**University of Leicester**

**BBSRC MIBTP Studentship Project 2024-5 entry.**

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| **Project Reference** |  |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | **Impact of Hypermutability and Restriction-Modification by *Campylobacter jejuni*, a foodborne pathogen, on Bacteriophage Control Measures** |
| **Project Summary** | |
| *Campylobacter jejuni* is a major foodborne pathogen responsible for thousands of cases gastroenteritis every year. The major source of infections by this bacterial pathogen is contaminated poultry products. *C. jejuni* is a commensal of birds and can spread rapidly within poultry flocks. Multiple approaches have so far failed to significantly reduce the infection burden within poultry farms and products. Bacteriophage treatments have been mooted as one potential approach but is usually disregarded due to high levels of bacterial resistance to infection.    One feature of *C. jejuni* biology is the presence of hypermutable sequences within the coding regions of surface-determinants. High frequency mutations in these sequences are responsible for rapid and reversible switches in expression of these antigens – referred to as phase variation. These switches are partly responsible for the phage resistance as the receptors for the phages can be switched off. As with many bacteria, *C. jejuni* also encodes multiple restriction-modification (RM) systems that are known to contribute to phage resistance. Campylobacter-specific phages have adjusted to the variability in receptor availability and RM systems by diversifying to target multiple receptors and developing resistance mechanisms (e.g. exclusion of RM restriction sites from genomes).    This project aims to assess the extent of phage resistance in *C. jejuni* that occurs due to hypermutability and RM systems. The key objectives are:- 1) to screen a panel of *C. jejuni* strains and phages to determine whether hypermutability and RM systems are major determinants of phage resistance; 2) to construct and test mutants in hypermutable genes and RM systems for altered phage resistance; 3) to co-evolve *C. jejuni* and mixtures of phages to determine the dynamics and mechanisms of phage resistance; 4) to perform *in silico* models to predict whether combinatorial phage therapy can overcome RM- or PV-driven resistance.  The methods will include growth of bacterial pathogens, propagation and testing of phage infections, construction of mutants in bacterial genes, PCR-based assays for detecting mutations in hypermutable sequences and *in silico* modelling of the co-evolution of phages and bacteria.  Techniques that will be undertaken during the project:  Key techniques: growth of bacterial pathogens; propagation of phages; screening bacterial strain collections for phage infectivity; bioinformatics of bacterial genomes; construction of mutants in bacterial genes; PCR-based assays for detecting mutations in hypermutable sequences; *in silico* modelling in Python; statistical testing in R. | |
| **References** | |
| [Phage exposure causes dynamic shifts in the expression states of specific phase-variable genes of Campylobacter jejuni.](https://pubmed.ncbi.nlm.nih.gov/28597819/)  Aidley J, Sørensen MCH, **Bayliss CD**, Brøndsted L.Microbiology (Reading). 2017 Jun;163(6):911-919. doi: 10.1099/mic.0.000470. Epub 2017 Jun 8.PMID: 28597819  [Phase variation of a Type IIG restriction-modification enzyme alters site-specific methylation patterns and gene expression in Campylobacter jejuni strain NCTC11168.](https://pubmed.ncbi.nlm.nih.gov/26786317/)  Anjum A, Brathwaite KJ, Aidley J, Connerton PL, Cummings NJ, Parkhill J, Connerton I, **Bayliss CD.**Nucleic Acids Res. 2016 Jun 2;44(10):4581-94. doi: 10.1093/nar/gkw019. Epub 2016 Jan 18.PMID: 26786317    [How does feedback from phage infections influence the evolution of phase variation in Campylobacter?](https://pubmed.ncbi.nlm.nih.gov/34125841/)  Sandhu SK, **Bayliss CD**, Morozov AY.PLoS Comput Biol. 2021 Jun 14;17(6):e1009067. doi: 10.1371/journal.pcbi.1009067. eCollection 2021 Jun.PMID: 34125841    [Phage-Resistant Phase-Variant Sub-populations Mediate Herd Immunity Against Bacteriophage Invasion of Bacterial Meta-Populations.](https://pubmed.ncbi.nlm.nih.gov/31333609/)  Turkington CJR, Morozov A, Clokie MRJ, **Bayliss CD.**Front Microbiol. 2019 Jul 5;10:1473. doi: 10.3389/fmicb.2019.01473. eCollection 2019.PMID: 31333609    [A bacteriophage cocktail delivered in feed significantly reduced *Salmonella*colonization in challenged broiler chickens.](https://pubmed.ncbi.nlm.nih.gov/37224439/)  Thanki AM, Hooton S, Whenham N, Salter MG, Bedford MR, O'Neill HVM, **Clokie MRJ.**Emerg Microbes Infect. 2023 Dec;12(1):2217947. doi: 10.1080/22221751.2023.2217947.PMID: 37224439 | |

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