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Pyrethroid insecticide resistance and treated bednets efficacy in malaria control

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Abstract

Most of the studies on insecticide impregnated bednets efficacy in malaria control have been undertaken in areas where mosquitoes are pyrethroid susceptible. The efficacy of pyrethroid-treated bednets was not compromised even when mosquitoes were kdr resistant. Here, we evaluate a case in which mosquitoes have kdr-like pyrethroid resistance coupled with metabolic mechanisms. Metabolic and kdr-resistance mechanisms in *Anopheles stephensi* were characterised in our previous study and this easily colonised species was used as a model to examine the efficacy of pyrethroid-treated bednets in the laboratory. Bioassays performed on adults of susceptible (Beech) and resistant (DUB-S) strains using WHO 0.75% permethrin-impregnated papers showed a resistance ratio of 9.75. The recovery rate of the mosquitoes of the DUB-S strain was significantly higher than that of the susceptible strain Beech. The overall permethrin metabolism rates by DUB-S, measured by HPLC method, were 1.5-fold more than by Beech strain. Bioassays performed on DUB-S mosquitoes using different pyrethroid-treated bednets showed that only deltamethrin at 25 mg/m^2 and α-cypermethrin at 40 mg/m^2 produced adequate mortality rates. Four other pyrethroids, including permethrin, were ineffective. The deterrency test performed on susceptible and resistant *An. stephensi* showed that there are significant differences between the entry rates of susceptible and resistant mosquitoes into the exposure tube containing permethrin-treated bednet. These data show that when mosquitoes have both kdr-type and metabolic resistance mechanisms, the efficacy of pyrethroid-treated bednets is questionable.

Keywords: ITN; Efficacy; Pyrethroids; Resistance; Malaria

1. Introduction

There is little or no doubt that mosquito nets especially when they are impregnated with insecticides play an important role in malaria control

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campaigns [1]. People may already use bednets as a custom in their ethnic groups, for privacy purposes [2] or to protect them from mosquito biting nuisance [3,4] and this community behaviour has been adapted and promoted in conducting insecticide-treated nets (ITNs) programmes. Centrally run malaria control campaigns involving residual spraying for malaria control are difficult to sustain [1]. In contrast, community-based use of insecticide-treated bednets can be highly cost effective [5–8] without compromising the malaria control efficacy [9]. ITNs incorporation into malaria control programmes in Africa has been advocated by the World Health Organisation (WHO) [10–12] and is a central part of WHO's current "Roll Back Malaria" strategy.

Studies on ITNs efficacy in different countries, particularly in Africa and Asia, have provided a voluminous amount of supportive documentation for their positive impact [13–18]. Providing that bednets are treated with the right insecticide at the correct concentration, they are effective in reducing entomological indices and malaria mortality and morbidity especially in children under five [19–22].

Most of the ITNs efficacy studies have been undertaken in areas where mosquitoes are pyrethroid susceptible or the resistance status of the vectors was not determined. Attention has recently been paid to study the efficacy of ITNs where mosquitoes are resistant. In laboratory tunnel tests using resistant (kdr) and susceptible strains of *Anopheles gambiae*, 75–83% of mosquitoes of both strains passed through holes in untreated nets, 63–69% blood-fed successfully, and 9–17% died. However, when the netting was treated with permethrin 250 mg/m^2, only 10% of the susceptible and 40–46% of the resistant genotype entered the nets. A total of 100% of the susceptible but only 59–82% of resistant individuals were killed and blood feeding success was 0 for susceptible and 9–17% for the kdr insects. When the netting was treated with deltamethrin (25 mg/m^2) 3.9% of susceptible and 3.5% of resistant mosquitoes went through the holes and blood-fed successfully. The mortality rates were 97% for the susceptible vs. 47% for the resistant [23]. In experimental hut trial with permethrin-treated bednets (500 mg/m^2) using susceptible and kdr-resistant *An. gambiae*, mortality rates were 95% vs. 45% and blood feeding rates were 1.3% vs. 8.1% in susceptible and resistant mosquitoes, respectively. With deltamethrin (25 mg/m^2) the mortality rates were 91% vs. 54% and blood feeding rates were 0% vs. 2.5% in susceptible and resistant strains [23].

In another experimental hut trial using permethrin-treated Olyset nets (a long lasting, polyethylene net with 2% permethrin incorporated within fiber) against a pyrethroid-resistant field population of *An. gambiae* (96% kdr), N'Guessan et al. [24] showed that newly treated Olyset nets reduced the mosquito house entry and blood feeding rates by 44 and 16%, respectively, increased the exophily by 19% and caused 27.5% mortality. In these studies, it is argued that even when mosquitoes are kdr resistant, the bednets still have much of their effectiveness. Darriet et al. [25] showed that pyrethroid-treated bednet can still reduce malaria vectorial capacity of kdr-resistant mosquitoes in experimental huts. The efficacy of treated bednet in reducing malaria transmission when mosquitoes are kdr resistant was also investigated in a village scale study [26].

The efficacy of treated bednets against resistant mosquitoes may be because kdr-type resistance allows prolonged contact with pyrethroids because of the reduced sensitivity to the usual irritant, deterrence, and knockdown effects of pyrethroids, which in turn results in relatively high mortality of the kdr individuals due to higher uptake of insecticide [23]. The kdr-resistant individuals do not seem to take advantage of the delayed knockdown to increase the blood feeding rate [27]. However, if the kdr mechanism is accompanied by a metabolic resistance like elevated monooxygenases or esterases, the situation is expected to be different as the prolonged exposure time to the treated surfaces and increased insecticides uptake does not necessarily result in higher mortality. The DUB-S strain of *Anopheles stephensi* showed evidence of both kdr and metabolic resistance mechanisms to pyrethroids. Exposure of free flying mosquitoes of DUB-S for 30 min to α-cypermethrin-treated bednets in a mosquito proof room produced 80% knockdown 1 h after the exposure period but only 50% mortality after 24 h [28]. It can be concluded from such experiments that enzymatic metabolism of pyrethroids is important in mosquito recovery.

The easily colonised species of *An. stephensi* with both kdr and metabolic resistance