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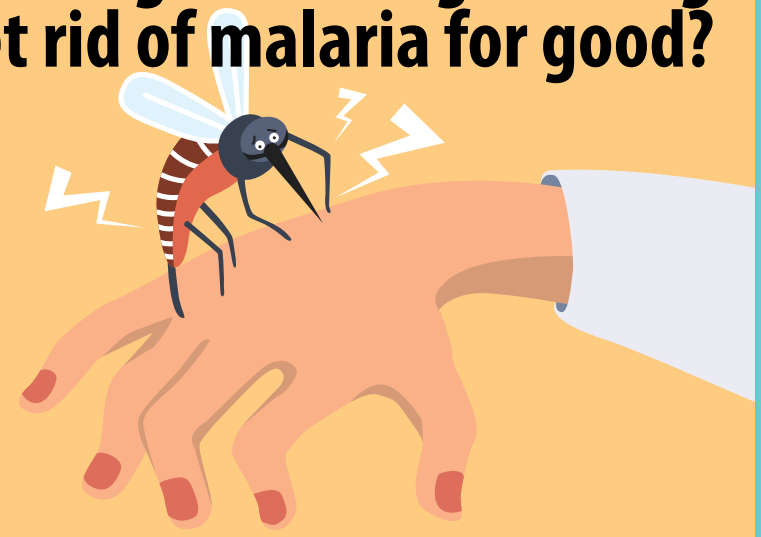
How can we use genetic engineering to get rid of malaria for good?



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Abstract

Nobody likes the buzzing sound or itchy bite of mosquitoes. But mosquito bites (only females bite, by the way!) are not just irritating: they can carry and spread deadly diseases such as *malaria*, dengue, yellow fever and many more. Every year, millions of people die from *mosquito-borne* diseases and most of them are young children. There are ways to get rid of mosquitoes and prevent such diseases, but they are not as effective as we would like.

What if we used *genetic engineering*? Here we modified the genetic makeup of *Anopheles gambiae* mosquitoes (the main carriers of malaria). The *mutation* prevented females from biting and laying eggs. It spread through our caged populations quickly and drove them extinct. Our results pave the way for lowering mosquito populations in the wild and getting rid of malaria in the future.

Introduction

You may have heard about malaria and the devastation it causes in Africa. But did you know that a child dies of malaria every two minutes? Despite global efforts, malaria remains one of the world's deadliest diseases. More than 400,000 people die of it every year, most of them children. Why can't we stop it?

Anopheles gambiae mosquitoes are the main *vectors* of malaria. This means they transmit malaria-causing parasites from one infected human to another. Available methods to control mosquito populations such as spraying *insecticides* or using sleeping nets have helped to prevent malaria, but they are not enough on their own. We believe genetic engineering could be the solution.

In this study, we used a gene-editing tool known as CRISPR/Cas9 (Fig. 1). We developed a way of genetically modifying *Anopheles* mosquitoes to disrupt their sexual development and force the whole population to collapse.

So how did our gene editing work and what could it mean for the future of mosquito control?

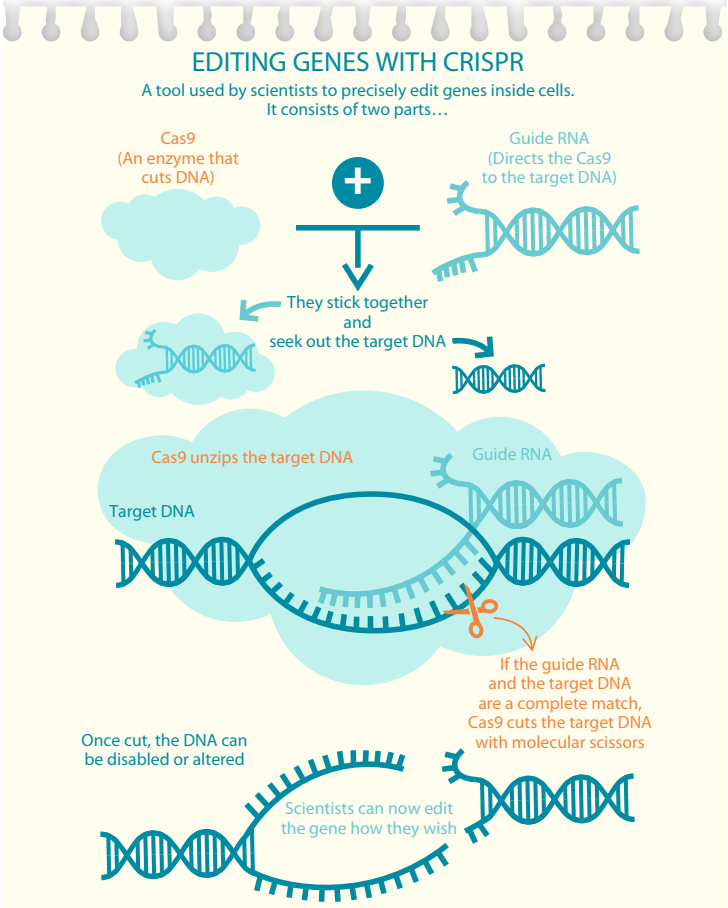


Figure 1:
How CRISPR/Cas9 works. (Adapted from Cancer Research UK.)

