Title of PhD project / theme	**Investigating the impact of insecticide resistance on malaria transmission in sub-Saharan Africa.**
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Brief description of project / theme	Insecticide resistance is now a pervasive global phenomenon affecting two-thirds of countries with ongoing malaria transmission. The severity of this threat is currently unknown because there is limited evidence linking the operational failure of vector control interventions to the presence of local, resistant mosquito species. This PhD project will employ next generation sequencing to characterize the mechanisms driving insecticide resistance among major mosquito vector species in Tanzania and Benin, identify resistance markers and design mathematical models for field surveillance and resistance management, and investigate the impact insecticide resistance has on malaria transmission dynamics, including mosquito fitness and vector-parasite interactions. The aim of this PhD project is to characterize the mechanisms of insecticide resistance to new candidate malaria vector control products in East (Tanzania) and West (Benin) Africa, in order to evaluate the impact of resistance on intervention efficacy and malaria transmission dynamics. Study findings will provide crucial evidence to local National Malaria Control Programmes, to inform country-specific resistance management schemes, and

to international stakeholders to guide cost-efficient procurement and deployment of vector control strategies.

PhD objectives:

1. Apply novel genomic (nanopore whole genome sequencing) and transcriptomic (RNA-seq) techniques to characterize the mechanisms of insecticide resistance to in field populations of *Anopheles gambiae* s.l. in Benin and *An. funestus* s.l. and *An. gambiae* s.l. in Tanzania.
2. Identify candidate genes for resistance diagnostic assay development for prospective field surveillance of intervention efficacy and resistance selection.
3. Design mathematical models for predictive insecticide resistance management schemes, to maximize current and future vector control intervention effectiveness
4. Investigate the impact of insecticide resistance on mosquito fitness (life-span, fecundity and fertility) and vector-parasite interactions (*Plasmodium falciparum* development).

References:

1. Protopopoff N, Mosha JF, Lukole E, Charlwood JD, Wright A, Mwalimu CD, Manjurano A, Mosha FW, Kisinza W, Kleinschmidt I, Rowland M. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomized controlled, two-by-two factorial design trial. Lancet. 2018 Apr 21;391(10130):1577-1588.
2. Stica C, Jeffries CL, Irish SR, Barry Y, Camara D, Yansane I, Kristan M, Walker T, Messenger LA. Characterizing the molecular and metabolic mechanisms of insecticide resistance in *Anopheles gambiae* s.l. in Faranah Guinea. Malari J. 2019 Jul 17;18(1):244.
3. Collins E, Vaselli NM, Sylla M, Beavogui AH, Orsborne J, Walker T, Messenger LA. Investigating the relationship between insecticide resistance, underlying molecular mechanisms and malaria prevalence in *Anopheles gambiae* s.l. from Guinea. Sci Rep. 2019 Jun 20;9(1):8846.
4. Sherrard-Smith E, Griffin JT, Winskill P, Corbel V, Pennetier C, Djénontin A, Moore S, Richardson JH, Müller P, Edi C, Protopopoff N, Oxborough R, Agossa F, N'Guessan R, Rowland M, Churcher TS. Systematic review of indoor residual spray efficacy and effectiveness against *Plasmodium falciparum* in Africa. Nat Commun. 2018 Nov 26;9(1):4982.
5. Dagg K, Irish S, Wiegand RE, Shililu J, Yewhalaw D, Messenger LA. Evaluation of toxicity of clothiandin (neonicitinoid) and chlorfenapyr (pyrrole) insecticides and cross-resistance to other public health insecticides in *Anopheles arabiensis* from Ethiopia. Malar J. 2019 Feb 22;18(1):49.

The role of LSHTM and NU in this collaborative project	The primary supervisor (MR) is currently leading two large-scale cluster-randomized controlled trials in Tanzania and Benin, evaluating the effectiveness of next-generation long-lasting insecticidal nets to control malaria transmitted by resistant mosquito vectors. Mosquito populations will be sampled from both of these field sites for in-depth characterization; and resistance diagnostic assays, developed during this PhD project, will be tested in these areas to determine their utility for monitoring resistance selection. The secondary supervisor (LM) will provide expertise in insecticide resistance, molecular assay development and next-generational sequencing techniques. Additional supervisors will support the laboratory characterization of mosquitoes (TW), the design of predictive mathematical models for resistance management (TC) and provide access to additional field sites and insecticide resistance expertise (NM and HK).
Particular *prior* educational requirements for a student undertaking this project	The ideal candidate will hold a masters or undergraduate (minimum) degree and have a passion for international public health, particularly malaria vector control. Experience of entomological methods, bioinformatics and fieldwork in Africa would be advantageous.
Skills we expect a student to develop/acquire whilst pursuing this project	This project is multi-disciplinary, combining substantial field work in East and West Africa (mosquito collections and phenotypic bioassays), basic entomology (investigating mosquito fitness and vector-parasite interactions), bioinformatics and next generation sequencing techniques (in-depth characterization of mosquito populations) and mathematical modelling (to design predictive resistance management schemes). The candidate student will develop skills in next generation sequencing (nanopore genome sequencing), transcriptomics (RNA-sequencing) and design and evaluation of multiplex TaqMan assays for resistance monitoring. The student will also receive training in population genetics analysis, to detect signatures of selection, and training in development and application of mathematical models, to provide predictive schemes of resistance managements, under different field conditions.