

Project Details	
Project Code	MRCIIAR24Ba Brown
Title	How are changing environments on our farms driving antifungal resistance in clinical fungal pathogens?
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Fungal pathogens cause deadly human infections, destroy our crops, and contaminate our food with toxins. Fungal pathogens of people are also present on our farms. Worryingly, we rely on a few antifungals to cure human infection and to secure our safe food supply. Here, we aim to understand how our changing environments and use of antifungals on farms may drive human pathogens to evolve cross-resistance to clinical treatments that result in poor patient outcomes.
Description	<p>THE FUNGAL THREAT: Fungal pathogens cause deadly human infections, destroy our crops, and poison our food with harmful toxins. Despite our best efforts, we still lose 10% of our crops to fungal diseases, 25% of all food is contaminated with fungal toxins, and human infections have extremely high mortality rates. Worryingly, our population is becoming more vulnerable to infection, as the numbers of susceptible patients with immune disorders, major trauma, or viral co-infections rises.</p> <p>ENVIRONMENTALLY ACQUIRED RESISTANCE: We rely on a few antifungals to secure our safe food supply and to cure human infection. This has created a perfect storm for the evolution of antifungal resistance (AFR), as many of the major fungal pathogens of people are also present on arable farms. It is believed that the exposure of pathogens to agricultural antifungals has driven the evolution of cross-resistance to similar antifungals in hospitals, termed environmentally acquired resistance. Examples include <i>Aspergilli</i> and <i>Fusaria</i> which cause toxic cereal rots and life-threatening pulmonary, skin and eye infections, where antifungal resistance has been reported to contribute to poor treatment outcomes. But what is driving the threat of environmentally acquired resistance, is it changes to our environment or altered agricultural practices? And where on our farms are these pathogens acquiring AFR?</p> <p>DIRECTED EVOLUTION: We will evolve <i>Aspergillus</i> and <i>Fusarium</i> species under conditions that replicate our changing agricultural environments in the presence of differing levels of agricultural antifungals. These environmental stresses will replicate the impacts of climate change and agricultural intensification, i.e. temperature, humidity, salt, and pH stress. Evolved and non-evolved strains will harbour constitutive GFP or RFP markers to facilitate comparative minimum inhibitory concentration (MIC) and competition assays, which will evaluate how adaptations to different stresses confer resistance to different antifungals. Competition assays and fitness cost experiments will be used to model how these adaptations may influence the structure of the fungal population. This will enable us to study which scenarios are driving the rise in environmentally acquired resistance on our farms. For example, does the use of irrigation in agriculture, which increases soil salinity, drive soil dwelling fungi such as <i>Aspergilli</i> and <i>Fusaria</i> to evolve stress tolerance mechanisms that promote AFR to both agricultural and clinical antifungals? Or, will future climatic environmental stress increase the rate at which AFR evolves? We will use genomics and RNA sequencing to identify genetic changes acquired</p>

	<p>through exposure to stress and antifungals, in multiple fungal lineages with phenotypic adaptations. Finally, CRISPR-Cas9 genome editing will be used to confirm these genetic adaptations confer phenotypic adaptations that enhance environmental stress tolerance and AFR evolution. PATHOGEN COMMUNITIES: We will sample distinct arable environments (crops, soils, residues) throughout the farming year to create a collection of <i>Aspergillus</i> and <i>Fusarium</i> species, supported by industry collaborations with Agrii, Syngenta and Eurofins field trialists. Monoclonal antibody diagnostics will be supported by Prof. Thornton ISCA Diagnostics. This collection will be used to monitor how pathogen aggressiveness, stress tolerance, toxin production and AFR profiles change in response to altered practices and environments. Comparative genomics will be used to identify the genetic basis of adaptation in natural pathogens, to be correlated with lab-evolved strains.</p> <p>IMPORTANCE: This research will help determine what is driving environmentally acquired resistance on our farms. This knowledge will support the development of improved farming practices and national risk mitigation policies, protecting the shelf-life of our limited antifungals, to the benefit of our food security and human health.</p>
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