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THEORY AND PRACTICE OF INSECTICIDE RESISTANCE MANAGEMENT: INSIGHTS FOR PUBLIC HEALTH VECTOR CONTROL

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Abstract Insecticide resistance can be defined as, a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species. There have been large gains in the fight against malaria, with a 40% reduction in the incidence of clinical cases since 2000. A significant proportion of this reduction has been attributed to the use of insecticidal vector control interventions. However, there is a growing concern that these gains are threatened by insecticide resistance in the anopheline vectors of malaria. Whilst there are currently only four insecticide classes recommended by WHOPES for adult mosquito control, initiatives are underway to facilitate and expedite the development and introduction of novel mosquito adulticides. It is argued that insecticide resistance management, or "insecticide susceptibility maintenance" programmes, need to be implemented to maintain the utility of the novel and effective vector control interventions being developed. It is further argued that such programmes can only be effectively implemented in the context of a wider Integrated Vector Management programme.

Key words Mosquito, Malaria.

INTRODUCTION

Insecticide resistance can be defined as, a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species (IRAC 2011). It has been around almost as long as the use of insecticides. For insects, it is a continuation of their evolutionary struggle to overcome the insecticidal and inhibitory compounds in their environment, and produced by the organisms they interact with and feed on.

Almost 60 years ago Brown (1958) wrote, "In July 1956 a WHO Expert Committee on Insecticides noted that the problem of insecticide resistance was growing more rapidly than the necessary measures to deal with it". In the same year, Hammerstrom (1958) reported that "insect resistance is internationally recognized by leading health authorities as the most important problem facing organized vectorborne disease control programs today". Unfortunately, both Brown and Hammerstrom's statements remain equally relevant today.

Whilst the first observations of insecticide resistance were made in agricultural pests in 1914 (Melander, 1914), over the next forty years the majority of reports describe insecticide resistance in public health pests. However, as Spiller (1958) pointed out, agriculture had not escaped the "infliction" of insecticide resistance, but that public health pests were often easier to maintain in the laboratory and had shorter life cycles, which facilitated their study. Whilst agricultural pests were more challenging to maintain, requiring the "tedious diversion" of rearing plants for them to feed upon, and hence their study had been neglected.

THESIS

Insecticide susceptibility is lost in an insect population when individuals with a heritable trait that allows them to survive an insecticide based intervention, or which suffer less of a fitness cost when exposed to the intervention, pass on the genes for that trait to the next generation. At first there may be a very small proportion of the population that express the trait, however, if the population is further exposed to the selection by the insecticide based intervention, then the less susceptible proportion will increase and eventually the intervention may fail to deliver the desired level of control. An insecticide resistance management (IRM) programme therefore has the aim of maintaining the proportion of the population that survive, below that which would cause the intervention to fail to deliver the desired level of control.

To minimise selection pressure, the target pest population should not be continually exposed to a given insecticide, or insecticides with the same mode of action. This forms the basis for all IRM programmes, which recommend rotating, or using mosaics, of insecticides with different modes of action, or using mixtures of insecticides (WHO 2012; Onstad, 2014). To facilitate the identification of which insecticides have the same mode of action, the Insecticide Resistance Action Committee (IRAC) has developed a numerical classification system (Sparks and Nauen, 2015). IRM should therefore be a simple exercise in the use of insecticides with different modes of action in a structured programme. However, the practicalities and logistics of insect pest control add multiple layers of complication.

Since 2000 there has been a 40% reduction in the incidence of clinical malaria, with an estimated 663 million clinical cases averted. 87% of this gain has been attributed to large scale mosquito adulticide based vector control interventions. (Bhatt et al, 2015). Insecticide based vector control therefore plays a key role in the prevention of malaria. However, this great achievement is considered by many to be under threat by ever increasing levels of insecticide resistance in the anopheline vectors of malaria.

IRAC identifies 27 insecticidal modes of action. However, currently only four subclasses of insecticide have sufficiently desirable characteristics for use in vector control, and meet the criteria for recommendation by the WHO Pesticide Evaluation Scheme (WHOPES). Only one of which, the pyrethroids, are currently recommended for use in Long-Lasting Insecticide treated Nets (LLINs). With the admirable aim of universal access to LLINs, for those at risk of malaria, mosquito populations in malaria endemic regions face almost constant selection pressure for pyrethroid resistance. It is therefore not surprising that susceptibility to pyrethroids in many Anopheles species is falling. There are reports of pyrethroid resistant mosquitoes entering damaged LLINs and successfully taking blood meals (Ochomo et al., 2013). It has also been reported that when a malaria control programme in Ghana switched from pyrethroid to organophosphate based residual wall spraying (IRS), the incidence of parasitemia fell (Ricks, 2015). Whilst not demonstrating a causal link between pyrethroid resistance and a reduction in malaria control, there is strong evidence that it could be a problem. Although, in late 2016 the WHO stated that there was no evidence that pyrethroid resistance was impacting malaria indices in areas where LLINs were widely used (WHO, 2016).

