Modified mosquitoes block malaria

Mosquitoes rapidly spread antimalaria genes throughout population, study says

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Feeding female Anopheles gambiae mosquito, a known carrier of malaria. This specimen had landed a human skin surface, and was in the process of obtaining its blood meal through its sharp, needle-like proboscis, which it had inserted into its human host. Note the red color of the proboscis, as it was filled with blood, as well as the bright red abdomen that had become enlarged due to its blood meal contents. — *CDC/James Gathany*

A breed of malaria-blocking mosquitoes that can spread disease resistance throughout their species has been developed, a team of UC San Diego and UC Irvine scientists (http://www.eurekalert.org/emb_releases/2015-11/uoc--uoc111815.php) said Monday.

If the technology can be deployed safely in nature, it would represent a giant advance in the struggle against the deadly disease. About 198 million people were infected with malaria and about 580,000 died in 2013, according to the World Health Organization. (http://www.who.int/malaria/media/world_malaria_report_2014/en/)

A study describing the technology was published Monday in Proceedings of the National Academy of Sciences (http://www.pnas.org/cgi/doi/10.1073/pnas.1521077112). More work is needed before actual use, the study says. And it won't be enough to eliminate malaria on its own.

Whether and how to use this technology is up to society, the scientists say. Numerous governmental and non-governmental organizations and the public must debate whether the benefits from the technology outweigh any potential risks from altering an ecosystem. There is no plan at this time to test this outside the laboratory.

Using the advanced gene editing method CRISPR, the scientists introduced engineered DNA into mosquitoes of the species Anopheles stephensi, one of the chief carriers of malaria in Asia. The DNA codes for engineered antibodies that attack the malaria parasite.

In lab experiments, the trait spread to 99.5 percent of the offspring of a mating between an unmodified and modified mosquito. This is made possible by another genetic engineering technology called gene drive. This has been recently refined by UCSD scientists Ethan Bier and Valentino Gantz, and described in a paper published in March (http://www.sandiegouniontribune.com/news/2015/mar/19/crispr-ucsd-gantz-bier/).

Bier and Gantz contributed the technology to a collaboration with scientists including UC Irvine's Anthony James, who has been working on ways to prevent mosquitoes from transmitting disease. Gantz was the study's first author; James was senior author.

The modifications spread extremely rapidly by traditional breeding standards, which can take many years.

"In principle, given the 99.5 percent transmission we have observed in our collaborative mosquito experiments, the gene drive element should be able to spread from an inoculating population from about 1 percent to nearly 100 percent of the population in 10 generations, which is less than one season for typical mosquitoes (10-20 generations per year)," Bier said.

The Bier/Gantz form of gene drive works in the reproductive cells by copying the introduced DNA from a modified chromosome inherited from one parent to the corresponding unmodified chromosome inherited from the other parent. It is custom-built to work only within one particular species, Bier said.

The mosquitoes themselves are unharmed, and in fact must remain reproductively fit for the gene drive technology to work. So they would remain a blood-sucking nuisance to be fought by other approaches.

Solid study

On the other hand, the malaria parasites themselves will be under evolutionary pressure to evolve resistance. That has been taken into account, Bier said.

"This concern has been addressed in the design of the anti-malarial gene cassette which target two different plasmodium surface proteins, one required for the parasite to cross from the gut into the body cavity and the other preventing the parasite from getting into the salivary gland," Bier said. "So, as in the case of using a combination of antibiotics or anti-cancer drugs, this arrangement should greatly reduce the likelihood of parasites evolving resistance since they would have to do so simultaneously to two agents, which is very unlikely."

One of the antibodies targets a highly conserved molecule in the parasite, Bier said, meaning that it is so necessary that it presumably can't evolve to a different sequence.

"That said, it is of course possible for parasite resistance to evolve and the development of additional anti-malarial effector proteins will be a priority as this technology moves forward," he said.

The study itself is scientifically "very solid," said Omar Akbari, an assistant professor of entomology at UC Riverside. It expands on the March paper by Bier and Gantz, performed in fruit flies, which only examined a few generations to test the gene drive.

Attempts to engineer gene drives have gone on for more than a decade, Akbari said, but have been hampered by various technical limitations.

"This is a very nice piece of work," Akbari said.

However, more research needs to be done before the method can be considered ready for testing in the wild, apart from the bioethical issues involved.

The system isn't stable in the female germline, he said, but the scientists can get around this flaw by using genetic promotors only in the male germline. Testing for more generations will determine if the modification could resist evolutionary pressures, he said.

New frontier

The technology crosses a threshold that requires a new level of examination, said bioethics experts who reviewed the study.

Bioethicist Dov Fox said the power to remake an entire species by "genetically hacking a trait directly into its wild population, was until recently science fiction."

"By distorting inheritance across a whole population, the 'gene drive' technique is like supercharged selective breeding," said Fox, who teaches health law and bioethics at the University of San Diego.

"Applied to malaria-carrying mosquitoes, it promises to reduce human suffering by reducing the hundreds of thousands every year, mostly children, that the disease kills each year," Fox said. "That makes this technique deeply attractive. But it also risks unintended consequences: introducing dramatic changes to a native population has the potential to throw off a complex ecosystem in unknown ways."

"Could the disappearance of a whole species threaten the existence of predators or others? Might a target parasite simply evolve to attach to a new carrier? We can’t know for sure. Concerns like these give reason to safeguard ongoing research and proceed with caution," Fox said.

UC San Diego bioethicist Michael Kalichman said the technology is "an exciting next step" in a strategy that could radically reduce malaria transmission. But other issues remain to be resolved.

"One issue is that even if the right genetic changes can be made, it isn't clear how that will play out in the wild," Kalichman said. "For example, is it possible that the proposed genetic change will successfully move through the population (as predicted), but that the change will also in some way make the species of mosquito less fit for survival?"

While the study authors cite previous work suggesting that reproductive fitness is not changed by the genetic manipulation, Kalichman said that question can't be definitively answered until a modified mosquito population is introduced into the wild.

"While there are many reasons we might be just as happy if a population of mosquitoes were completely eliminated, that begs the question of what will happen when this component of an ecosystem is removed," Kalichman said. "There could be profound downstream consequences that we can't yet anticipate. This isn't necessarily an insurmountable challenge, but one which argues for caution in moving forward."

Kalichman said that risk can be reduced by keeping a captive population of unmodified mosquitoes. If the wild population is completely eliminated, the unmodified mosquitoes could be released to restore ecological balance.

The human element also needs consideration, he said. This includes what people think of genetically modified organisms, what local regulatory requirements need to be met, and international considerations.

Other topics include how to get informed consent and what level of agreement is necessary to go ahead with introducing the genetically engineered mosquitoes," Kalichman said.