**University of Leicester**

**BBSRC MIBTP Studentship Project 2025-6 entry.**

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**Section 2 – *Project Information***

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| **Project Title** | Evaluating the epidemiology, genetic basis and molecular evolution of antimicrobial drug resistance in *Helicobacter pylori* in a populational model  |
| **Project Summary**  |
| Antimicrobial Drug Resistance (AMR) is a growing and major public health threat facing the worldwide population within the next 30 years, imposing considerable burden on health systems. AMR has been developed against virtually all antibiotics in clinical use. Although clinical and laboratory studies have been using DNA sequencing to identify antibiotic resistance genes (ARGs) and to analyse the transmission of major pathogens and their ARGs between patients, animals and their environment, there are significant gaps in the understanding of the evolutionary emergence and persistence of AMR in these natural reservoirs.  To contribute to bridging this gap, this project will focus on the stomach-infecting bacterium *Helicobacter pylori* in the African nation of Cabo Verde. *H. pylori* infection is the most common infection in the world and causes peptic ulcer and gastric cancer; gastric cancer is the second cause of death from malignancy. Preliminary results from our work indicate that the prevalence of infection in the general (asymptomatic) population of Cabo Verde is ~83%, and that the level of AMR of isolated strains to four antibiotics used in *H. pylori* eradication is high across all subjects’ age groups despite no screening for *H. pylori* in the country’s health system. We hypothesize that this resistance is due to the continuous antibiotic use for unrelated heath issues, and that this leads **to a strong selective pressure** for AMR and AMR persistence in the Cabo Verdean community. The features of high frequency of resistance and of correlation with age in healthy subjects will allow to develop evolutionary models to characterise the AMR dynamics of *H. pylori* ARGs *in vivo.*  **Thus, the main aim of this project is to use Cabo Verde as a population model and apply innovative experimental, computational and genomic approaches to characterise the genetic basis, evolution and persistance of AMR in *H. pylori***. The objectives are: 1. **To identify new genetic determinants of AMR in *H. pylori*.** Known resistance variants do not fully explain the observed AMR in Cabo Verdean *H. pylori*. We have a dataset composed by >220 sequenced strains characterized for AMR levels that will allow to perform genome-wide association analyses (GWAS)1 or employ machine learning algorithms2 to prioritise of ARGs in *H. pylori*. We will then evaluate the evolution of the frequency of newly found resistance variants with time and use natural selection models to calculate fitness costs and the length of persistence in the population.

 1. **To use an experimental evolution approach to characterize the evolution of AMR, to complement the GWAS analyses.** We will grow a diverse set of *H. pylori* isolates with sub-lethal antibiotic concentrations. This weak selection pressure has been shown to select for diverse resistance pheno- and genotypes in bacteria3. We will collect samples at extended time points for AMR characterization and whole genome sequencing. The experiments will extend further after the development of resistance, when we will remove the antibiotic to evaluate the reversal of the resistant phenotype and the fitness of resistant and of potential compensatory variants. Questions addressed include: What genomic and phenotypic changes underlie adaptation to antibiotics in bacteria with different genomic backgrounds? Are these changes common to all different bacteria? Do these changes persist after removal of the antibiotic? We will then compare these results with our population dataset analysed in 1.

 This project will provide a more complete understanding of AMR in *H. pylori* and potentially will provide new drug targets and resistance mechanisms. Information about the origin, evolution and persistence of AMR in a major pathogen will inform global health policies on AMR.    Techniques that will be undertaken during the projectThe project provides an opportunity to integrate laboratory experiments with computational analyses. The laboratory component includes microbial techniques (bacterial isolation and culture, tests for antimicrobial drug susceptibility), molecular genetics (e.g. DNA extraction, DNA library construction, PCR), and Next-Generation Sequencing using paired-end sequencing. The computational component includes genomics (genome assembly and alignment), evolutionary (testing for selection and applying selection models) and statistical (genetic association, machine learning) analyses.  |
| **References** |
| 1. Power et al. (2017). Microbial genome-wide association studies: lessons from human GWAS. *Nat Rev Genet* 18: 41–50. doi: 10.1038/nrg.2016.132

 1. Peng et al. (2022).Whole-genome sequencing and gene sharing network analysis powered by machine learning identifies antibiotic resistance sharing between animals, humans and environment in livestock farming. PLoS Comp Biol 18(3): e1010018. doi: 10.1371/journal.pcbi.1010018

 1. Sonnenkalb et al. (2023). Bedaquiline and clofazimine resistance in *Mycobacterium tuberculosis*: an in-vitro and in-silico data analysis. Lancet Microbe 4: e358–e368. doi: 10.1016/S2666-5247(23)00002-2
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