**Project Title**

Combining a novel phenotypic virulence screen with genomic approaches to uncover bacterial acquisition of multi-drug resistance and virulence in aquatic environments

**Lead Supervisor Name**

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**Full Project Description**

Poor water quality poses a major threat to human health, and even in the developed world the disease burden and economic costs of waterborne diseases are significant. Exposure to pathogens is likely to increase due to population growth, climate change and intensification of agricultural practices. Potentially more dangerous than the increased likelihood of exposure to environmental pathogens is the dramatic increase in antimicrobial resistance (AMR), threatening the effective treatment of a wide range of infections and forming a global challenge to public health. The role of the natural environment in the dissemination of, and selection for, AMR through pollution with resistant bacteria, antibiotic residues, biocides and heavy metals is increasingly appreciated (Wellington et al., 2013). The risk to human health posed by resistant bacteria present in the environment are likely to be significant. For example, it has been estimated that there are over six million exposure events to cephalosporin-resistant E. coli through recreational use of coastal bathing water in England and Wales alone. There is evidence for a range of pathogens that AMR and virulence genes can be carried on the same plasmids (Mangat et al., 2017), and these mobile genetic elements could potentially spread between species. However, current microbial water quality standards rely on the quantification of faecal indicator bacteria and do not consider either virulence or AMR, and so we know very little about the diversity and distribution of multidrug-resistant pathogens in aquatic environments. In this project, we will selectively isolate pathogenic bacteria using the Wax Moth larva Galleria mellonella, a well-established model for the mammalian innate immune system. Using the novel approach of directly injecting environmental samples into Galleria and tracking mortality allows isolating infectious bacteria without bias (Hernandez et al., in prep.). Combining these assays with antibiotic selection and the ability to mobilise plasmids from freshwater microbial communities into model recipient bacteria will enable capture of novel plasmids carrying both AMR and virulence genes. Using both Illumina and Nanopore technologies to sequence chromosomes and plasmids of bacterial clones isolated from Galleria will give detailed information on pathogen identity, origin (i.e. hospital- or environment-associated) and carriage of known virulence- and antibiotic resistance genes. Functional genomics will be employed to identify unknown virulence and antibiotic resistance genes. Prevalence of multi-drug resistance and virulence will be related to catchment scale variables, revealing associations with water quality variables and point and diffuse sources of pollution. Although microbiologically safe water is considered a fundamental human right, it is not exactly clear what this constitutes and how it is best monitored. This project will employ novel approaches enabling us to characterize the diversity and prevalence of antibiotic resistant pathogenic bacteria and their ecological drivers to ultimately assess human infection risk.

**Real Life challenges this project will address**

Poor microbiological water quality poses a major threat to environmental and human health and is likely to deteriorate through climate change and changes in land use. Worryingly, the global increase in antibiotic resistance could mean that exposure to contaminated waters leads to infections that are very hard or impossible to treat. This project will for the first time uncover the distribution, diversity and origin of multidrug resistant bacterial pathogens present in fresh water sources.

**What you should know about this project**

This is a multidisciplinary project that uses novel methodology to detect and characterize bacteria that are both pathogenic and resistant to antibiotics in environmental water sources. Evidence suggests that multi-drug resistance plasmids can also carry virulence determinants, meaning that bacteria can acquire virulence- and antimicrobial resistance (AMR) traits in a single evolutionary step. The data collected in this project will elucidate the evolutionary drivers of virulence and antibiotic resistance in freshwater systems, which will contribute to regulatory and policy changes to reduce aquatic pollution, thereby protecting environmental and human health. The student will benefit from working with experts in evolutionary microbiology (MV), the environmental dimension of AMR (WG), bacterial genomics (EF) and water quality (JP) at the Universities of Exeter and Bath and the Environment Agency (EA). State-of-the-art labs at Penryn Campus, bioinformatics expertise at the Milner Centre for Evolution (Bath) and access to water samples and associated meta-data via the EA Starcross labs will greatly facilitate this project. WG is currently PI and CoI on grants in excess of £3 million including a NERC Environmental Microbiology & Human Health grant on AMR in the Thames river catchment and a £1.5 million Cross-Council grant on selection for AMR in aquatic systems. EF currently holds NERC, BBSRC, EPSRC and MRC funding and MV has received NERC (New Investigator) and BBSRC funding. The student will be encouraged to participate in the wide range of professional development opportunities available at the University of Exeter and will be embedded within a multi-disciplinary research group with NERC, MRC and BBSRC PhD students situated within the Medical School laboratory based in the Environment and Sustainability Institute at the Exeter Cornwall Campus.

**What expertise you will develop**

The student will develop expertise in environmental microbiology and bacterial pathogenesis, genomics and bioinformatics. This will include field sampling, microbiological and molecular biology techniques, statistics, writing and data presentation. The student will engage with the Environment Agency and other stakeholders engaged in research with the supervisory team (Defra, Water Industry, Pharmaceutical Industry).

**Why this project is novel**

The project will combine a novel bioassay with state-of-the art genomics methods to characterise the ecological drivers of antibiotic resistant pathogens in freshwater environments. Specifically, we will use state-of-the-art genetic and genomic methods to determine co-carriage of resistance and virulence genes on plasmids carried by environmental bacteria, a potentially highly significant, but virtually unexplored topic.

**Rest of Supervisory Team:**

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