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Malaria – Beating the Threat of Insecticide Resistance

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LLIN

100% Polyester net

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INTECERPTOR
la solution durable
pour protéger la nuit contre
la transmission du paludisme

INTERCEPTOR FENDOZIN
protège pendant la nuit contre
la transmission du paludisme

Malaria – beating the threat of insecticide resistance

By Janet Anderson

“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

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.

Eradicating Malaria – A Bold Proposal

Malaria is a problem in 106 countries, particularly in the African, South-East Asian and Eastern Mediterranean regions. According to the latest figures in the WHO World Malaria Report published in 2015, an estimated 3.2 billion people are at risk of being infected with malaria and developing the disease. The WHO estimates that 214 million people globally contracted malaria in 2015 and 438,000 died of the disease. Of these deaths, 90 percent were in Africa and 70 percent were 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 was one of the UN Millennium Development Goals. The ultimate aim, though, is to eradicate the disease. Bill and Melinda Gates made this bold proposal at a conference of experts in Washington, D.C., USA 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.”

Between 2000 and 2015, huge progress has been made. The number of new cases has declined by 37 percent globally and deaths from malaria have fallen by 60 percent. WHO estimates that 5.9 million children’s lives have been saved since 2000. The number of countries on the path to eliminating malaria is increasing.

This progress has been achieved by fighting on several fronts: by using Rapid Diagnostic Tests

In 2015:

3.2 billion

people in over 100 countries were at risk of being infected with malaria

214 million

people contracted malaria globally

438,000

people died of malaria

90%

of deaths caused by malaria were in Africa

70%

of deaths were children under the age of five

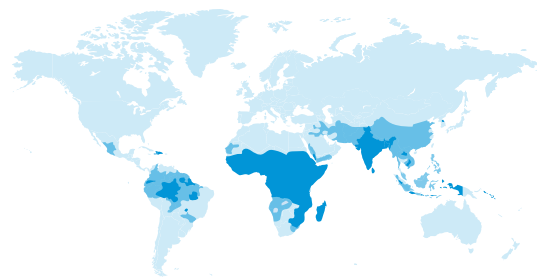
Source: WHO Malaria Fact Sheet: World Malaria Report 2015

(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 levels are reduced. According to the 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 (LLIN) 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 2014, 116 million people were protected by IRS.

“MAINTAINING EFFECTIVE CONTROL IS BECOMING DIFFICULT AS CONVENTIONAL TOOLS BECOME LESS EFFECTIVE YEAR ON YEAR.”

Anton Gericke
 Consultant for BASF
 Partner, Avima



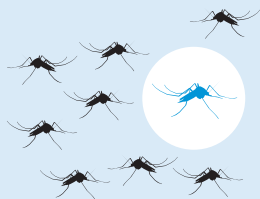
- Malaria transmission occurs throughout
- Malaria transmission occurs in some parts
- Malaria transmission is not known to occur

Shrinking The Malaria Map

In 2014, of the 106 countries with ongoing malaria transmission, 16 countries reported zero cases. Fifty-seven countries achieved reductions in new malaria cases by at least 75% by 2015.

HARSH SELECTION: HOW INSECTICIDE RESISTANCE INCREASES IN THE MOSQUITO POPULATION

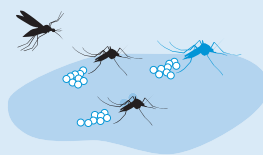
The naturally occurring genetic mutations which allow for insecticide resistance in mosquitoes are rare.



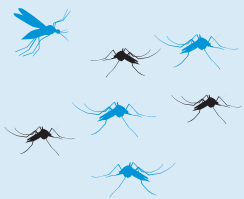
When mosquitoes are exposed to insecticides in treated bed nets, sprays and other insect controls...



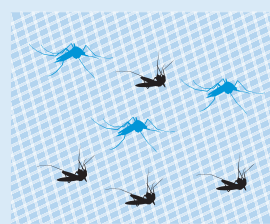
...the susceptible are killed but the survivors go on to reproduce, transferring the genetic changes that confer resistance to their offspring...



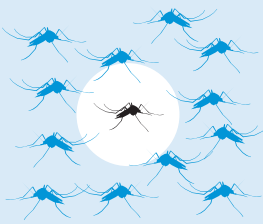
...and so the resistant population grows.



If this advantage is maintained by continually using the same insecticide...



...the resistant mosquitoes eventually become numerous within the population.



