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Malaria: Dangerous resistance and new hope

Successes in the battle against malaria could be negated because the most important weapons appear to be losing their efficacy. The insecticide pyrethroid is no longer effective; resistance to the active pharmaceutical ingredient artemisinin has developed in some regions.

Experts are concerned about the artemisinin-resistance of parasites that has been detected along the border between Thailand and Cambodia. Because nearly all of the medicines that are used to control *malaria tropica*, the most common type of malaria in Africa, contain artemisinin.

Controlling resistant parasites is suboptimal

In February 2009, the Bill & Melinda Gates Foundation made USD 22.5 million available to the World Health Organization (WHO) to address the new malaria control challenges. The WHO plans to use the funds to control artemisinin-resistant parasites and to prevent them from spreading further. Unfortunately, the only therapy available to do this is ACT, artemisinin-based combination therapy. ACTs consist of artemisinin and a second active ingredient. Due to the second element they are not completely ineffective in this situation, but using them to control artemisinin-resistant parasites is suboptimal. The key to whether controlling artemisinin-resistant parasites will work or not is the choice of the second active ingredient.

There is the danger that the use of ACTs will foster the selection of resistant parasites. The time of year when the parasites are managed – likely in the middle of the malaria season – could also be problematic. There are disproportionately more cases to treat at this time of year than at any other time.

Although the development of resistance is a cause for concern, we need to remember "that it takes a long time from the initial signs of malaria resistance until there is global lack of effectiveness for a medicinal product", notes Harald Noedl of the Institute for Specific Prophylaxis and Tropical Medicine at the Medical University in Vienna, Austria. ACTs are still extremely effective in the grand scheme of things.

Toxic alternatives to the insecticide pyrethroid

Not only have the parasites themselves developed resistance to a key

Background information

Malaria is a constant threat in many areas. In 2008, 109 countries were dealing with ongoing, serious malarial infections. While malaria is still a rural disease, infections are also rising in cities.

Malaria is caused by parasites from the genus *Plasmodium*. The parasites are transmitted by the *Anopheles* mosquito to humans.

There are two main ways to combat malaria:

1. The mosquitoes are controlled with insecticides and the parasites that they are carrying die with them. This way the parasites are not even transmitted to humans.
2. Parasites already in the body are treated with medicines.

Photo: Iafi

Children on a bed protected by mosquito nets in Burundi. The insecticides used to impregnate the nets are losing their efficacy.

insecticide, but the mosquito *Anopheles funestes* has as well. *Anopheles funestes*, one of the most common malaria vectors in Africa, is very resistant to the insecticide pyrethroid. Four classes of insecticides are used to control mosquitoes. The most important are the pyrethroids, which are the least toxic option for humans. But in areas where pyrethroids have lost their efficacy, other insecticides need to be used. "For example, DDT (dichlorodiphenyltrichloroethane) is now being used in Mozambique", reports Charles S. Wondji of the Liverpool School of Tropical Medicine. He is on a team of scientists who recently identified the enzyme responsible for pyrethroid resistance in *Anopheles funestes*. Now an inhibitor needs to be found that blocks the enzyme's effect. Finding an inhibitor would be doubly worthwhile because the second most important malaria vector in Africa, *Anopheles gambiae*, has also developed resistance to pyrethroid. What the researchers did not anticipate, though, is that the enzymes responsible for this resistance are very similar to those that cause pyrethroid resistance in *Anopheles funestes*. The same inhibitor could be used to combat the resistances of both *Anopheles* species.

A very promising outlook, especially since the use of insecticides such as DDT is an alternative with adverse effects. The use of DDT has been banned in most industrialised nations for decades because the active ingredient is not only highly toxic to insects, it is toxic to the environment and humans as well.

Vaccination and traditional pest control

In the not too distant future a new solution to the malaria problem could become available: vaccination. Researchers at the PATH Malaria Vaccine Initiative have developed a malaria vaccine. In a new study, it protected fifty percent of the babies from being infected with malaria. The vaccine, which is called RTS,S/AS, triggers an antibody reaction that prevents the infection from being transmitted from mosquitoes to humans. "We will probably be able to use the vaccine in four to five years", states Philip Benjon, co-author of the study.

It is possible that vaccination will be an effective way to combat malaria in the future, but it could be that malaria is best controlled by returning to traditional methods, such as killing mosquito larvae using the natural toxin found in the seeds of the neem tree. This toxin is also manufactured synthetically and is available on the market as a commercial product. However its cost is so high that it is impossible to use it in the affected countries, for example, Niger. This is why the use of neem tree seeds is a good solution, especially in rural areas. "The idea of managing the environment and using local solutions seems to be very interesting in and of itself, but it has to be developed in a complementary way with conventional approaches", says Jean-Bernard Duchemin, of the Insitut Pasteur, Genetics and Genomics of Insect Vectors (GGIV) Unit, Paris, France. "It would be dangerous to think that only one solution could eradicate the malaria problem."

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