University of Basel

The Resistant Mosquito

Video Transcript

Mechanisms of insecticide resistance

The fact that mosquitoes transmitting malaria develop phenotypic resistance to the insecticides used in their control raises concerns. If you observe such a resistance in the mosquito field population, you need to identify the most effective insecticides to use. In addition, you need to develop a suitable insecticide resistance management strategy that is tailored to the local mosquito population.

Both tasks start from the same question. You need to identify which mechanism is causing the resistance. In this video, we will identify the major mechanisms that enable the malaria vectors to survive the insecticides. A mosquito surviving vector control has either adapted its behaviour or developed physiological resistance. With these two options, we know of four basic mechanisms that lead to insecticide resistance: Behavioural avoidance, cuticular thickening, metabolic detoxification and target site modification. We will explore all four.

Insecticide-treated bed nets and indoor residual spraying are highly effective approaches to prevent malaria transmission. Both tools target mosquito species that rest or bite indoors. Some years after the massive scale-up of these interventions, researchers have started to observe changes in the behaviour of mosquitoes. The changes reduced the mosquitoes' interaction with the insecticides.

The strategies with which mosquitoes avoid this interaction come in three major forms. The first is temporal. Mosquitoes avoid having to interact with a bed net as they bite people earlier in the evening, before people go to bed. The second avoidance strategy is spatial. Mosquitoes that bite or rest outdoors avoid coming into contact with bed nets or insecticide-sprayed walls. In the third strategy, mosquitoes shift from human hosts to animal blood sources to increase survival. This avoidance strategy is called "trophic".

Avoiding contact with the insecticides seems like an obvious strategy. However, behavioural resistance is extremely difficult to study. As a result, it is far less well understood than the seemingly complex physiological resistance mechanisms. I will explain these next.

An adult mosquito lands on an insecticide-treated surface. The first body parts to touch the insecticides are the tarsi, which are the insect's feet. The insecticide has to penetrate through the mosquito's cuticle. This is the outer non-cellular part of the exoskeleton made of chitin, hydrocarbons and proteins. The insecticide then travels to its target site.

When researchers looked at the cross-section of mosquito legs, they came across an interesting fact. Insecticide-resistant *Anopheles* mosquitoes have significantly thicker cuticles than insecticide-susceptible individuals of the same species. This makes it harder for the insecticide to get through. This mechanism is called cuticular resistance.

Physiologically, the mosquitoes' resistance against insecticide may also derive from its metabolism: the metabolic resistance. In this case, as the insecticide enters the mosquito's body, increased excretion, sequestration or biodegradation of the insecticide may reduce the amount reaching the target sites. This enables the survival of the mosquito. Metabolic resistance can be caused by the increased production of detoxification enzymes, or the production of enzymes that more efficiently detoxify the insecticide.

Target site resistance is caused by genetic mutations that result in slight changes to the molecular structure of ion channels, enzymes or other proteins, that are the insecticides' targets, such that they don't bind or 'fit' efficiently.

For example, insecticides from the pyrethroid and organochlorine classes act as sodium channel modulators. In mosquitoes that are susceptible, these modulators bind to the sodium channels of neurons, forcing them to stay open. This quickly paralyses and knocks down the insect.

Knockdown resistance are mutations in the sodium channels of neurons. They change the structure of the sodium channels such that the modulators can no longer bind properly to their target. Knockdown resistance mutations reduce the impact of both pyrethroids and organochlorines on malaria vector control. In this case, a mechanism that confers resistance to one insecticide also allows mosquitoes to resist other insecticides with the same mode of action. We refer to this phenomenon as cross-resistance.

During my field work in Côte d'Ivoire, I investigated the molecular resistance mechanisms of *Anopheles coluzii* populations that were resistant to a range of insecticides from different classes. I found that several different mechanisms can be present simultaneously in the same individual and within the same mosquito population. We call this multiple resistance.

Multiple resistance and cross-resistance are common phenomena in the field. As they restrict the insecticide choices available, they present a real challenge to mosquito vector control. However, knowing the resistance mechanisms will enable us to optimise vector control as well as the insecticide resistance management strategies.