Project Details	
Project Code	MRC21IIRBa Jones
Title	Evolution of biocide tolerance in Klebsiella pneumoniae and its impact on antibiotic resistance and virulence.
Research Theme	Infection, Immunity & Repair
Summary	Biocides are used extensively in healthcare as antiseptics and disinfectants. Working with Public Health England, you will employ molecular, genomic, bioinformatic, and biochemical techniques to answer fundamental questions about the contribution of biocides to evolution of antibiotic resistance and virulence in bacterial pathogens.
Description	Background Biocides are antimicrobial agents used extensively in healthcare settings as antiseptics or disinfectants. Efforts to reduce antibiotic use have led to increased use of biocides to prevent infection and control multidrug resistant pathogens. However, there is growing evidence that exposure to biocides may also select for undesirable traits in bacterial pathogens, including antibiotic resistance. We have previously demonstrated that exposure of Klebsiella pneumoniae to biocides 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. 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 This project will answer important questions regarding the evolution of bacterial biocide tolerance and the clinical relevance of associated phenotypes. These questions will be addressed using K. pneumoniae (Kp) as a clinically relevant model organism, in conjunction with representative models of microbial communities commonly exposed to biocides in hospitals: polymicrobial infections of the catheterised urinary tract and the sink-trap environmental microbiome. Objective 1 - Evolution of biocide tolerance in clinically relevant microbial communities: Microbial communities in models of the catheterised urinary tract or hospital environment, will be exposed to relevant biocide containing products. The response of the Kp population within these communities will be evaluated through phenotypic and genomic characterisation of isolates recovered pre and post treatment. Metagenomic profiling of target genes in the Kp population as a whole will also be undertaken using the Breseq bioinformatic pipeline. This will allow us to identify mutations that confer increased biocide tolerance and understand their impact on antibiotic resistance and virulence mechanisms. Objective 2 - Clinical prevalence of mutations associated with biocide adaptation: An extensive collection of >3000 Klebsiella genomes from clinical and non-clinical environments across Europe, will be analysed to identify mutations analogous to those related to biocide exposure in microbiome models. Changes in susceptibility will be confirmed by MIC and a sub-set of isolates subject to the same phenotypic and genetic characterisation as for microbiome model isolates exhibiting increased biocide tolerance. Objective 3 - Impact of biocide exposure on plasmid transfer and maintenance. Recently described plasmids encoding colistin resistance (mcr-1) protect cells through mechanisms similar to those arising in Kp strains adapted to

	grow at high biocide concentrations. This raises the potential for biocide exposure to also promote the transfer and maintenance of multidrug-resistance plasmids in Kp and other species. We will investigate this using direct mating experiments as well as more complex evaluations of plasmid transfer in microbiome models.
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