Phenotypic and genotypic diversity in Neisseria gonorrhoeae: Using population biology to understand antimicrobial resistance and pathogenesis

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Project description:
The global spread of antibiotic resistance is a significant and increasing threat to global human health. Amongst increasing threats is the sexually transmitted disease gonorrhoea, for which last resort treatment failures (i.e. third generation cephalosporins) have been reported in numerous countries. The WHO has highlighted that gonorrhoea may soon become untreatable as no vaccine or new drugs are currently available. The population structure of the causative pathogen Neisseria gonorrhoeae is complex and non-clonal due to the high level of genetic recombination that occurs between isolates. Prolific genetic recombination can confound population studies on gonococci, especially as such studies often focus on limited gene numbers such as Multi-locus sequence typing (MLST). Genetic plasticity allows gonococci to quickly generate a range of phenotypes though gene phasing and recombination, the fittest of which can be selected for in vivo, facilitating rapid adaptation within the different mucosal niches infected by these bacteria. This PhD aims to profile the antibiotic resistance of gonococcal isolates from distinct mucosal sites and study the genomic and virulence related phenotype of these isolates. Linkage of these traits to the dynamics of infection transmission will be examined through mathematical modelling. The successful candidate will determine the presence of key virulence factors by distinct immunoassays and proteomic, and infect cell lines representative of the male and female mucosal surfaces mimicking in vivo culture conditions with a diverse range of clinical isolates of Ng. Minimal inhibitory concentrations (MICs) for clinically relevant antibiotics will be assayed. For each isolate selection the genome will be sequenced plus any associated plasmid identified. Finally, data for MIC, virulence factor presence genomic diversity and cell line infectivity will inform mathematical models to investigate potential evolutionary mechanisms of action.

The outcomes are of translational importance: we will improve understanding of in vivo selection in relation to antimicrobial susceptibility and virulence. In addition, we will identify if niche specificity is an important consideration for bacterial phenotypes that may then be utilised in using antimicrobials. Overall this project will provide multi-discipline training and improve our understanding of gonococcal population biology.