Methods

The *doublesex (dsx)* gene determines the sex of each mosquito. The gene is the same in both sexes, but female *dsx* has an extra region of *DNA* called exon5. This female-specific region is responsible for the fertility and body structures of females that allow them to bite and suck blood. Using CRISPR/Cas9 we modified exon5 in mosquitoes. The females changed and the males were unaffected (but still carriers of the altered gene).

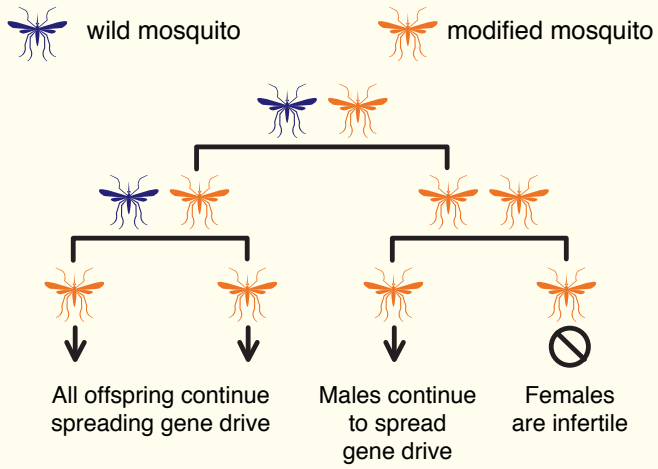
Then, we developed a *gene drive* for the modified exon5 region in the *dsx* gene. Mosquitoes, like humans, carry two copies of each gene in their cells. In sexual reproduction, individuals receive one copy of the gene from the father, and the other from the mother. A gene drive is a genetic technology that enables the mutated gene to copy itself and then replace the unmutated gene that comes from the unmodified parent. This ensures that all of the offspring will carry the mutated gene (see Fig. 2). Therefore, the new mutation will spread through a population at a much higher rate than normal.

Our mathematical model showed that in an initial population with 25% *heterozygous* individuals (those with a single copy of the mutated gene), the mutation would spread to the whole population in 9-13 generations. To test this, we created two caged populations of 600 mosquitoes each. In each group there was:

300 wild-type female + 150 wild-type male + 150 males carrying one copy of the mutation

In each generation, we counted the hatched larvae and genetically screened them for the presence of the modified gene.

Figure 2:
When a modified mosquito mates with an unmodified mosquito in the wild, their offspring are fertile, contributing to the spread of the gene drive. When two modified mosquitoes mate with each other, the female offspring becomes infertile. As the gene drive increases in frequency, the infertile females become more common and eventually the population size reduces.



Results

- Male mosquitoes were unaffected. They continued to breed and spread the modified gene until there were no more eggs.
- Females with one copy of the mutation behaved normally. They had lower fertility but passed the mutation to their offspring.
- Females born with two copies of the mutation had characteristics of both males and females. They had male-type mouthparts (so they couldn't bite or transmit the disease), they were infertile and they couldn't lay eggs. When the mutation spread to enough female mosquitoes, the population couldn't produce offspring and it crashed (Fig. 3).
- In Cage 2, all of the mosquitoes in the 7th generation were mutated. 8th generation females couldn't lay eggs and the population collapsed. Cage 1 reached 100% mutation at the 11th generation, and the collapse happened at the 12th generation. The mutation spread at different rates but both were within the predicted range of our mathematical model. It took about 6 months for both populations to crash.

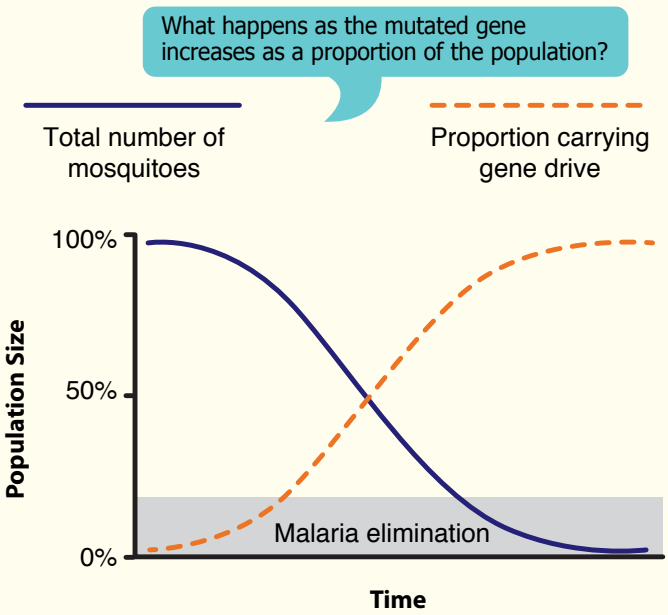


Figure 3:
Effect on mosquito population as the mutated gene spreads. This would lead to the elimination of malaria in the wild.

