Will We Soon Be Living in a Post-Fungicide Era?

Derreck Carter-House
University of California, Riverside, Plant Pathology and Microbiology Department, Boyce Hall 1463
Riverside, CA 92521
Corresponding author: dcart001@ucr.edu
Keywords: fungi; antifungals; drug resistance; antifungal development

Executive Summary: Antifungals treat fungal infections in humans and agriculture, but there are far too few currently available. As fungi begin to develop resistance to these drugs, it is urgent that we begin to develop new antifungals and educate the public about being responsible stewards of antifungals. New antifungal development should be encouraged by awarding more exploratory grants. The markets enabled by these new antifungals would more than cover their research and development costs.

This spring, as hundreds of thousands of people packed into a dusty, windy Las Vegas Speedway for Electric Daisy Carnival and swarmed to Southern California for the Coachella Valley Music and Arts Festival, few knew they were in areas where Valley Fever is a concern ("Valley Fever Maps | Fungal Diseases | CDC" 2019; Miller 2019). Valley Fever is a disease contracted by about 14,000 people every year in the southwestern United States that can cause fatigue, coughs, fevers, shortness of breath, headaches, night sweats, muscle aches, joint pain, and rashes. Symptoms persist for a few weeks to months and are caused by a fungus called *Coccidioides*.

Fungal infections are silent killers, causing 1.5 million deaths worldwide every year (Microbiology Society n.d.). Approximately 97,000 Americans die from hospital-related fungal infections each year alone; ninety percent of these often deadly infections are caused by just two common fungi, *Candida* and *Aspergillus* (Stein et al. n.d.) and *Cryptococcus* (Ballou 2017). We are being invaded by fungi (Dunham 2019), but where is the push for new treatments?

Most fungi are microscopic and can be found on every continent. Mushrooms, the mold on the strawberries in your fridge, and the yeast that makes your favorite beer are all types of fungi. Many people do not realize that we are surrounded by tiny fungal spores--microscopic biological particles that enable fungi reproduction--that spread easily. They are in the air we breathe, food we eat, and on our skin. Fungi can be deadly, killing more people than malaria every year ("WHO | Number of Malaria Deaths" 2019). Some fungi, like the Mucrorales, are so deadly that the patient mortality rate is between 50-90% (Chibucos et al. 2016; Microbiology Society n.d.). But why are fungal infections so deadly? The answer is simple: they are difficult to treat and the few antifungals that can kill or damage fungi often have serious side effects. There are also only a few antifungal agents approved by the FDA, most of which are derived from bacteria, very small organisms that are quick-growing and ubiquitous. Bacteria naturally produce antifungals to fight fungi and protect their territory. However, fungi and bacteria dwell together in the soil, so fungi are already developing resistance to antifungals before we even begin treating an infection in the hospital. Antifungal resistance is outpacing our ability to create new antifungals (Fisher et al. 2018). Because fungi adapt so quickly, it is challenging for manufacturers to recoup the costs associated with research and testing trials of their new antifungal compounds.

As a result, our current arsenal of medical antifungals includes the same ones that are being used to preserve timber and to treat crops and livestock (Fisher et al. 2018). Because these antifungals are being used for many purposes, there is a chance for fungi that naturally have resistance to grow and spread. If these resistant fungi are more prevalent, they are more likely to spread their resistance to fungi that might infect humans. Therefore,

developing systems to reserve certain classes of antifungals exclusively for human use may help increase longevity. This practice has been shown to be effective in reducing resistance to antibiotics in bacteria (Tang et al. 2017).

We see scientists going to the far reaches of the earth to find drugs for bacterial infections. Why don't we see the same research enthusiasm for fighting fungal infections? Research funding is very competitive and driven by application-based research proposals. As a result, funding for basic science, like exploring the corners of the earth for novel antifungals, is limited when compared to work with a clear hypothesis and application. For example, searching coral reefs for novel compounds is basic research. It could lead to many discoveries including antifungals, but there is no guarantee. Applied research, on the other hand, uses an antifungal (found in coral reefs) to fight fungal infections in humans. Applied research immediately benefits us, but we need basic research in order to begin the work. The National Institute of Health (NIH) spent $522 million last year alone on "antimicrobial resistance" and about $60 million specifically on "antifungals" according to the NIH's Award Reporting service. While $60 million sounds like a lot of money, in reality, it is less than 0.2% of the annual NIH budget. With the cost of fungal diseases in humans estimated to be $7.2 billion in the U.S. (Benedict et al. 2019), increasing funding should be a priority.

While it is important to devote funding to explore novel compounds that kill fungi, a more immediate and attainable goal is to create policy that protects our current arsenal of antifungals. We must create a structure that not only helps determine how and when to administer antifungals, but also supports public education campaigns on microbial persistence and the development of resistance. This policy can be modeled after the U.S. National Strategy for Combating Antibiotic-Resistant Bacteria, a national plan established to address the rising concern of resistant bacteria, which increased basic and applied research and development of new antibiotics, surveillance of outbreaks, and international collaboration.

The bad news for all those who attended EDC is that there is currently no vaccine for Valley Fever. Fortunately, however, there seems to be a light on the horizon. Recently, there has been a major push by the offices of US Congressmen McCarthy and Schweikert to fund research on *coccidioidomycosis* (Valley Fever) and other fungal pathogens, H.R. 6562, the bipartisan FORWARD Act. These offices are currently collecting letters of support for the bill.

Fungal infections and antifungal resistance are serious and growing problems. It is important that we discover new antifungals, protect our existing ones, and educate ourselves and others. If we do not act soon and antifungal resistance continues to rise, nearly 100,000 Americans will face fungal infections every year empty handed.

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Derreck Carter-House studies bacterial fungal interactions in the lab of Jason Stajich at the University of California in Riverside. He is currently serving as Co-Chair for the National Science Policy Network's Graduate Education Committee. His future goals include working in policy as an advocate/lobbyist for science.