Evolution of critically important aminoglycoside resistance in humans and farmed animals and transmission between them

Supervisory team:
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Project description:
Aminoglycoside antibiotics are routinely used for treatment of farmed animals (spectinomycin, neomycin, streptomycin) and are critically important for treating serious human infections (gentamicin, amikacin, plazomicin) e.g. sepsis, for which the most common cause in the UK is Escherichia coli, a bacterium found in human and animal faeces and in the environment. Bacteria become resistant to aminoglycosides primarily through production of aminoglycoside-modifying enzymes, which are encoded by genes carried on mobile genetic elements. The newly developed aminoglycoside plazomicin was recently licenced for clinical use, but has not been deployed in the UK. It is derived from gentamicin, and designed to evade existing gentamicin modifying enzymes. Resistance to amikacin and gentamicin in E. coli is rare on farms, but can be found, and is increasingly common among E. coli from human infections, where it is caused by the aminoglycoside modifying enzymes AAC(6')-Ib-cr and AAC(3)-II, respectively. Worryingly, in gentamicin-resistant isolates we have identified mutations that lead to plazomicin resistance, and plazomicin-resistant isolates can be found among E. coli from bloodstream infections, despite the fact that it has not yet been used. Changes in plazomicin susceptibility are caused by mutations in various core metabolic end envelope functions, and within AAC(3)-II. In this cross-disciplinary project you will apply a wide range of bioinformatic and experimental techniques to address the important questions of whether critically important aminoglycoside resistance can be selected for on farms, and is then transmitting to humans, and to investigate what effects mutations within aminoglycoside modifying enzymes have on the acetylation of aminoglycoside substrates.

The objectives – which the student can tailor to their own interests – are:

- Bioinformatics screens of sequenced E. coli from farmed animals and human infections (7000 in our collection) to identify mechanisms associated with amikacin, gentamicin and plazomicin resistance.
- Phylogenetic analysis of sequenced E. coli to determine the degree of human/animal transmission of critically important aminoglycoside resistance within two main study sites: SW England and Bang Len District, Thailand; targeted long read sequencing to determine the degree of plasmid mediated horizontal gene transfer of critically important aminoglycoside resistance in these bacterial populations.
- Competitive mixed-culture experiments to test whether aminoglycosides licenced for use in farmed animals can select critically important aminoglycoside resistance.
- Cloning, expression and purification and mutagenesis of AAC(3)-II and AAC(6')-Ib-cr and assays of acetyltransferase activity versus aminoglycoside substrates; together with crystallisation and structure determination of wild-type and mutant enzymes and their complexes with aminoglycoside substrates.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.