Trends in Parasitology

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Opinion

Malaria Vector Control Still Matters despite Insecticide Resistance

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Mosquito vectors' resistance to insecticides is usually considered a major threat to the recent progresses in malaria control. However, studies measuring the impact of interventions and insecticide resistance reveal inconsistencies when using entomological versus epidemiological indices. First, evaluation tests that do not reflect the susceptibility of mosquitoes when they are infectious may underestimate insecticide efficacy. Moreover, interactions between insecticide resistance and vectorial capacity reveal nonintuitive outcomes of interventions. Therefore, considering ecological interactions between vector, parasite, and environment highlights that the impact of insecticide resistance on the malaria burden is not straightforward and we suggest that vector control still matters despite insecticide resistance.

The Threat of Insecticide Resistance to Malaria Control

Since the beginning of the millennium, renewed efforts in fighting malaria have had a substantial impact. In sub-Saharan Africa, where malaria exerts its heaviest burden, preventive and curative interventions halved the prevalence of *Plasmodium falciparum*, and it was estimated that more than half a billion clinical cases were averted [1]. Most of this progress has been attributed to the use of insecticide-treated nets (ITNs), which have been, and still are, massively distributed in endemic areas [1]. To date, only one family of insecticides, the pyrethroids, is approved for use in ITNs. However, several mechanisms of resistance to these insecticides have been selected and are now widespread among malaria vectors (Box 1). Therefore, it appears as a major threat to sustain the efficacy of malaria control. Insecticides may also elicit behavioral changes in mosquito vectors [2], and increased coverage of ITNs has been associated with changes in feeding behavior in vector populations [3,4]. The ability to avoid insecticide exposure by seeking hosts outdoor at dawn and dusk are expected to limit the efficacy of ITNs.

Based on entomological data, the modeled impact of pyrethroid resistance on malaria incidence in humans suggests dramatic consequences [5]. Alternative insecticides, or an alternative strategy in insecticide-based practices, are therefore under scrutiny for vector control. The most advanced alternative strategy is the combination of pyrethroids with synergists (i.e., piperonyl butoxide, PBO), with molecules that will affect the offspring of female mosquitoes (i.e., pyriproxyfen) or with non-neurotoxic insecticide (i.e., chlorfenapyr) (www.who.int/malaria/publications/atoz/use-of-pbo-treated-llins-report-nov2015.pdf?ua=1). While several studies evidenced that these combinations impacted pyrethroid-resistant mosquitoes [6–8] their benefits in terms of epidemiological impact remains to be measured [9] and evaluated in regard to the increased financial cost [10]. Another strategy for vector control, elaborated

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The use of insecticide-based vector control, long lasting insecticidal nets and indoor residual spraying (IRS), has been the most successful method for reducing the incidence of malaria.

Insecticide resistance is a major threat to vector control when we consider its entomological outcome, but its epidemiological impact is less obvious than expected.

In areas where resistance is detected, insecticides may still be efficient at reducing the proportion of older and potentially infectious vectors, thus controlling malaria transmission.

Considering the ecological interactions between vector, parasite, and environmental factors reveals that the impact of insecticides on malaria transmission is not straightforward and may explain their persisting efficacy despite widespread insecticide resistance.

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Box 1. Characterization of Insecticide Resistance in Malaria Vectors and the Limits for Predicting Malaria Control Efficacy

