ACRONYM: **PREPARE**

Title: **Predicting the Persistence of Resistance Across Environments**

Keywords: **Costs of resistance; compensatory evolution; reservoir; evolutionary theory; genomics; animal models**

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Abstract:

Antimicrobial resistance poses a serious challenge to health care worldwide. Attempts to control resistance by stopping antimicrobial use have met with mixed success. Failures of a critical assumption underlying such strategies – that resistant strains suffer a disadvantage in the absence of drug (the "cost of resistance") – may be responsible for difficulties in controlling resistance by cessation of drug use. In particular, resistance mutations may be cost free, and hence persist, in some environments or on some genetic backgrounds.

Furthermore, even when resistance is initially costly, compensatory evolution – the accumulation of mutations that restore fitness while maintaining resistance – may allow resistant strains to persist. Using two pathogenic bacterial species, we propose to undertake a systematic study of the costs of resistance across multiple genetic backgrounds, as well as across a variety of relevant conditions across the human-animal-environment axis.

Moreover, we will determine whether resistant pathogens take the same, or different, routes to compensation in different environments. Taking advantage of evolutionary theory, we will determine the feasibility of predicting the costs of resistance in one environment using information from another environment, which would aid in predicting the persistence of resistant strains using limited information from laboratory studies. The proposed work will provide crucial information for public health policy on strategies for controlling resistance.