Uncovering the Role of *Staphylococcus aureus* Carriers in Antibiotic Resistance

Antimicrobial resistance (AMR) is one of the most pressing global health challenges, threatening to make common infections untreatable. Among the leading contributors to this crisis is *Staphylococcus aureus* (SA), a bacterium responsible for a wide range of infections, from mild skin conditions to life-threatening diseases such as sepsis and pneumonia. Of particular concern is methicillin-resistant *Staphylococcus aureus* (MRSA), which resists multiple antibiotics, complicating treatment and increasing mortality rates. Globally, infections caused by SA are linked to over 1 million deaths annually, with this number projected to rise to 10 million by 2050 if AMR remains unchecked.

A key factor in *S. aureus* persistence and spread is its ability to live harmlessly in approximately 30% of the global population. These asymptomatic carriers (equivalent to over 1.9 billion people worldwide) serve as a vast reservoir for the bacterium, silently contributing to the transmission of resistant strains within communities and healthcare settings. While extensive research has been conducted on *S. aureus* infections, the role of these carriers in driving the evolution and dissemination of antibiotic resistance remains poorly understood. Addressing this knowledge gap is critical to mitigating the AMR crisis.

Project Goal

This project seeks to understand how *S. aureus* survives, persists, and evolves in human carriers, ultimately leading to the development of resistant strains and disease emergence. By integrating genomic, epidemiological, and experimental approaches, we aim to identify the genetic and environmental factors driving these processes.

Our research leverages a unique dataset of over 21,000 SA carriage samples and 10,000 disease samples from the UK. All positive samples will undergo whole-genome sequencing, making this one of the largest and most comprehensive datasets of its kind. Preliminary findings already indicate that:

1. Diseases frequently originate from the carriage population.
2. Clonal prevalence in disease mirrors that observed in carriers.
3. Disease populations exhibit higher genetic resistance across multiple antibiotic classes.

These findings underscore the urgent need to explore the interplay between asymptomatic carriage and disease emergence.

Research Objectives

To address these challenges, the project is structured around four interconnected work packages:

1. **Population Structure and Disease Emergence**
   Comparative genomic analyses will investigate evolutionary relationships between *S. aureus* strains in carriers and disease cases. This work aims to define the pathways and frequency of disease emergence while identifying genetic factors that facilitate the transition from carriage to infection.
2. **Clonal Persistence and Dynamics**
   Temporal shifts in clonal prevalence will be analysed using phylogenetic and statistical approaches, focusing on the impact of antibiotic usage and host-specific adaptations. Techniques such as skyline analyses and molecular dating will provide insights into the drivers of clonal success over time.
3. **Genetic Determinants of Clonal Success**
   Genome-wide association studies (GWAS) and pangenome analyses will identify genetic traits that enable *S. aureus* clones to persist in carriers. These traits may include antibiotic resistance, immune evasion, and metabolic adaptability, providing a deeper understanding of clonal persistence and spread.
4. **Experimental Validation and Clonal Competition**
   Key genetic traits identified in WP3 will be experimentally validated using cutting-edge techniques like CRISPR-Cas9 and allelic exchange mutagenesis. These experiments will assess the functional roles of these traits in clonal persistence and competition, providing critical validation for computational findings.

Public Health Implications

This research has significant implications for public health and AMR management strategies. By elucidating the mechanisms that allow *S. aureus* to maintain resistance within carrier populations, our findings will inform infection control policies, such as targeted screening and decolonization strategies for high-risk groups. These insights will also guide interventions to disrupt the transition from carriage to disease, reducing the prevalence of resistant strains in both community and healthcare settings.

Additionally, this research contributes to the global fight against AMR by advancing our understanding of bacterial evolution and adaptation. Combining state-of-the-art genomic analysis, experimental validation, and interdisciplinary collaboration, this project represents a major step forward in addressing one of the most critical challenges in modern medicine.

Supported by world-class genomic facilities at Cambridge and partnerships with leading experts in microbial genomics, this project aims to deliver actionable insights that improve global health outcomes.