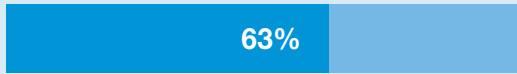
REPORTED INSECTICIDE RESISTANCE, 2015

60 countries reported mosquito resistance to at least one insecticide used for malaria control.



Total number of countries reporting: **70**

49 countries reported mosquito resistance to two or more insecticides used for malaria control.



Total number of countries reporting: **78**

Source: WHO World Malaria Report 2015

The resistance heat map shows current incidents of resistance in countries across the world:

<http://irmapperjavascripwtwcfservice.cloudapp.net/>

WITH THEIR RELATIVELY SHORT LIFE CYCLE AND HIGH RATES OF REPRODUCTION, MOSQUITOES ARE ABLE TO DEVELOP RESISTANCE RAPIDLY.



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, DDT, carbamates and organophosphates. It has been more than 30 years since a new public health insecticidal active ingredient has appeared on the commercial market. All 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 49 report resistance to all four.

“Resistance is a reality,” says Anton Gericke, 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. Gericke 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.



Dr James Austin (middle) with Professor Frank Moshia, principle investigator at the Kilimanjaro Christian Medical Centre (right), and August Mtuy, research assistant scientist at Mabogini experimental hut station, Tanzania (left).

“WHAT WE TRIED TO DO IS TO LOOK AT HOW QUICKLY RESISTANCE IS INCREASING. IT WAS ALREADY CLEAR THAT MOST OF THE MOSQUITO POPULATION HAD SOME LEVEL OF RESISTANCE.”



Professor Hilary Ranson
Head of the Vector Biology Department at the Liverpool School of Tropical Medicine

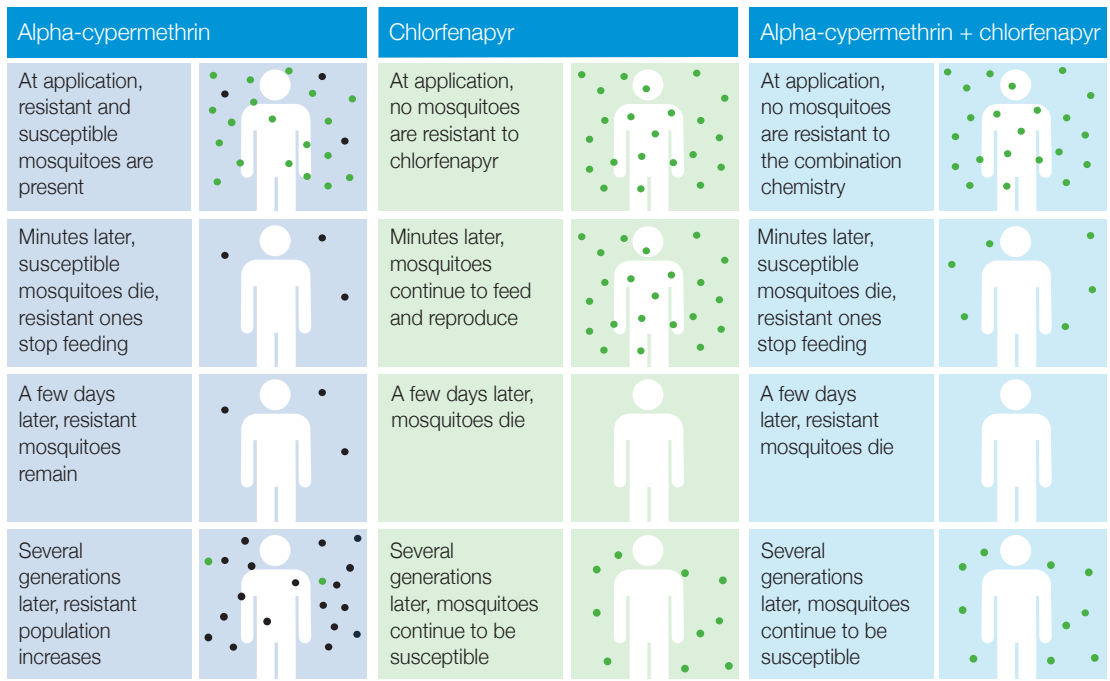
Tests show chlorfenapyr:

- 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

As an IRS: it has been shown to cause mortality to mosquitoes for up three months when applied as a residual spray to surfaces such as wood, thatch, cement, or mud.

“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 Vallée de Kou, in Burkina Faso by Professor Hilary Ranson, 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



- Susceptible mosquitoes
- Resistant mosquitoes

“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.”

