A conversation with Professor Hilary Ranson, March 18, 2016

Participants

- Hilary Ranson, PhD – Professor, Medical Entomology, Liverpool School of Tropical Medicine
- Chelsea Tabart – Research Analyst, GiveWell
- Josh Rosenberg – Senior Research Analyst, GiveWell
- Milan Griffes – Research Analyst, GiveWell

Note: These notes were compiled by GiveWell and give an overview of the major points made by Prof. Ranson.

Summary

GiveWell spoke with Professor Hilary Ranson of the Liverpool School of Tropical Medicine as part of its investigation into the impact of insecticide resistance on malaria control interventions. Conversation topics included the challenges researchers face in measuring the extent and impact of insecticide resistance, evidence related to insecticide resistance and its impact on malaria transmission, and relevant ongoing research by Prof. Ranson and others.

Challenges to measuring the impact of resistance

Researchers lack a clear understanding of both the extent and the clinical impact of insecticide resistance. In particular, there are not any high-quality studies that enable researchers to confidently estimate the expected impact of current levels of insecticide resistance on clinical outcomes (e.g., mortality due to malaria).

Resistance variation among mosquito populations

Looking across the entire continent of Africa paints a complicated picture of resistance. Resistance is rapidly evolving, and the level of resistance varies significantly between locations. At least three distinct resistance mechanisms have been found in various combinations in different mosquito populations, with the highest levels of pyrethroid resistance seen in the Anopheles funestus and Anopheles gambiae species (the level of resistance varies even within species, however).

Prof. Ranson believes bed nets are still working well in most places, but researchers have found evidence of bed net failure in some areas with high resistance. She also cautions that while resistant mosquito populations vary widely across the continent right now, the most potent resistance mechanisms may eventually spread everywhere. It takes time for selection pressure to scale up resistance mechanisms so that researchers can see bed nets begin to fail.

Decrease in bed net efficacy over time

Most bed nets are expected to be effective for approximately three years. Individuals using older nets, which often have holes and a lower concentration of insecticide after being laundered, may be more susceptible to insecticide-resistant mosquitoes.

Many of the current studies fail to take this into account. While researchers may find that nets are still performing well in areas with high levels of resistance, they rarely conduct the two or three year studies necessary to measure the impact of insecticide resistance on the efficacy of worn nets.

The need for more quantitative bioassays

In Prof. Ranson's opinion, researchers have relied for too long on World Health Organization (WHO)-standard bioassays. These bioassays are designed so that exposure to a given level of insecticide kills 100 percent of a susceptible mosquito population (any survivors indicate resistance), which makes them useful tools for detecting the appearance of resistance in a population. However, they don't measure the degree of resistance.

Recently researchers have pushed for bioassay data that is useful in predicting the impact of resistance rather than just monitoring its spread. Some (including those working on the President's Malaria Initiative (PMI) five-country investigation of the impact of insecticide resistance on malaria vector control) have begun to use more quantitative bioassays that expose mosquitoes to increasing doses of insecticide to determine how much is needed to exterminate a given population.

An alternative approach, which is now being used more widely, is to expose mosquitoes to the insecticide product (e.g. a bed net) for three minutes, and then measure the mortality level. For a susceptible mosquito population exposed to a new bed net, the mortality level should be 100 percent, but researchers have identified populations with less than 20 percent mortality.

Modeling the impact of resistance on transmission

Researchers must balance their reluctance to send an overly alarming message about the prevalence of resistance and the imminent failure of bed nets with the pressing need to more accurately predict where the problem areas will be. However, researchers hoping to model the impact of resistance on transmission face several challenges.

No central data source

There is currently no central source of information on resistance levels. The data in IR Mapper are based on WHO-style discriminating dose bioassays, but Prof. Ranson and other researchers are working on guidelines for more bioassays that will be more informative in decision making.

Lack of epidemiological data on PBO nets

Combination nets, containing the insecticide and piperonyl butoxide (PBO) to combat pyrethroid resistance are available from two companies (Sumitomo Chemicals Ltd and Vestergaard).

Although there have been many experimental hut studies on PBO nets, researchers lack epidemiological data on the efficacy of these nets, which makes it difficult to model their impact on transmission.

The World Health Organization (WHO) recently organized a meeting to make recommendations on the use of PBO nets in the presence of resistance, but was unable to issue a strong recommendation because of the lack of public health data. As a consequence, their use is currently limited.

Prof. Ranson has discussed how best to evaluate PBO nets with the Against Malaria Foundation (AMF). Generating high-quality data would require distributing nets at scale in an area of high resistance and then monitoring them to detect any improvements over classical nets. There may be such a study conducted alongside AMF's upcoming distribution in Uganda.

