Project Details	
Project Code	MRCIIAR25Br Avison
Title	Emerging co-resistance to first and second line antibiotics in urinary pathogens and implications for the control of urosepsis.
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Reducing antibiotic resistance (ABR) among urosepsis pathogens - derived from urinary tract infection (UTI) via pyelonephritis - is central to the UKs ABR-reduction strategy. This PhD is based within an inter-disciplinary consortium aiming to reduce trimethoprim use for UTI by promoting switching to an alternative first-line antibiotic. This may reduce resistance to second-line UTI/pyelonephritis and urosepsis therapies among UTI pathogens, reducing hospital admissions and saving lives. You will use genomic epidemiology and functional genomics to identify and explain links between resistance to several alternative first-line, second-line and urosepsis therapies with findings helping the consortium to inform UK antibiotic prescribing policy.
Description	Urinary tract infection (UTI) is a very common presentation in primary care, and the most common infection leading to microbiological examination and antibiotic treatment. For many years, trimethoprim was the drug of choice, since it is capable of treating UTI, but also works in the kidneys, preventing pyelonephritis (kidney infection) and reducing the chances of hospitalisation with this condition, or with urosepsis - bloodstream infection caused by bacteria originating in the urinary tract. Due to widespread use, trimethoprim resistance, particularly in the most common UTI pathogen, Escherichia coli, increased in prevalence, peaking at 35-40% of all infections in England. At this point, policymakers sought to act, and chose nitrofurantoin as the favoured first choice antibiotic for most suspected UTIs. Resistance to nitrofurantoin has remained low at around 2% of E. coli UTIs, but a reduction in trimethoprim use has been associated with a reduction in trimethoprim resistance to around 25%. However, trimethoprim use has plateaued across England, and so have resistance rates, and this is primarily because nitrofurantoin does not work in the kidneys, and so many clinicians are concerned about prescribing nitrofurantoin for patients they consider high risk for pyelonephritis and urosepsis, and prescribe trimethoprim instead. This PhD project will be based within a National Institute for Health Research-funded interdisciplinary consortium, which is investigating ways to further reduce trimethoprim prescribing, and so resistance by suggesting a third alternative and driving education to stimulate its use. GP practices will therefore be randomised to either change their prescribing policies or stay the same, and the impact that this has on resistance and patient outcome for UTI will be monitored. The "third choice" antibiotic will be based on phenotypic and genotypic surveillance of resistance rates in E. coli from UTI in each Integrated Care Board. The two main alternatives to nitrofurantoin are fosfomycin or pivmecillinam. The consortium is led by the University of Bristol, and involves colleagues from the NHS and UK Health Security Agency locally and nationally. The student will be primarily based within the the genomics workstream of the project, but will be exposed to the whole range of consortium activities.

	Whilst switching away from trimethoprim prescribing aims to reduce trimethoprim resistance, making a future return to trimethoprim as first-choice UTI therapy more likely, switching to an alternative - nitrofurantoin, pimecilinam or fosfomycin - may lead to increased resistance to these agents. However, our early phenotypic surveillance suggests that this is not the only concern. We have identified that there is co-resistance between each of these first line UTI antibiotics, and antibiotics reserved for use to treat pyelonephritis, and urosepsis. Hence it is possible that a switch to one of these alternatives for UTI may make UTI, and more serious complications of UTI more difficult to treat in the future. The main aim of this project is to investigate the molecular basis for co-resistance between the four main first-line UTI antibiotics - trimethoprim, nitrofurantoin, pivmecillinam an fosfomycin, and those agents used to treat pyelonephritis and urosepsis. We would generally refer to these as second line agents. The specific objectives are: To use genomic surveillance across multiple integrated care boards in England to identify clonal and/or plasmid based linkages between mechanisms of resistance to first and second line agents. To use functional genomic analysis based on laboratory selected mutants and clinical isolates with various resistance and co-resistance phenotypes to investigate mechanisms of co-resistance not involving multiple linked genes. This will involve mutant selection experiments, proteomics and genomics coupled with gene knock-out and complementation cloning experiments. To make predictions about the likely impact of antibiotic usage choice change in these regions, and test these predictions using data on phenotypic and genotypic antibiotic resistance made available by UK Health Security Agency, and generated by the student, respectively. Given the wide range of antibiotic/antibiotic combinations being considered, the student will be able to prioritise based on their own judgement, and based on the needs of policymakers and the consortium. They will also be able to focus their work into the various main areas of the project: bioinformatics, functional genomics/molecular bacteriology, data analytics and epidemiology/mathematical modelling. All whilst working within a supportive interdisciplinary research environment with direct policy implications.
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