Discussion

The CRISPR/Cas9 gene drive generated a mutant gene leaving female mosquitoes unable to reproduce. It also allowed the males to continue spreading this female infertility mutation to offspring. If used in the wild, our method could quickly reduce local *Anopheles* populations. Releasing 200 drive-carrying mosquitoes in each village would eliminate malaria across significant areas of Africa in a couple of decades.

But introducing a gene drive into the wild would require agreement at local, national, and international levels. Once released, we cannot keep it in a single country or disable it easily. Some people are worried about the ecological consequences of gene drives. Luckily, every insect species has its own version of the *doublesex* gene so a *dsx* gene drive in *Anopheles gambiae* mosquitoes cannot jump to other insects such as bees. For that same reason, eliminating other mosquito-borne diseases would require different *dsx* gene drives targeting each species of mosquito that carries them.

Conclusion

Gene drives give us a powerful tool in our long and frustrating fight with malaria and other mosquito-borne diseases. But we still need some time for small-scale *field trials* and public approval. In the meantitme, you can do many things to limit mosquito populations and protect yourself:

- Get rid of sources of standing water, like buckets. These are breeding grounds for mosquitoes.
- Protect yourself from mosquito bites when traveling to a high-risk country by wearing long-sleeved shirts and pants, using insect repellents and sleeping under a net.
- Educate yourself and others about the potentials of genetic engineering and genetically modified organisms. Understanding how the technology works and who it affects can build trust in this new technology.

Glossary of Key Terms

Anopheles gambiae – mosquito species that serves as the main vector (carrier) for malaria.

CRISPR/Cas9 – a genetic engineering method used to change the genetic makeup of living organisms. The proteins and RNA molecules used in CRISPR cut and edit targeted sections of a gene very precisely.

DNA (short for DeoxyriboNucleic Acid) – a molecule that carries the genetic instructions used in the growth, development, functioning, and reproduction of all known living organisms, including humans.

Doublesex gene (dsx) – a gene that controls the sexual development of insects.

Field trials – Experiments designed for and conducted outside of the laboratory in a 'real world' setting that is relevant to the question being explored.

Gene – A small section of DNA with the instructions for characteristics of the organism.

Genetic Engineering – the direct manipulation of an organism's genes using technology.

Gene drive – a genetic engineering method that increases the chances of passing down a mutated gene during sexual reproduction. A gene drive gene (mutated gene) copies itself to its counterpart that comes from the normal (unmutated) parent.

Heterozygote – an individual that has two different versions of a particular gene or genes.

Insecticide – a substance (usually chemicals) used to kill insects.

Malaria – a blood disease caused by a *Plasmodium* parasite, transmitted by the bite of infected mosquitoes. The severity of malaria varies based on the species of *Plasmodium*. Symptoms include chills, fever, and sweating, usually occurring a few weeks after being bitten. Treatment includes antimalarial drugs.

Mosquito-borne diseases – diseases that are transmitted by infected mosquitoes. Some examples are malaria, dengue, yellow fever, Zika, and West Nile virus. Different species of mosquitoes transmit different diseases.

Mutation – a change that occurs in a DNA sequence and genes. These changes may result in changes to physical traits.

Vector – an organism that carries and transmits disease-causing pathogens.

Check your understanding

1. *Anopheles gambiae* mosquitoes are a vector species for malaria. What is a vector species? Can you find out about some other vector species and the diseases they transmit?

2. Scientists genetically engineered *Anopheles gambiae* mosquitoes. What were the characteristics of engineered mosquitoes that drove the lab populations to extinction?

3. Scientists used a new approach that made this study so successful at wiping out mosquito populations: CRISPR/Cas9 gene drive. What is the purpose of a gene drive? How does it speed up the spread of a useful genetic mutation?

4. **Writing connection:** This study gives us a very powerful tool in our fight against malaria and other mosquito-borne diseases. But we need public support and approval to use it. Write a letter to a skeptical audience and persuade them to support the genetic engineering method used in this study.

   Consider: Who is your target audience? What are their concerns? How would you address these concerns using scientific evidence?

REFERENCES

Kyros Kyrou, Andrew M Hammond, Roberto Galizi, Nace Kranjc, Austin Burt, Andrea K Beaghton, Tony Nolan, Andrea Crisanti (2018). A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes. Nature Biotechnology.
https://doi.org/10.1038/nbt.4245

World Health Organization: Malaria
https://www.who.int/malaria/en/

Gene Drives Explained: How to Solve Problems with CRISPR
https://www.synthego.com/blog/gene-drive-crispr