**Original Article (DOI): --** 10.1126/science.aaw8737

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**Word count (700-750 max): --**750

**Field: --**Vector biology, mycology, biotechnology

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**Keywords: --** Malaria, Mosquitoes, Vector biology, Mycology, Biotechnology

**Title: --** A special delivery: modifying an insect pathogen to deliver a spider toxin into mosquito blood

**Abstract:--** Female mosquitoes transmit malaria parasites that infect hundreds of millions of people each year. Despite progress we have made toward prevention of this disease, the chemical insecticides we have relied upon to control mosquitoes are not as effective as they used to be. New tools are required to prevent them from transmitting malaria parasites. We have developed a fungus that can deliver an insect-specific toxin into mosquito blood to kill mosquitoes quickly. In a contained trial under field conditions, this biotechnology was shown to be effective at killing wild-caught mosquitoes and hindering their ability to reproduce.

**Suggested Picture--** To be suggested by editor.

**Text: --** Sick female *Anopheles* mosquitoes deliver malaria parasites to hundreds of millions of people worldwide, killing nearly half a million people every year. Without their bites, there would be no malaria. In our lifetimes, chemical insecticides sprayed in houses and applied to bed nets have stopped enough female mosquitoes from biting to decrease the global malaria burden by half. Unfortunately, we did not have much time to savor this victory, as our progress has stalled in recent years.

Efforts have stalled because *Anopheles* mosquitoes gained resistance to chemical insecticides. Imagine these mosquitoes are a taxi delivering malaria parasites (their passengers) to a new person. In 2000, chemical insecticides acted as an effective roadblock, stopping these vectors in their tracks. Today, many mosquitoes can simply avoid this roadblock: this means chemical insecticides, our major tool to control *Anopheles* mosquitoes, are not able to hold back these vectors like they used to. We need more tools to stop mosquitoes from delivering malaria parasites to new people.

A tool that we are developing in Burkina Faso improves on a natural fungal pathogen of mosquitoes. This pathogen, called *Metarhizium pingshaense*, has a taste for mosquitoes, just like some mosquitoes have a taste for us. Close relatives to this fungus, with a taste for other insects, are already applied worldwide to control insects that eat our crops. These fungi are quite common in nature and have been shown to be safe to us.

This mosquito pathogen will kill mosquitoes it touches, just like chemical insecticides. Unlike chemical insecticides, this fungus is alive. If it tastes a mosquito, it will burrow into its blood. This is only half the battle, as the mosquito’s blood is an unsafe place for a fungus. To protect itself from fungus-killing cells in the mosquito blood, the fungus cloaks itself in a protein that makes it invisible to the mosquito. The fungus only wears this invisibility cloaks inside insect blood. With its cloak on, the fungus will slowly multiply until it kills the mosquito.

Impressive as they are naturally, the wild fungus does not kill mosquitoes fast enough to effectively control mosquitoes. If *Metarhizium* infects a mosquito that will soon deliver malaria parasites, these parasites may still make their way into the next person and the female mosquito may even have time to lay eggs. When it comes to human diseases, we don’t have time to wait.

Fortunately, there are many ways we can speed up these fungi. The most promising involves insect-specific toxins that we can borrow from spiders. Though the words “spider toxin” may sound scary, spiders produce a range of proteins in their venom: some target their insect prey specifically, with no effect on us. For our studies, we have borrowed one of these insect-specific toxins called Hybrid from the Blue Mountains funnel-web spider in Australia.

Using the right tools in the lab, we can make the fungus produce Hybrid toxin only when wearing its invisibility cloak. Here, we have given a natural mosquito pathogen the ability to deliver an insect-specific toxin into mosquito blood.

In labs in both the United States and Burkina Faso, we found that this super-charged fungus is more effective against mosquitoes than the natural fungus. To see if this works in field conditions, we tested this strain against wild-caught mosquitoes in a purpose-built facility in the village of Soumousso. This MosquitoSphere has multiple compartments for experiments, separated from each other and the outside by a double layer of mosquito netting. This contains our experiments inside our facility, but allows us to see how well this strain works in field conditions.

Working together on this NIH-funded international collaboration, we were able to test the efficacy of this Hybrid toxin producing fungus in fine detail. We found that in the MosquitoSphere it kills more mosquitoes and kills them faster than the normal fungus, as we saw in the lab. We also found that this new strain dampens the ability of infected mosquitoes to reproduce.

The path forward in our effort to control malaria is one where scientists around the world and technologies, like chemical insecticides and transgenic fungus, work together. This project is an exciting development for this new fungal biotechnology, and it provides an additional tool for us to stop mosquitoes from carrying pathogens from a sick person to a healthy one. Though we have been struggling against malaria parasites and the mosquitoes that carry them from the dawn of civilization, new technologies like this one offer a hopeful glance into our malaria free future.