Dr Pedro Alonso
 Director, WHO Global Malaria Program

spot for insecticide resistance,” she said. “There is a lot of awareness that resistance is there. What we tried 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.”

The 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 than the currently available insecticides – it needs 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 an innovative LLIN to combat resistance, combining the insecticides alpha-cypermethrin and a completely new insecticide in the public health sector, chlorfenapyr. Chlorfenapyr has been used in agriculture 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



Field work: discovering how insecticide resistance is tested in the field at IVCC's trial site in Moshi, Tanzania. (l to r) Raphael N'Guessan, Bill Gates, Sue Desmond-Hellman, Dave Malone. Photo: ©Bill & Melinda Gates Foundation/Samantha Reinders

“WE ARE PLEASED TO BE ABLE TO MAKE THIS CONTRIBUTION TO THE FIGHT AGAINST MALARIA. AS A VIABLE ALTERNATIVE TO THE CURRENTLY USED INSECTICIDES, WE HOPE IT WILL CONTRIBUTE TO SAVING MANY LIVES.”

Egon Weinmüller

Head of Business Management,
Global Public Health, BASF

different mode of action, making it unlikely to show cross-resistance in mosquitoes that are resistant to neurotoxic insecticides.

“Alpha-cypermethrin acts on the insects’ central nervous system and causes paralysis,” said Dr James Austin, global product development manager at BASF and a trained entomologist. “Its mode of action has proven extremely effective in quickly knocking down mosquitoes. However, when large parts of an insect population die off quickly, they fail to reproduce, leaving a small number that are resistant. As those remaining insects reproduce, the number of resistant members grows.”

Unlike the fast knockdown of alpha-cypermethrin, chlorfenapyr disables an insects’ ability to produce energy. The delayed mortality allows insects to reproduce and pass on susceptible genes to the next generation.

The combination of chlorfenapyr and alpha-cypermethrin often yields a unique metabolic effect in resistant mosquitoes. Alpha-cypermethrin activates the detoxifying P450 enzymes in the insect which would typically render it less effective. However, the same

detoxifying P450 enzymes that deactivate alpha-cypermethrin, speed up the activity of chlorfenapyr, likely providing improved performance against resistant mosquitoes.

The IVCC, too, sees great promise for the future. “New approaches that safeguard and expand active agents currently available are essential. That’s the only way we are going to get a handle on the ever-increasing levels of resistance,” said Dr Robert Sloss, former portfolio manager for public health products at the IVCC.

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 Sylando® 240 SC.

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 (WHOPES) to ensure it meets international safety standards. Sylando 240 SC is currently at an advanced stage of WHOPES testing, while Interceptor G2 is under evaluation.

Biological tests are being carried out by LSHTM, supported by IVCC, to prove chlorfenapyr can be effective against mosquitoes that have developed resistance to other insecticides and that, when applied to a LLIN, it can still be effective after 20 washes. Tests are being carried out in experimental huts set up in Benin, Burkina Faso and Tanzania – all malaria endemic areas. These tests are a necessary addition to lab tests. “Ultimately, you only get a true picture of how a new product is likely to work against real mosquitoes in an African setting,” said Dave Malone, IVCC’s technical manager.

Dr Raphael N’Guessan, a lecturer in medical entomology at LSHTM and a West Africa IVCC program manager, is carrying out the trials at a research station in Benin. The results so far are promising. “The early lab tests of chlorfenapyr showed that there was no cross resistance with the other classes of insecticides currently in use,” he says. “Although highly toxic against mosquitoes, chlorfenapyr is slow-acting and, unlike pyrethroids, does not prevent bloodfeeding. Interceptor® G2 is therefore coated with a mixture of chlorfenapyr and a pyrethroid, alpha-cypermethrin. In experimental huts, these nets significantly improved control of pyrethroid-resistant malaria vectors compared to pyrethroid-only nets and withstood WHOPES standard washing over 20 washes.”

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

Progress Only Counts If We Keep Going

Professor Ranson has been watching the development of chlorfenapyr with great interest. “I think it is one of the tools that is the closest to being available and doing something about tackling pyrethroid resistance,” she said. “We’ve got to take pyrethroid resistance extremely seriously. New products with alternative insecticides in them are urgently needed and very welcome.”

For those living in malaria-endemic regions, it is vital that the fight continues. As Bill Gates said in a speech he made in 2007, “If you stop half way, you don’t get half the benefit, you could end up with zero percent of the benefit. The progress counts only if we keep it going.”

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