For most insecticides used in malaria-control programs, the protocols for detecting insecticide resistance among mosquito vectors have been standardized by the World Health Organization Pesticide Evaluation Scheme (WHOPES, whqlibdoc.who.int/hq/1998/WHO_CDS_CPC_MAL_98.12.pdf). Development of molecular tests enables the detection of insecticide resistance in field populations at low frequency – thus, before resistance jeopardizes the control of vector populations. In malaria vectors (as well as several other mosquito species [46]), two mutations in the *para sodium channel* gene – L1014F (*kdr*-west) and L1014S (*kdr*-east) – are responsible for pyrethroid resistance [83,84]; one mutation in the *Rdl* gene, A302S, is responsible for dieldrin resistance [85], and the unique G119S mutation in the *ace-1* gene is responsible for resistance to organophosphorus and carbamate insecticides [86]. Metabolic resistance regroups various mechanisms involved in detoxification (degradation and elimination) of xenobiotics. Among them, three major families of enzymes (glutathione *S*-transferases, cytochrome P450-associated monooxygenases, and carboxylesterases) have been implicated [87,88] but no simple, cost-effective molecular test has been developed yet for malaria vectors. Insecticide resistance is usually measured using WHO-provided susceptibility test kits that rely on one insecticide dose, one exposure time, and the observation of mortality 24 h post-exposure. This type of data has the advantage of being comparable among laboratories; however, it does not take into account the factors influencing the biology and ecology of vectors in natural settings. For instance, the phenotype of resistance is highly dependent upon environmental variables such as temperature [60], food quality/quantity [62], multiple blood meals [61], and pre-existing pesticide exposure [63]. Therefore the standard protocols, while useful to monitor insecticide susceptibility during vector control campaigns, may not provide evidence for failure of disease control. In addition, they cannot capture the delayed mortality induced by insecticides, that is, the mortality observed more than 24 h post-exposure [82]. Similarly, the level of resistance has been shown to decline with age (reviewed in [89]), so that individuals bearing resistance alleles could still die from exposure to insecticides when they get older. The fact that resistant vectors tend to become more susceptible to insecticides when aging can, however, have tremendous implications in terms of epidemiology. Indeed, malaria vector mosquitoes become infectious about 10–14 days after ingesting malaria parasites in a blood meal [13]; thus, most of the infectious mosquitoes are old. Therefore, insecticides may still be efficient at reducing the proportion of older and potentially infectious vectors, thus controlling malaria transmission in areas where resistance is detected.

almost a decade ago, is based on an elegant evolutionary concept: using late-life-acting (LLA) insecticides that would specifically kill old mosquitoes [11,12]. This is especially relevant for malaria control as the incubation period of *Plasmodium* parasites in the vector (10–14 days [13]) is long relative to the daily survivorship of the female *Anopheles* vector (approximately 0.8/day in nature [14]). Then, shortening the longevity would prevent mosquito vectors from reaching the infectious stage and thus from transmitting parasites. The benefit of this 'kill them old' strategy is that the LLA insecticide would exert a minimal selective pressure for new resistance mechanisms as most of the reproduction (i.e., most of the eggs laid) would be accomplished before the mosquito's death [12]. Entomopathogens that would kill mosquitoes several days after exposure [15] may work as LLA insecticides but, so far, this strategy remains conceptual and has not been implemented yet. In this context, intensive research on alternatives to pyrethroids in vector control must be a priority to sustain the recent advances against malaria. The costs and benefits of any new intervention need to be evaluated in regard to the currently used strategies [16]. For this purpose, it is crucial to assess the real impact of insecticide resistance on insecticide-based vector control and the malaria burden [17]. Here we discuss nonintuitive effects of interactions between vectorial capacity, insecticide resistance, and the use of insecticides. We suggest that, while insecticide resistance has been shown to reduce the effectiveness of insecticides to control vector abundance, insecticide-based vector control may continue to provide partial individual protection against malaria infection.

Discrepancy between Entomological and Epidemiological Studies

ITN efficacy is first assessed by measuring mortality of malaria vectors in the laboratory (cone and tube tests) and in experimental hut trials. Meta-analysis of published results on the influence of insecticide resistance revealed a high heterogeneity of ITN-associated mortality in vector populations [18] and predicted a strong epidemiological impact [5]. However, the few trials that have assessed the efficacy of pyrethroid-based interventions (ITNs and indoor residual spraying, IRS), and which have included parasitological indices in humans (i.e., incidence/prevalence of infection, child mortality and morbidity), showed a good impact