Project Details	
Project Code	MRCIIAR24Ex Padfield
Title	Will climate change worsen the problem of antibiotic resistance?
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Recent studies have shown that levels of antimicrobial resistance (AMR) increase at higher environmental temperatures, but we have very little idea about the mechanisms causing this pattern. To improve our ability to control AMR, we need to know much more about the mechanisms through which temperature alters the selection and spread of AMR. This project will combine lab-based experiments, theory, and genome sequencing to achieve this.
Description	The evolution and spread of antimicrobial resistance (AMR) are major threats to human health. Recent correlational studies have shown that levels of AMR increase at higher temperatures in environmental and pathogenic bacteria. However, an almost complete lack of empirical evidence to explain the mechanisms of these broad scale-patterns limits our ability to quantify, understand, and ultimately control potential synergistic impacts of climate change and AMR. One of the major ways AMR spreads is through horizontal gene transfer (HGT), which allows bacteria to acquire DNA from individuals other than their immediate ancestors and is driven by mobile genetic elements, such as plasmids. This project's key research question is whether the spread of plasmids increases at higher temperatures. If this is the case, then climate change may increase environmental reservoirs of AMR that can then spread into clinically relevant bacteria. Below we suggest four different components of this project, but we will encourage any PhD student to lead the design of their own project to align closest to their interests. The project can take advantage of a library of >3000 well-characterised isolates of Klebsiella spp. collected from the environment and from humans. These isolates cover 15 species, including the human pathogen K. pneumoniae, have variation in resistance profiles, and have high quality genomes from previous work. This gives us an unprecedented study system to understand how temperature alters plasmid transfer and persistence of AMR across a diverse set of closely-related isolates, including many opportunistic pathogens. Objectives 1. Explore variation in the response of environmental and clinical Klebsiella spp. to temperature. Theory predicts that clinical Klebsiella spp. should have higher optimal temperatures and a narrower tolerance range than environmental Klebsiella spp.. 2. Understand how plasmid transfer rate changes across temperatures in environmental and clinical Klebsiella spp.. Plasmid transfer rate is linked to the growth rates of the donor and recipient bacteria. We therefore expect plasmid transfer across Klebsiella spp. to be highest close to their optimal temperatures. 3. Understand how selection for resistance changes across temperatures. We will quantify the cost of plasmid carriage and the impact of environmentally-relevant antibiotic concentrations on susceptible Klebsiella spp. across their full temperature range to understand how the selection for resistance changes with warming. 4. Understand how plasmid spread and dynamics of Klebsiella spp. change across temperatures in natural sewage communities. We will use sequencing to test whether plasmids spread more at higher environmental

	temperatures in natural communities, and investigate whether clinical Klebsiella spp. dominate Klebsiella spp. diversity in a warmer world. This interdisciplinary project will combine experiments, sequencing, and mathematical modelling to increase our mechanistic understanding of how temperature alters the selection and spread of antibiotic resistance in the Klebsiella group. The experimental work will be supervised by Padfield, Leonard, and Buckling and will approaches well developed from previous work, such as phenotypic assays to measure growth and plasmid transfer across temperatures, fluorescence microscopy, flow cytometry, qPCR, and metagenomic sequencing. Bioinformatics training will be provided by Padfield & Feil. This work will be complemented by mathematical modelling to generate testable predictions, guidance and training for which will be provided by Padfield & Kuijper. Depending on the student's interests, opportunities exist to do long-term experimental evolution to understand how warming impacts AMR resistance evolution, mine existing metagenomic datasets to test questions about temperature, plasmids, and AMR, and use empirical data to predict exposure risk in the natural environment.
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