Project Details	
Project Code	MRC23IIARBa JonesB
Title	Evolution of antimicrobial resistance in bacterial microbiomes
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	Biocides are broad spectrum antimicrobial agents used extensively in healthcare as antiseptics and disinfectants. Working with the United Kingdom Health Security Agency, you will employ molecular, genomic, bioinformatic, and directed evolution techniques, in conjunction with models of polymicrobial infection, to answer fundamental questions about the role of biocides in evolution of antimicrobial resistance.
Description	Background Biocides are antimicrobial agents used extensively in healthcare settings as antiseptics or disinfectants. The increasing use of biocides has been driven by efforts to reduce antibiotic use and Covid-19 pandemic. However, evidence is accumulating that biocides can select for undesirable traits in bacterial pathogens, including antibiotic resistance. For example, our work with urinary tract pathogens has shown that biocide exposure in Klebsiella pneumoniae can select for mutations conferring resistance to colistin (an antibiotic of last resort). The genes found to acquire mutations following biocide exposure include phoPQ and pmrAB, which are also linked to immune evasion during infection. We have also identified mutations related to biocide adaptation in clinical isolates of Proteus mirabilis, showing that these traits arise in the clinical environment. This raises the possibility that the increased use of biocides in hospitals could lead to the emergence of bacterial strains that are both more virulent and more difficult to treat. Aims & Objectives Bacteria predominantly exist as polymicrobial communities, or microbiomes, in many clinically relevant habitats. However, it is unclear how biocide exposure contributes to the emergence of antimicrobial resistance in members of these microbiomes. This project will answer important questions regarding the role of biocide exposure in the evolution of antimicrobial resistance within bacterial communities, using a clinically relevant model of polymicrobial catheter-associated infection. This simple 4-member community model provides a tractable microbiome system facilitating the application of directed evolution, genomic, and metagenomic approaches to understand evolution of antimicrobial resistance. Objective 1 - Impact of biocide exposure on community dynamics and selection of antimicrobial resistance. Polymicrobial models of catheter associated UTI will be used to simulate antiseptic treatment with the biocides. The response of bacterial communities will be evaluated through phenotypic and genomic characterisation of populations recovered pre and post treatment. Metagenomic profiling of mutations associated with biocide exposure will also be undertaken using the Breseq bioinformatic pipeline. This will allow us to understand the impact of biocide exposure on community members and if mutations relevant to biocide tolerance and/or antibiotic resistance arise in in these microbiomes. Objective 2 - Biocide exposure and plasmid transfer. The transfer of plasmids between bacterial species is a key mechanism in the dissemination of antibiotic resistance. Catheter microbiome models and simulated biocide treatment scenarios will be used to understand the impact of biocide exposure on transfer of

	plasmids encoding antibiotic resistance determinants between community members. This will include plasmids encoding resistance mechanisms already linked to biocide adaptation, such as colistin resistance, as well as plasmids encoding unrelated resistance genes. Objective 3 - Biocide adaption and modulation of virulence: The adaptation of bacterial pathogens to biocides has been linked with mutations that are also potentially relevant to virulence, and in particular the evasion of antimicrobial peptides relevant to the innate immune response. We will use our novel insect models of infection to understand if adaptation to biocides in microbiome models modulates the virulence of community members. Student Ownership The student will be encouraged and supported to take ownership of the project from the outset. The supervisory team will enable the student to take the lead on experimental design and the specific focus of work in each objective. Initial "prep-period" activities and training will enable the student to more specifically define the research questions and lead implementation of experiments to test hypotheses they develop.
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