Differentiating between mosquito resistance to insecticide and fitness to transmit malaria

Researchers studying resistance often measure the effect of insecticide on mosquitoes 24 hours after exposure, but a mosquito must live longer than 24 hours to transmit malaria. Depending on the temperature, a parasite needs 10-12 days to develop and infect a mosquito's salivary glands. Because it must bite to transmit the parasite, a mosquito may need as long as 14 days to transmit the disease.

Although a mosquito that survives 24 hours after exposure is considered resistant, its daily survival rate may have been reduced. After 14 days, very few "resistant" mosquitoes may survive. Researchers should therefore consider not only the effect of exposure on mosquito fitness, but also its ability to transmit the parasite.

Prof. Ranson believes bed net exposure impacts both fitness and transmission, and that this may be one reason researchers have not yet observed catastrophic bed net failure. However, she cautions that resistance is still a significant problem and that continuing to rely solely on pyrethroid insecticides will likely eventually lead to catastrophic failure.

Evidence related to resistance

Strode et al. 2014

One of the only substantial reviews of entomological outcomes of resistance is *The Impact of Pyrethroid Resistance on the Efficacy of Insecticide-Treated Bed Nets against African Anopheline Mosquitoes: Systematic Review and Meta-Analysis* by Strode et al. 2014.

It suggests some impact of resistance on the efficacy of nets, but identified too many study design problems to draw firm conclusions.

Burkina Faso

Burkina Faso is one of the countries where resistance was first detected, and Prof. Ranson estimates that the dose of insecticide that mosquito populations there can survive increased ten-fold following the introduction of bed nets and has steadily increased each year since then.

Although the country has had two massive bed net distribution programs (in 2010 and 2013), and small studies of individual districts in Burkina Faso have shown that nets are used at a rate similar to other parts of Africa, researchers have observed no significant impact on malaria mortality and the number of malaria cases is increasing.

Parts of Uganda and Mali (where there is universal coverage and good monitoring of malaria cases) are reporting similar trends, with no impact on local mosquito populations or decline in malaria transmission despite the use of nets.

Anecdotal evidence

Much of the evidence related to resistance is anecdotal. There are ethical barriers to conducting trials, and even where studies are feasible (Prof. Immo Kleinschmidt of the London School of Hygiene and Tropical Medicine has conducted some research in this area), resistance can change rapidly between the beginning and end of a study, making the data difficult to interpret.

Prof. Ranson has reports from both researchers and village residents who sleep under nets that they find blood-fed mosquitoes in their houses in the morning, even when using new nets. In Kenya, researchers in some areas have found that prolonged contact with insecticide-treated nets has no impact; the blood-fed mosquitoes live long enough after exposure to develop the parasite and become infectious.

Prof. Ranson expects that insecticide resistance has increased the number of malaria cases, but there haven't been any randomized control trials to confirm this.

Identifying the threshold of resistance

Dr. Ranson and colleagues at Imperial College London have used discriminating doses bioassay data and the Imperial College model of malaria transmission to try to identify the threshold of resistance at which malaria cases are likely to increase, resulting in a proposed relationship between bioassay results and clinical malaria. However, as these estimates are based on transmission models, they need to be validated in the field.

Professor Ranson's research

Pyriproxyfen net trial

Prof. Ranson is currently collaborating with colleagues in Burkina Faso and Professor Steve Lindsay at the University of Durham to conduct a trial in Burkina Faso comparing traditional insecticide-treated nets to nets that have also been treated with PPF, an insect sterilizing agent (because it is under trial, this net – the Olyset Duo – is not yet available on the market).

The trial is complete and researchers are analyzing the results, which should be available this summer.

Generating better data on PBO nets

Entomological data

Prof. Ranson is working on a systematic review of experimental hut studies of PBO nets to better understand the quality of entomological-level data about the increased efficacy of these nets. Comparing PBO and traditional nets is challenging because the nets differ in other ways, including:

- PermaNet 3.0 nets made by Vestergaard have an increased concentration of insecticide as well as the addition of PBO when compared to the PermaNet 2.0, which will likely lead some to claim any increased efficacy is due to the increased insecticide.
- Olyset Plus nets (with PBO) are made of yarn with a smaller mesh size compared to Olyset nets.

However, Prof. Ranson believes that these confounding factors may not be a significant issue.

Ideal study design

Policymakers need high quality evidence about the efficacy of PBO nets to guide their decision-making. Although PBO nets work in exactly the same way as conventional nets, the only difference being that they are able to kill both susceptible and resistant mosquitoes, net donors and policy makers are unwilling to make a recommendation on these nets in the absence of data on malaria cases. The roll out of PBO nets at scale in Uganda provides an excellent opportunity to collect this data.

All GiveWell conversations are available at http://www.givewell.org/conversations