

A Conversation with Abraham Mnzava on October 18, 2013

Participants:

- Abraham Mnzava - Coordinator, Malaria Vector Control Unit, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Elie Hassenfeld – Co-founder and Co-Executive Director, GiveWell

Summary

GiveWell spoke with Abraham Mnzava regarding the issue of mosquitoes becoming resistant to insecticides, and the threat that poses to the effectiveness of long-lasting insecticide-treated nets. Dr. Mnzava discussed the fact that there is a shortage of evidence on the issue because the operational impact of resistance is difficult to measure due to a number of confounding factors – some of which may not necessarily be related to the implementation of nets per se. Since treated nets with pyrethroids work in a number of different ways – through killing, blood feeding inhibition and as a physical barrier, in the presence of resistance, nets could still offer some level of protection. For this reason and in the absence of alternative active ingredients (molecules) to treat nets other than with pyrethroids, the World Health Organization continues to recommend the use of nets.

Moreover, given the efforts that have gone into scaling up this intervention, explaining to countries that nets should not be used when the evidence is weak, will be difficult. Our message to countries and partners should be: insecticide resistance is a potential threat, while countries continue to promote the use of nets, they should at the same time strengthen their capacity to routinely monitor resistance and malaria cases and use that information to implement strategies that will delay and stop the spread of resistance. Since resistance is focal, the introduction of rotational use of insecticides for house spraying will help in preserving the few tools we have at our disposal to manage resistance. There is a need for more research on this issue, as well as a need for more investment in human resource capacity so that effective research, monitoring, and implementation of appropriate interventions can be carried out.

Dr. Mnzava also discussed the World Health Organization's process of recommending new malaria control tools/technologies, as well as opportunities for donors to get involved in human capacity investment and on insecticide resistance monitoring, research and management.

Note: This set of notes was compiled by GiveWell and gives an overview of the major points made by Dr. Mnzava.

Current state of insecticide resistance

Only weak data on the impact of mosquito resistance to insecticide on malaria control currently exists. It is very difficult to design studies to accurately measure the impact of

resistance on malaria transmission. Randomized controlled trials are not possible because resistance isn't homogeneously or randomly distributed.

There has only been one instance of pyrethroid resistance contributing to malaria control failure, in South Africa, and in that case it was related to indoor residual spraying (IRS) and not to long-lasting insecticide-treated nets (LLINs).

Current levels of insecticide resistance are unlikely to have an impact on the overall effectiveness of LLINs. The World Health Organization's (WHO) Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM) argues that resistance can develop but remain at a low level for some time. It is not clear when we should expect resistance levels to impact on the number of malaria cases. For this reason, countries need to routinely monitor resistance, identify the different types of resistance mechanisms and preemptively introduce measures that mitigate the potential impact of resistance.

Resistance mechanisms

There are two kinds of resistance mechanisms. KDR-based resistance is not expected to have an impact on malaria transmission. Most scientists agree that the other type, metabolic resistance, will contribute to the number of malaria cases increasing.

LLINs protect people in more ways than simply killing mosquitoes. The insecticide in the net may have a deterrence effect to mosquitoes, and could make them less likely to feed (except when the vectors have metabolic resistance). LLINs also still have protective effects in areas of resistance since they act as physical barriers to prevent mosquitoes from biting.

An experimental hut study by Mark Rowland in western Africa found 30-40% of the protective effect of nets to be due to factors other than the mosquitoes being killed. These effects have been documented in numerous studies. However, more research is needed on this topic.

World Health Organization recommendation

LLIN distribution has been scaled up for years, so recommending the total removal of LLINs at this point will be premature when the evidence of control failure is weak and when in fact there are measures that can be used along with LLINs to manage and preserve pyrethroids. While this approach would be costly and perhaps a bit challenging due to lack of capacity at country level, WHO continues to recommend the use of LLINs. In addition, while resistance has been detected in some locations, it is likely that in some other areas, mosquitoes continue to be susceptible to pyrethroids.

The consensus among stakeholders has been to continue to promote the use of LLINs but at the same time encourage countries and control programs to introduce IRS with rotating insecticides.

If there were well-priced and effective alternatives for IRS as well as for treating nets, the WHO would not continue to encourage the use of pyrethroid-treated LLINs. For countries

without experience with IRS, it would require substantial work and cost to establish IRS programs.

Combating resistance

If countries had sufficient capacity, teams could map the areas for resistance and target areas with documented resistance with IRS with non-pyrethroid insecticides, such as carbamate insecticides. One to three years later they could switch to another class of insecticide, and later another, and then eventually it might become possible to return to pyrethroids.

On Bioko Island, pyrethroid resistance began to develop, so they switched to using a carbamate. With strong monitoring systems, it was possible to show that pyrethroid resistance fell, and it became possible to use pyrethroids again.

GPIRM discusses how to preserve the effectiveness of malaria control interventions with the few products available, while, in the longer term, promoting the development of new products.

