

Project Details	
Project Code	MRC21IIRCa Toleman
Title	Reversing antibiotic resistance and sepsis rates of Escherichia coli in the United Kingdom via bacteriophage engineering of the human microbiome.
Research Theme	Infection, Immunity & Repair
Summary	E. coli is the most important bacterial pathogen in Europe. Sepsis and antibiotic resistance rates caused by E. coli are soaring. We hypothesize that the cause of this is high gut carriage of virulent and resistant E. coli strains. Using the principle of my enemy's enemy is my friend we will research the use of bacterial viruses to engineer the human microbiome towards non-virulent/antibiotic sensitive strains.
Description	<p>Background: The pathogen Escherichia coli is a bacterial paradox. It is a harmless commensal that is carried in the gut of all humans. However, it is also the cause of 80% of common urinary tract infections and the leading cause of sepsis (serious blood-stream infections) throughout Europe. In the UK sepsis rates have increased dramatically over the last decade, leading calls by the government to reduce rates by 50% in the next few years. The UK problem is exacerbated by a high carriage rate (c. 10%) of a resistant and virulent E. coli strain ST131. Current studies in the Toleman lab: Our studies in S. Asia have determined ST131 carriage to be below 1% in Pakistan and undetectable in Northern India. We have also found that bacteriophages (viruses that are harmless to humans but lethal to E. coli) able to kill ST131 are very common in sewage in S. Asia but uncommon in the UK. Thus giving a reasonable explanation for the different E. coli strains carried in different countries. Very recently, we characterized 100 randomly selected E. coli on entry to a local sewage works in South Wales. Over twenty-five per cent of these belonged to known virulent groups ST73, ST69, ST95, ST1193 as well as ST131. These strains cause the majority of E. coli sepsis cases in the UK. However, we are yet to detect any of these additional strains in S. Asia. We postulate that S. Asia has higher bacteriophage variety and numbers due to a lack of sanitation yet paradoxically has less virulent extra-intestinal pathogenic E. coli (EXPEC) types than Europe. Hypothesis: 1. The current high sepsis rate in the UK is directly related to a high carriage rate of virulent strains of E. coli in the UK population. 2. The high carriage rate of virulent E. coli strains in the UK is directly related to a low carriage rate of bacteriophages that are able to kill virulent strains.</p> <p>Aims: 1 To determine the % carriage of virulent E. coli strains in the community in several UK cities (Bristol, Cardiff, Exeter, London) by random isolation of E. coli from sewage and determination of virulence type by specific PCR. 2 To determine the abundance and variety of E. coli bacteriophage in the UK community by isolating bacteriophage from sewage collected from the same sites and testing activity against well-characterized virulent and/or resistant strains: Cardiff, c. 300x ST131, 73, 69, 95 bacteraemia isolates; Exeter, c. 100x ST131 environmental isolates; Bristol c. 300x ST131, 69, 73, 1193 urinary tract infection isolates and others collected through MRC grants: MR/T005408/1; MR/S004769/1. 3 To compare abundance and variety of E. coli bacteriophage between countries by simultaneously testing sewage previously collected from UK, S. Asia and Africa. 4 To isolate and</p>

	characterize a bank of bacteriophages that kill UK virulent and/or antibiotic resistant strains that can be used as a handwash and/or probiotic to reduce carriage rates of virulent E. coli in care homes and in the community. 5 To test the ability of specific bacteriophage to clear gut carriage of matched E. coli strains in the insect Galleria mellanoma and mouse gut models.
<b>Supervisory Team</b>	
<b>Lead Supervisor</b>	
Name	Dr Mark Toleman
Affiliation	Cardiff
College/Faculty	Infection and immunity
Department/School	School of medicine
Email Address	Tolemanma@cardiff.ac.uk
<b>Co-Supervisor 1</b>	
Name	Professor Mathew Avison
Affiliation	Bristol
College/Faculty	Infection and immunity
Department/School	school of cellular and molecular medicine
<b>Co-Supervisor 2</b>	
Name	Professor William Gaze
Affiliation	Exeter
College/Faculty	European centre for Environment and human health
Department/School	University of Exeter medical school
<b>Co-Supervisor 3</b>	
Name	
Affiliation	
College/Faculty	
Department/School	
<b>Co-Supervisor 4</b>	
Name	
Affiliation	
College/Faculty	
Department/School	