Malaria – beating the threat of insecticide resistance
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BY JANET ANDERSON

Great progress has been made in recent years in the fight against malaria, but increasing insecticide resistance poses a serious problem. There are currently only four classes of insecticides available for adult mosquito control in public health and the number of species developing resistance to them is on the rise. BASF is working with international public health partners to develop a new generation of malaria prevention products to help address this challenge.

“The mosquito is the most dangerous animal in the world, because, when it comes to killing humans, no other animal even comes close.”

Bill Gates, Bill & Melinda Gates Foundation
Malaria is preventable and treatable but it still affects more than half of the world’s population, predominantly women and children.

In 2013:
- 3.3 billion people in nearly 100 countries were at risk of being infected with malaria
- 198 million people contracted malaria globally
- 584,000 people died of malaria
- 90% of deaths caused by malaria were in Africa
- 78% of deaths were among children under the age of five

**ERADICATING MALARIA – A BOLD PROPOSAL**

Malaria is a problem in nearly 100 countries across the world, particularly in the sub-Saharan Africa, Western Pacific and South East Asia regions. According to the latest figures in the WHO World Malaria Report published in December 2014, an estimated 3.3 billion people are at risk of being infected with malaria and developing the disease. WHO estimates that 198 million people globally contracted malaria in 2013 and 584,000 died of the disease. Of these deaths, 90 percent were in Africa and 78 percent were among children under the age of five.

Philanthropist Bill Gates has described malaria as a “mass killer” and has made it a top priority of the Bill & Melinda Gates Foundation. “The mosquito is the most dangerous animal in the world,” he says, “because, when it comes to killing humans, no other animal even comes close.”

Halting and reversing the incidence of malaria by 2015 is one of the UN Millennium Development Goals. The ultimate aim, though, is to eradicate the disease globally. Bill and Melinda Gates made this bold proposal at a conference of experts in Washington, US in 2007. “To aspire to anything less is just far too timid a goal for the age we’re in,” Melinda Gates said. “It’s a waste of the world’s talent and intelligence, and it’s wrong and unfair to the people who are suffering from this disease.”

Since then, huge progress has been made. In the last decade, the number of new cases has declined by 25 percent globally and deaths from malaria have fallen by 47 percent. WHO estimates that 3.9 million children’s lives have been saved since 2000. The number of countries on the path to eliminating malaria has increased.

This progress has been achieved by fighting on several fronts: by using Rapid Diagnostic Tests (RDT) and drugs against the plasmodium parasite that causes malaria, while simultaneously fighting the mosquitoes, or “vectors”, that transmit plasmodium. Vector control is an essential part of the fight. Drugs and vaccines can only have a chance of eliminating the disease when transmission rates are reduced. According to WHO, vector control is the only intervention that can reduce malaria transmission from a very high level to close to zero.

There are two modern methods of preventing mosquitoes from biting people: insecticide treated bed nets and insecticide sprays. Long-lasting insecticide treated nets (LLINs) protect people while they sleep and kill mosquitoes that touch the nets. Indoor residual spraying (IRS) coats walls and ceilings of homes with an insecticide that kills the mosquitoes. In 2014, over 200 million LLINs were delivered across Africa. Worldwide, in 2013, 124 million people were protected by IRS.

The success of these two methods has been impressive, the fight against malaria has been going in the right direction for over a decade and the malaria map is shrinking. But now there is a serious risk that these gains could be lost.

**THE RISK OF INCREASING INSECTICIDE RESISTANCE**

The problem of growing resistance to the insecticides currently in use is recognized by public health workers, scientists and the WHO.

Part of the problem is that there are currently only four classes of insecticides available for adult mosquito control in public health – pyrethroids, DDTS, carbamates and organophosphates. It has been more than 30 years since a new public health insecticidal active ingredient has appeared on the commercial market. At the insecticides used for LLINs are based on pyrethroids. Their widespread use has enabled the highly adaptable mosquito population to develop resistance to these chemicals.

The number of countries reporting resistance grows each year. Reduced susceptibility to pyrethroids has been confirmed in mosquitoes in West, Central and East Africa. Over 60 countries have reported resistance to at least one insecticide and some report resistance to all four.

“Resistance is a reality,” says Anton Gerické, a consultant for Avima, a South Africa-based company and BASF partner. He has been working in malaria vector control since 1990. Avima supplies insecticides across southern Africa and supports the implementation of IRS campaigns. Gerické and his colleagues have extensive experience training people who work in the field. They see, first hand, the threat of resistance. “We know resistance is growing in some places because the people treating and monitoring the disease are reporting increases in cases of malaria where previously the numbers had been dropping,” he said.

“Maintaining effective control is becoming difficult as conventional tools become less effective year on year. There needs to be detailed monitoring of resistance.”

The problem has been the focus of a three-year research project carried out in Vallen de Kou, in Burkina Faso by Professor Hilary Ramson, head of the Vector Biology Department at the Liverpool School of Tropical Medicine in the UK, and her colleagues. “Burkina Faso is known to be a hot spot for insecticide resistance,” she said. “There is a lot of awareness that resistance is there. What we need is an adequate and robust tool for measuring resistance.”

The resistance heat map shows current incidents of resistance in countries across the world:
http://mappalaria光彩tech.biovigilant.com. The resistance heat map shows current incidents of resistance in countries across the world:

**HARSH SELECTION: HOW INSECTICIDE RESISTANCE INCREASES IN THE MOSQUITO POPULATION**

- The naturally occurring genetic mutations which allow for insecticide resistance in mosquitoes are rare.
- When mosquitoes are exposed to insecticides in treated bed nets, sprays and other insect controls...
- …the susceptible are killed but the survivors go on to reproduce, transferring the genetic change that confers resistance to their offspring...
- …and so the resistant population grows.
- If this advantage is maintained by continually using the same insecticide...
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**REPORTED INSECTICIDE RESISTANCE, 2010-2013**

- 53 countries reported mosquito resistance to at least one insecticide used for malaria control.
- 41 countries reported mosquito resistance to two or more insecticides used for malaria control.