GiveWell: Is the following correct to say? The bottom line is that there are major questions about the current effectiveness of LLINs, but LLINs have been part of a major scale-up through countries over the last few years, and while in some sense the ideal approach would be IRS with rotating insecticides it's not feasible to do that immediately. There are likely some locations where resistance is real and leading to control failure, and likely some places where it's not, and even in cases where resistance exists there are other reasons to believe nets are effective. Altogether, there are reasons to continue to support nets while also moving towards encouraging IRS with rotating insecticides, and at the same time monitoring insecticide resistance and developing new products.

That is true, and the other important factor is that the capacity to monitor is crucial. It is important to adequately map areas where resistance is occurring and then use that data to make local procurement decisions and where possible policy decisions.

LLIN physical lifespan and coverage

Nets develop holes over time and the process of hole formation varies from place to place and sometimes even with the same setting. Most nets form small holes at a similar rate, but it is the rate at which they develop larger holes that is key to their lifespan. Evidence is emerging that nets with holes offer less protection in areas of insecticide resistance than intact ones. LLIN replacement models often assume a 3-year lifespan but in the field they generally last about two years.. The collection of local data on the comparative durability of LLIN products, using rigorous and auditable methods, allows procurement decisions to be made on the basis of *price per year of protection* rather than *unit price per net*. This, in turn, is expected to lead to substantial cost savings. It is important to get industry to create more durable nets but to do so they need a system that will reward their investment.

While there is an understanding that population coverage with nets must be high for the nets to be an effective vector control tool, some recent modeling data has shown that the coverage does not need to be as high as 80% as currently recommended. More research is needed in this area of work.

WHO's product approval process

Given the existence of insecticide resistance, the development of new products is crucial. Evaluating the efficacy and safety of such products can take a significant amount of time. When a new product comes out, the WHO evaluates the product for efficacy and safety via three stages, which start at laboratory trials (phase 1) and go through large-scale field tests (phase 3). A group of experts examine the evidence and make recommendations. Many countries base their procurement decisions on this process.

Due to the need for new tools for vector control and for managing insecticide resistance mechanisms of fast-tracking the process from an idea to registration of a product at country level was thought necessary. It is for this reason that the WHO established a Vector Control Advisory Group (VCAG). VCAG reviews ideas for new vector control tools, paradigms and technologies, and can recommend them to the Malaria Policy Advisory Committee based on the data provided by the manufacturer. While the WHO process of developing product specifications will continue, it will be shortened with VCAG in place.

Improving human resource capacity in entomology and vector control

Over the last two decades, investment has focused on commodities (nets, insecticides and vector control equipment). The huge reductions in malaria burden we have witnessed are a result of that investment. But commodities do not distribute themselves – we need human resource. Many implementation problems are specific to local areas, so having qualified people at the local level to solve them is crucial. In particular, significantly more human resource capacity in entomology and vector control is needed in all African countries.

Capacity building was one of the issues recently discussed during the Malaria Policy Advisory Committee meeting in September. A recommendation was adopted requesting countries and partners to invest in this area.

The WHO Regional Office for Africa (WHO/AFRO) provides technical support to 48 countries but has only 1 dedicated entomologist for malaria vector control. For WHO to adequately fulfill its mission, human resource capacity is key. For example, how do countries roll out GPIRM implementation without additional capacity?

Dr. Mnzava has personal experiences in capacity building in entomology and vector control. While working in the WHO Regional Office for the Eastern Mediterranean (EMRO), the Regional Office worked with countries and Ministries of Health to support a postgraduate training programme for entomologists and vector control experts. Ministries of Health were supported by WHO through fellowships, identify an institution to host the programme, developed a training curriculum, and identify experts to facilitate training

programs. Through this programme, Sudan has been able to train over 100 entomologists at a master's degree level. They now have 2 postgraduate-trained entomologists in every province, have established over 70 sentinel sites across the country to regularly monitor insecticide resistance, and have a mechanism at the national level to analyze the data the sentinel sites produce for policy decisions.

Donors could fund work similar to this in other countries through WHO. There is now interest from a number of potential donors. One immediate human resource need is filling 3 entomologist positions in the WHO/AFRO.

Further research

Malaria control programs typically do not have staff who are trained in entomology – including skills on monitoring insecticide resistance. Documenting the impact of resistance and the use of nets and other vector control interventions is essential. For such programmes to be able to do that, they will likely require the support of research and academic institutions.

Advocacy is needed for implementing GPIRM and for funding and support for operational research.

The Gates Foundation is funding a project to measure the impact of insecticide resistance on LLIN effectiveness in four countries in Africa and one in South East Asia. The project will measure malaria cases in randomly allocated clusters with different interventions while at the same time monitoring resistance among the local mosquito population. It is a \$13 million, 5-year project. This project is coordinated by the Global Malaria Programme in WHO.

Other people for GiveWell to talk to:

On insecticide resistance research:

- Janet Hemingway, Liverpool School of Tropical Medicine
- Mark Rowland, London School of Hygiene and Tropical Medicine

On the formation of holes in LLINs and LLIN lifespan:

- Albert Killian, TropHealth
- Steve Smith, Centers for Disease Control and Prevention

On human resource capacity building:

- Michael MacDonald, Consultant, GMP/WHO.

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