Researchers create mosquito resistant to dengue virus

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Genetically engineered mosquitos resist dengue fever virus. Credit: Army Medicine, Flickr

Researchers from the Johns Hopkins Bloomberg School of Public Health have genetically modified mosquitoes to resist infection from dengue

virus, a virus that sickens an estimated 96 million people globally each year and kills more than 20,000, mostly children.

The research, published Jan. 12 in *PLOS Neglected Tropical Diseases*, shows it is possible, in the lab, to boost the Aedes aegypti mosquito's natural ability to fight the dengue virus as a first step toward suppressing its ability to spread the disease. The findings could be a prelude to developing a strategy to eliminate the threat of dengue. Forty percent of the world's population live in areas where they are at risk of the virus, which is most common in Southeast Asia and the western Pacific islands and has been rapidly increasing in Latin America and the Caribbean.

"If you can replace a natural population of dengue-transmitting mosquitoes with genetically modified ones that are resistant to virus, you can stop disease transmission," says study leader George Dimopoulos, PhD, a professor in the Department of Molecular Microbiology and Immunology and a member of the Johns Hopkins Malaria Research Institute. "This is a first step toward that goal."

While the new mosquitoes significantly suppressed dengue virus infection they did not show any resistance to Zika or chikungunya, two other viruses carried by *Aedes aegypti*. "This finding, although disappointing, teaches us something about the mosquito's immune system and how it deals with different viruses. It will guide us on how to make mosquitoes resistant to multiple types of viruses" he says. While being resistant to one disease is a good start, "ideally, you want a mosquito that is resistant to other viruses as well," he says.

Mosquitoes acquire viruses by feeding on the blood of humans who are sickened with them. Once the mosquitoes are infected, they bite other healthy humans and pass the disease along to them. Many efforts are underway to figure out how to break that cycle, and most scientists agree that the use of multiple methods will be required to eliminate dengue and

other mosquito-borne diseases.

Researchers say that *Aedes aegypti* mosquitoes do mount an immune system response when exposed to the dengue virus, but it appears to be too weak to stop transmission. Knowing this, Dimopoulos and his colleagues were able to manipulate a component of the immune system, the JAK-STAT pathway, that regulates production of antiviral factors. They did this in a part of the mosquito known as the fat body, its version of the liver. Notably, the JAK-STAT pathway is involved in antiviral activity in humans as well.

The genetic modification resulted in fewer mosquitoes becoming infected, and most of those that did had very low levels of dengue virus in their salivary glands, the location from which it gets transmitted to humans. These experiments, however, didn't lower the level of virus in all mosquitoes to zero, something that puzzled the scientists. They say more research is needed to understand whether this level of virus suppression would be enough to halt disease transmission, and they are working on other experiments to see if they can produce antiviral factors in the gut, which could assist in inducing a stronger immune response and possibly confer resistance to the other viruses.

The researchers found that the dengue-resistant mosquitoes live as long as the wild mosquitoes, though they do produce fewer eggs, most likely because the same mechanism involved in dialing up the immune system to fight dengue also plays a role in egg production.

"It's likely if we turn this on in the gut we could have a much stronger effect, without compromising egg production," Dimopoulos says.

Once genetically modified mosquitoes resistant to dengue are developed, scientists would test them in large field cages to see how they compete with wild mosquitoes in very controlled experiments.

The best way to ensure that the genetically modified mosquitoes become the dominant type is for researchers to add something known as a "gene drive" to the new mosquitoes. This essentially makes them genetically superior mosquitoes by ensuring that all offspring of wild- type and genetically modified mosquitoes will be disease resistant.

"In this way, you could convert a disease-transmitting mosquito population to one that does not transmit disease," Dimopoulos says.

Scientists acknowledge there are concerns with the release of genetically modified mosquitoes in the environment since they can't be recaptured. They are there to stay.

"This is why extensive lab and semi-field studies are required to get it right," he says. If the scientists can get this to work, however, it could become a very effective way of controlling disease. It could be done without people having to actively participate. They would get long-lasting protection without having to take medication, get vaccinated or use bed nets or repellants.

Dimopoulos and other researchers are working on similar models in *Anopheles* mosquitoes which carry the parasite that causes malaria.

The entire process of developing and introducing disease-resistant mosquitoes into the wild could take a decade or more.

More information: "Engineered Aedes aegypti JAK/STAT pathway-mediated immunity to dengue virus" *PLOS Neglected Tropical Diseases*, 2017. journals.plos.org/plosntds/art … journal.pntd.0005187

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