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# Characterisation of resistance mechanisms in the major malaria vector *Anopheles arabiensis* from southern Africa

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# ABSTRACT

The continual increase in insecticide resistance in malaria vector mosquitoes is threatening the efficacy and sustainability of most malaria control programmes. The major problem facing malaria vector control programmes is lack of scientific information to assist in resistance management strategies. The objective of this thesis is to elucidate insecticide resistance mechanisms in *Anopheles arabiensis* from southern Africa. This information is necessary to predict cross resistance spectrum, facilitate choosing alternative insecticides and assist in mapping areas with resistant populations. Field studies to update data available on insecticide susceptibility and characterise the resistance mechanisms were carried out in Gokwe, a malaria endemic area in Zimbabwe. In addition this study reports changes in insecticide resistance levels, detoxification enzymes and P450 gene profile following artificial permethrin and bendiocarb selection of laboratory colonies originating from Mamfene, South Africa.

A total of 943 anophelines belonging to four different taxa were collected over a two year period with the majority (98.8%) being members of the *An. gambiae* complex. Species in the *An. gambiae* complex were identified by polymerase chain reaction (PCR) and *An. arabiensis* (72.0%) predominated over all the other sibling species. Among the *An. arabiensis* females 0.5% and 4.8% was positive for *Plasmodium falciparum* in 2006 and 2008 respectively. WHO diagnostic tests on wild *Anopheles arabiensis* populations showed resistance to permethrin at a mean mortality of 47% during 2006 and a mean mortality of 69.4% in 2008. DDT resistance (68.4% mean mortality) was present in 2006; however in 2008 a mean mortality of 94.8% was recorded. Insecticide susceptibility tests on $F_1$ *An. arabiensis* families showed that 25.4% (n = 59) and 14.2% (n = 14) of the families were resistant to DDT in 2006 and 2008 respectively. For permethrin exposures 56.8% (n = 37) and 78.8% (n = 14) families were resistant in 2006 and 2008 respectively. Eight families were resistance to both DDT and permethrin during the two collection periods. Biochemical assays of $F_1$ *An. arabiensis* families reared from 2006 collections revealed comparatively high levels of monooxygenase (48%.5% of families tested, n = 33, $p<0.05$), glutathione S-transferase (26.7% of families tested, n = 30, $p<0.05$) and

general esterases activity compared to the reference colony. No knockdown resistance (*kdr*) and ace-$I^R$ mutations were found.

After 12 generations of bendiocarb and permethrin selections of *An. arabiensis* mosquitoes from Kwazulu/Natal there was approximately a 2.8-fold and 3.8-fold respective increase in the $LT_{50}$ compared to the parental colony. Selections resulted in increased levels of non-specific esterase and monooxygenase activity for the permethrin selected cohorts, and elevated glutathione S-transferases and general esterases for the bendiocarb colonies. Involvement of monooxygenase and glutathione S-transferase in pyrethroid and bendiocarb resistance was confirmed by synergist studies using piperonyl butoxide and diethyl maleate respectively.

P450 gene profiling of the permethrin selected line showed that 4 genes CYP6Z1 (4.67-fold), CYP6Z2 (1.72-fold), CYP6M2 (2.24-fold) and CYP4G16 (1.39-fold) were over expressed in the resistant cohorts.

Continued use of pyrethroid insecticides by the Zimbabwean National Malaria Control programme (NMCP) is likely to further select resistant vectors. Use of insecticides such as organophosphates and carbamates, mosaic insecticides or rotation of insecticides is recommended. These results contribute to our limited knowledge of metabolic resistance mechanisms and provide useful information for future studies to come up with new insecticides and diagnostic tools for detection and management of resistance.