- Total number of countries reporting: 65
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**WITH THEIR RELATIVELY SHORT LIFE CYCLE AND HIGH RATES OF REPRODUCTION, MOSQUITOES ARE ABLE TO DEVELOP RESISTANCE RAPIDLY.**

For more information about resistance management, including the latest version of the Insecticide Resistance Management Manual v.3.0 from April 2014, visit the IPAC website: http://www.irs-online.org/learn/public-health.
try to do is to look at how quickly it is increasing. It was already clear that most of the mosquito population had some level of resistance. The real surprise to us was that the strength of resistance was increasing very rapidly. Within 12 months, the mosquitoes increased their level of resistance 10-fold. The local malaria vector population is now more than 1,000-fold more resistant than a susceptible strain.”

WHO recognizes the seriousness of this threat. At the 2014 meeting of the American Society of Tropical Medicine and Hygiene, Dr. Pedro Alonso, director of the WHO Global Malaria Program, said, “I don’t think we can overemphasize how critical insecticide resistance is, or the threat that it imposes on the gains achieved over the last decade. We need to pay very close attention to this problem.”

A NEW APPROACH IS NEEDED

At the heart of the campaign to tackle the threat of insecticide resistance is the Innovative Vector Control Consortium (IVCC), set up in 2005 with a grant from the Bill & Melinda Gates Foundation to combat insect-borne diseases. IVCC works with international partners to support the development and introduction of new insecticides.

In order for a new insecticide to beat resistance, it has to work in a different way to the currently available insecticides and to have a new “mode of action.” Pyrethroids, DDT, carbamates and organophosphates are neurotoxins, which means they kill mosquitoes by impeding nerve transmission. Since 2010, BASF has been collaborating with the IVCC and LSHTM to develop and bring to the market a new public health insecticide called chlorfenapyr, which has been used in agricultural and urban pest control worldwide since 1995. Unlike any of the currently available insecticides for malaria use, it belongs to the pyrrole class of chemistry and has an entirely different mode of action, making it unlikely to show cross-resistance in mosquitoes that are resistant to neurotoxic insecticides.

“Pyrethroids work by preventing the transmission of signals between synapses,” said Dr. Austin, global product development manager at BASF and a trained entomologist. “They act on the insects’ central nervous system and cause paralysis. Chlorfenapyr, on the other hand, is a physiological toxin. It disrupts energy generation in the mitochondria.” A key difference is the speed with which the two insecticides kill the mosquito. Pyrethroids are a relatively quick-kill. Chlorfenapyr by contrast, is a pro-drug, meaning it has to be metabolized by the insect to the active form. In most cases, it takes from 24 to 72 hours for the insect to die. Although it is slower to act than pyrethroids, the same metabolic mechanism that protects pyrethroid-resistant mosquitoes from neurotoxins, acts against them with chlorfenapyr – their metabolisms convert the drug with higher efficiency.

The delayed mortality has its benefits, according to Dr. Austin. “Before it is metabolized by the insect, chlorfenapyr is relatively innocuous, which means the insect doesn’t see it in the environment and so doesn’t avoid it. Also, by being slower to act, it allows time for a female to lay her eggs, thus preserving genes that are susceptible to chlorfenapyr and meaning that resistance is less likely to develop as quickly,” said Dr. Austin. “But the most important point is that it kills resistant mosquitoes.” Chlorfenapyr is unique in a market that’s almost entirely neurotoxic insecticides.

“Pyrethroid resistance is increasing, and so is the demand for new products,” said Dr. Austin. “Although highly toxic against mosquitoes, pyrethroids, alpha-cypermethrin. In experimental huts, these nets significantly improved control of pyrethroid-only nets and withstood WHOPES standard washing over 20 washes.”

It is clear that chlorfenapyr has an excellent potential for LLIN and IRS, which is why BASF is investing in its development. “We are enthused to be able to make this contribution to the fight against malaria,” said Egon Weinmüller, head of business management for global public health at BASF. “As a viable alternative to the currently used insecticides, we hope it will contribute to saving many lives.”

PROMISING EARLY RESULTS

As this is the first use in public health for chlorfenapyr, it has to be tested through the WHO Pesticide Evaluation Scheme (WHO-PECS) to ensure it meets international safety standards. Sylondio® 240 SC is currently at an advanced stage of WHO-PECS testing, while Interceptor® G2 is under evaluation.

“The early lab tests of chlorfenapyr shows no cross resistance to the other four classes of public health pesticides. As an IRS: It has been shown to cause mortality to mosquitoes for up three months when applied as a residual spray (IRS) to surfaces such as wood, thatch, cement, or mud. BASF is developing an IRS and an LLIN based on chlorfenapyr. The LLIN is a new generation of BASF’s Interceptor mosquito nets, with the trade name Interceptor® G2. The IRS is called Sylondio® 240 SC. Tests show chlorfenapyr:

- is safe for people when used correctly
- is rapidly metabolized and excreted by mammals and fish
- is suitable for LLIN and IRS shows no cross resistance to the other four classes of public health pesticides

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Published by BASF SE
Professional & Specialty Solutions
67117 Limburgerhof
Germany

Layout & Design by
Axel Springer SE
Corporate Solutions
Axel-Springer-Straße 65
10888 Berlin

April 2015