There are numerous reports of insecticide resistance in agricultural pests, with the Arthropod Pesticide Resistance Database containing 4276 reports of insecticide resistance in the Lepidoptera alone (2017). However, a steady stream of novel insecticides have been developed, enabling, in most cases, effective pest control to be re-established. The relative ease with which insecticides from different mode of action classes can be used in crop husbandry facilitates the implementation of IRM programmes. Multiple generations of a given pest species need not be exposed to selection from the same class of insecticides. In contrast, an LLIN is designed to remain effective for three years, exposing multiple generations of mosquito to the same insecticide.

The paucity of insecticidal modes of action available for adult mosquito control has a number of root causes, including an unattractive return on investment. Historically, insecticides were developed that had both agricultural and public health utility. However, in recent decades, regulatory pressure and environmental concerns have focused development on those with a limited spectrum and characteristics that are less suitable for use as mosquito adulticides. To address this, a number of initiatives have been initiated with the aim of developing novel solutions for the control of malaria vectors. These include public private partnerships that aim to facilitate the research and development required to deliver novel insecticide solutions and expedite the transition of novel vector control concepts to effective interventions (Hemingway et al., 2006). It is anticipated that the next decade will see a number of adulticides brought to market, to which mosquitoes resistant to the current recommended insecticide classes are susceptible.

To enable the greatest utility to be derived from novel mosquito adulticides, a programme of resistance management should be developed and implemented to coincide with their initial deployment. However, IRM should not be considered alone, but only in the context of Integrated Vector Management (IVM). IVM has been defined by the WHO as "a rational decision-making process for the optimal use of resources for vector control. The approach seeks to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of disease-vector control. The ultimate goal is to prevent the transmission of vector-borne diseases" (WHO, 2014). Vector control is not sustainable if the limited number of effective interventions are lost to resistance development. IRM is therefore implicit in the requirement for sustainability of vector control.

IVM should not be considered an activity to overlay an existing insecticide based vector control programme, but insecticide based vector control should only be used as a component of an IVM programme. Mosquito adulticides should be part of a holistic approach that embraces all activities, including larvicides, which reduce mosquito populations, and minimise their interaction with humans. This will not only increase the effectiveness of the vector control programme, but will also help to minimise the selection of resistance.

An effect IRM programme requires an understanding of the susceptibility status of the target population to the available insecticidal modes of action, to identify the most appropriate insecticide to use. Currently, there is a limited choice of insecticidal modes of action available, and evidence of insecticide resistance, it is therefore appropriate to identify which insecticides still provide a satisfactory level of control, i.e. which are not resisted at the target application rate. However, when novel insecticidal modes of action become available, measuring smaller changes in the susceptibility of the population becomes a vital tool in the "susceptibility maintenance" programmes that should be implemented to gain the greatest utility from a given class of insecticide. This shift from resistance to susceptibility monitoring may require novel tools and strategies to be developed and deployed. It may also require the training of the practitioners who undertake the susceptibility monitoring, and of those who use the information to design and implement IRM programmes.

The insecticide susceptibility status of a mosquito species may change significantly between geographically dispersed populations. It is therefore important to regularly characterise it over the entire range of the insecticide intervention. Changes in susceptibility to the available insecticidal tools can then be identified, and remedial steps taken before reduced susceptibility becomes widely spread, or intensifies further.

During the development of a novel insecticide, it is imperative to identify whether there is any cross resistance with existing insecticides. Cross resistance occurs when the mechanisms that reduces the susceptibility of an insect to one insecticide, confer reduced susceptibility to a second insecticide. To undertake cross resistance studies in the field with experimental insecticides can be problematic. However, maintaining resistant mosquito populations for use in laboratory studies, whilst not having the "tedious diversion" of the need to rear plants, is highly challenging in its own right. Therefore, to facilitate the timely evaluation of cross resistance, and to identify whether novel insecticides effectively control all relevant field populations, a collaborative effort between the insecticide research and development, and the wider vector control communities needs to take place.

A good understanding of the susceptibility status of all important mosquito species and populations is therefore not only vital for implementing effective IRM, but also in the expeditious development of novel insecticides, on which vector control and IRM rely.

CONCLUSION

Through the implementation of IRM, or "insecticide susceptibility maintenance", in the context of IVM, vector control programmes can be made more resilient to insecticide resistance development. The ongoing initiatives facilitating the development of novel vector control insecticides, and expediting their transition to effective vector control interventions, may be a once in a generation opportunity. It is therefore vital that the utility of new public health tools is maintained for as long as possible through their use in such "resistance resilient" vector control programmes.

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