNA and insert changes, then build something called a “gene drive” that makes those changes more likely to be inherited by future generations, altering them. Normally, genes have only a 50% chance of being inherited.

Prof. Adelman and Virginia Tech biochemistry professor Zhijian Tu see a way to do this with genes involved in mosquito reproduction. In a paper published in Science last year, the researchers identified a gene that makes Aedes aegypti mosquitoes male.

“This was the master switch that controls sex,” says Prof. Tu. He and Prof. Adelman were co-authors of the research.

The researchers now are working on a system to program mosquitoes to develop as males. Since only females bite, that change could reduce the ability to spread viruses. The researchers aim to then use Crispr/Cas9 to build a gene drive that would spread the change through successive generations.

“If you’re successful, then you end up with all males, and the local population crashes,” says Prof. Tu. Prof. Adelman cautions that a system to target Aedes aegypti would have to be designed to leave the African forest-dwelling mosquito Aedes aegypti formosus intact. That type of mosquito doesn’t threaten human, he says.

Prof. Akbari at UC Riverside is using Crispr/Cas9 to design a gene-drive system that would inactivate a fertility gene in female Aedes aegypti mosquitoes and then pass on the inactivated gene. That would sterilize future generations of females.

He hopes to test the system within the next several months. “We’re working as fast as we can,” Prof. Akbari says.

Using different technology, Oxitec Ltd. has developed what it calls a “self-limiting” Aedes aegypti mosquito, a male genetically modified to produce offspring that don’t survive or reproduce.

In August, the Food and Drug Administration allowed Oxitec to go ahead with a field trial in Key Haven, Fla. Oxitec is a unit of biotechnology firm Intrexon Corp., based in Germantown, Md.

Oxitec’s technology isn’t as powerful as those using gene drive, because the trait isn’t pushed through multiple generations of mosquitoes. As a result, Oxitec’s genetically modified mosquitoes need to be released regularly.

The company says its tests in Brazil, Panama and the Cayman Islands, where the engineered insects are released in a small area, have cut the Aedes aegypti population in those areas by more than 90%.

In one field trial in a district of Piricicaba, Brazil, cases of dengue fever fell 91% from the same period a year earlier, Oxitec says.

“We focused on Aedes because we saw it as a great unmet need,” says Haydn Perry, Oxitec’s chief executive. “If you look at the statistics, the rise in dengue has been absolutely shocking since the 1970s.”

In June, a committee of the National Academies of Sciences, Engineering and Medicine said in a report that organisms modified by gene drive aren’t ready to be released into the wild.

More research is needed on how the modified organisms work and might affect the environment, the report said, concluding that their proposed uses “are based on limited proof-of-concept studies.”

“We need to think through what responsible conduct looks like when you have these tools in your hand,” says James Collins, a professor of natural history and the environment at Arizona State University who is one of the committee’s leaders.

Field trials and releases of genetically modified mosquitoes require regulatory approval and can take years.

In the Florida Keys, Oxitec’s “self-limiting” mosquitoes face opposition from residents who worry that the insects could harm local ecosystems.

The field trial that got a go-ahead from the FDA will face a nonbinding referendum from voters in Key Haven on Nov. 8. After that, the field trial must be approved by the Florida Keys Mosquito Control District, spokeswoman Beth Ranson says.

Winning consent from the many countries infested with Aedes aegypti for eradication through the use of gene drive will be difficult. That could limit the impact of the mosquito-fighting technique.

“How on earth are we going to manage informed consent and diplomatic agreement?” says Kevin Esvelt, an evolutionary engineer at the Massachusetts Institute of Technology. In 2014, he outlined how using Crispr/Cas9 gene drives could spread genetic traits through wild populations.

Some scientists and foundations say total eradication isn’t necessary. One alternative strategy is to suppress the population of virus-carrying mosquitoes low enough that there are too few left to transmit pathogens from one person to another. That approach could be combined with traditional mosquito-control strategies such as spraying and bed nets.

“We’re not targeting to eliminate mosquitoes. We’re really targeting to eliminate the human diseases,” says Scott Miller, deputy director of the malaria team at the Bill & Melinda Gates Foundation.

The foundation started by Bill Gates and his wife, Melinda, is investing in a genetic project aimed at cutting the population of malaria-carrying mosquitoes. During World War II, U.S. forces at Guadalcanal worked on mosquito control.PHOTOS: DAVE THOMPSON/AFP/GETTY IMAGES; ASSOCIATED PRESS

In December, researchers at Imperial College reported in the journal Nature Biotechnology that they engineered genetic changes that could make Anopheles gambiae populations plummet. That is the most common carrier of the deadliest form of malaria in sub-Saharan Africa, where the vast majority of cases and deaths occur.

The researchers used Crispr/Cas9 to disrupt genes involved in producing eggs in females, then built a gene drive that passed that trait along to as many as 99.6% of their offspring. As the trait spreads, more females become sterilized, gradually reducing the population, the researchers said.

Imperial College evolutionary geneticist Austin Burt says he and his colleagues are now refining their work.

The Gates Foundation is investing $75 million in the Target Malaria project, partly to help prepare laboratories in Mali, Burkina Faso and Uganda, lay the groundwork to seek regulatory approvals and train staff to conduct field trials. Dr. Miller says release of the engineered mosquitoes into the wild is about a decade away.

Researchers in Australia have developed a way to inject mosquito eggs with a common, naturally occurring bacteria. The eggs need to be injected just once and then pass down the bacteria.

The method is likely to be ready for use far sooner than gene-drive strategies, says Scott O'Neill, director of vector-borne diseases at Australia's Monash University and head of the mosquito-injection program, called Eliminate Dengue. Large-scale trials are planned in Brazil and Colombia. Financial backers include the Gates Foundation.

Despite the early progress in using gene-editing to conquer the world's deadliest mosquitoes, many scientists are chastened by history.

A truck sprays the pesticide DDT on Jones Beach, N.Y., in 1945. The push to go after Aedes aegypti mosquitoes with DDT was largely abandoned by the 1970s.

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In the 1940s, public-health leaders declared war on Aedes aegypti, going after the insects with aggressive spraying campaigns that included DDT, or dichloro-diphenyl-trichloroethane. By the 1970s, the push was largely abandoned. It succumbed to high costs, feared health risks from DDT, a lack of strong U.S. support and the insect's resurgence in some areas.

Right now, says Texas A&M's Prof. Adelman, gene drive seems like "an all-powerful tool that will win the war for us, but that is exactly the sentiment that people felt when things like DDT first came along.…It's good to be optimistic. But we need to be realistic as well."

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