END OF PROJECT REPORT

Project Reference	CRTA-17-30
Project Title	Clinical Research Time Award – Lim Jones
Lead Researcher	Dr Lim Jones
Host Institution	Public Health Wales Cardiff
Project Start Date	01/04/2018
Project End Date	01/09/2021
Costs (Original)	£74,734
Costs (Final expenditure)	£74,734

Executive Summary

Over the course of his Clinical Research Time Award (CRTA) Dr Jones was involved in a number of clinical microbiology research projects focussed on the study of the epidemiology of infections with antimicrobial resistance (AMR) in bacterial pathogens. This builds on existing research collaborations that Dr Jones developed with groups at Cardiff University and his role as clinical lead for the Specialist Antimicrobial Chemotherapy Unit (SACU) and the Antimicrobial Resistance and Genomic Typing Project (ARGENT). The latter project is funded by Welsh Government and intended to develop a sequence typing and surveillance service for Wales targeted at aerobic bacterial pathogens, especially those associated with Health-Care Associated infections (HAIs) and AMR. This project depends on the work of Public Health Wales' Pathogen Genomics Unit (PenGU). In addition Dr Jones with colleagues supporting SACU and ARGENT has further developed collaboration with Cardiff University Microbiology, Immunology and Clinical Trials Unit; University of Oxford departments of Zoology and the Centre for Genomic Pathogen Surveillance; and Cardiff and Vale Adult Critical Care Directorate.

Dr Jones is the principal investigator for the project "The epidemiology and impact of bacterial secondary infections and antimicrobial resistance on Intensive Care during the SARS-CoV-2 pandemic." Dr Jones was the main applicant for funding of £175,517.00 from a Health and Care Research Wales project grant. The primary aim of this research is to characterise the epidemiology of bacterial pathogens in patients on the intensive care unit (ICU) during the COVID-19 pandemic. The focus will be on temporal shifts in predominant bacterial strains, resistance rates, and resistance determinants. These will be related to changing prescribing and infection prevention & control (IPC) practices and staff-patient ratios from the winter months of 2020 onwards. The project will also feed detailed microbiological data on certain sample types into existing projects led by Cardiff University Immunology on sepsis in critical care. The study has already collected over 1000 bacterial isolates and has undertaken antimicrobial susceptibility testing (AST) by gold standard methods, with whole genome sequencing (WGS) of certain key pathogen groups to follow soon.

Dr Jones has also recently been adopted as Principal Investigator for a Welcome Trust Funded project led by Oxford University, “Understanding the impact of COVID-19 on bacterial sepsis, antibiotic consumption and stewardship, and antimicrobial resistance.” This is an observational cohort study using both retrospective and prospective data. This will incorporate individual clinical data on patients with COVID, pneumonia, Acute Respiratory Distress Syndrome and non-pneumonia sepsis. This study will document the impact of COVID-19 pandemic on bacterial sepsis, antibiotic consumption and stewardship, and antimicrobial resistance over a two-year period through a global network involving 11 countries, including low, middle and high income countries.

During the course of the CRTA Dr Jones has been a co-author on 5 original research articles. These have related to work on existing collaborations with teams at Cardiff University Microbiology and Oxford University Department of Zoology, and their international networks. A Lancet Infectious Diseases paper “Effects of antibiotic resistance, drug target attainment, bacterial pathogenicity and virulence, and antibiotic access and affordability on outcomes in neonatal sepsis: an international microbiology and drug evaluation prospective substudy (BARNARDS)” raised important questions about the efficacy of the main combination of antibiotics used in many LMICs for the treatment of neonatal sepsis. It demonstrated that rates of AMR to first choice empirical treatment regimens in some centres had an impact on drug target attainment and potentially clinical outcomes.

Four further publications report on clinical, basic microbiology and pathogen WGS data from a retrospective cohort study performed at a tertiary care hospital in Bangladesh. The published data includes identification of important outbreaks with drug resistant Gram-negative pathogens on a neonatal unit and a burns unit; and the discovery of mobile colistin resistance in clinical isolates from this hospital. A further article is currently awaiting a decision on publication and highlights the burden of carbapenem resistant Enterobacterales (CRE) in Bangladesh. This study includes clinical outcome data, risk factors for infection with CRE, and detailed WGS identifying the main clones associated with CRE. Together these data highlight the high burden of antimicrobial resistance, its clinical impact and the consequences of under developed infection control, antimicrobial stewardship, basic microbiology and

detailed surveillance of AMR in Bangladesh. The data from this study has implications for other LMICs in South Asia, and in a globalised world the uncontrolled AMR epidemic in South Asia also has long term implications for AMR infections and there control in the UK.

Through the collaboration with Pathogen Genomics Unit (PenGU), the Centre for Genomic Pathogen Surveillance and Cardiff University Dr Jones has helped to undertake an analysis of an extensive collection of clinical, screening and environmental *Klebsiella* spp. isolates collected from 2007-2020 by SACU. Analysis of the initial data set is complete and an original research article is intended to be submitted to Microbial Genomics imminently. This study has facilitated a detailed description of the evolutionary dynamics of *K. pneumoniae* and identified important clones and plasmids driving spread of AMR in Wales. Further work has followed on from this on ST1788 *K. pneumoniae*, the second most common clone in our *Klebsiella* data set, which has rarely been described outside of South Wales but has been responsible for an ongoing outbreak, is associated with an AMR phenotype and has been shown to be capable of causing severe sepsis. This is also at an advanced stage of development and includes a description of new rapid molecular test to screen for this clone designed by SACU, and includes a larger strain collection with more detailed clinical and epidemiological analysis. Dr Jones has also helped to direct a project led by a clinical scientist in SACU to look at the potential of WGS data to predict antimicrobial susceptibility of *Escherichia coli* and *Klebsiella* spp. This study shows that this approach has potential but has important limitations at the present time. The study is unique in that it uses gold standard broth microdilution as a comparator for the WGS predictive models. A journal article for submission to the Journal of Antimicrobial Chemotherapy is at an advanced stage of drafting.

Through the programs of work identified Dr Jones is continuing to develop a research portfolio that attempts to define the epidemiology of AMR in a variety of AMR pathogens, define clinical impacts and identify real world uses for emerging technologies for AMR surveillance. This is vitally important work at a time when AMR is identified is a burgeoning public health threat which is currently responsible for considerable global morbidity and mortality. Without research to curb the spread of

AMR bacterial infections it is predicted that this impact will only increase in the coming decades.