ANGEL N. DESAI AND GEORGE R. THOMPSON III

Foiling the Growing Threat of Fungal Pathogens

In recent years, wildfires have ravaged millions of acres across the western United States. The environmental effects of such fires are profound and evident, but the more subtle harm to public health may prove to be devastating. Wildfire smoke has been associated with microbial proliferation and dispersion, leading to an increase in fungal infections in affected areas, as evidenced by a rise in hospital admissions within a few months of large-scale wildfires in California. Investigators have suggested that inhalation of fungal spores, coupled with wildfire smoke interfering with the immune system, may be driving these illnesses.

It's hard to "see" these environmentally related fungal infections in classical surveillance efforts, so they are likely underrepresented, eclipsed by more salient bacterial, viral, and mycobacterial diseases. But the global burden of fungal disease is already immense: 6.5 million invasive fungal infections occur annually, and the number of cases rises every year. As fires, floods, and other weather events exacerbated by climate change become more frequent and intense, the spread of fungal pathogens, called *mycoses*, are likely to become increasingly common and harmful to public health.

What makes this trend particularly concerning is that mortality associated with invasive fungal pathogens exceeds 40%, and few drugs are currently available to treat these infections. A coordinated response to the movement, adaptation, and proliferation of these understudied pathogens will be essential to mitigating and reversing their adverse health impacts. Policymakers and public health workers need a clear understanding of the factors that amplify these threats and affect the rise of antifungal resistance, as well as a diversified policy strategy that encompasses agricultural practices, forest management, and health care.

Thermal détente derailed

Fungal spores may well be in the air you're breathing right now. But despite the ubiquity of fungi in nature, invasive fungal infections are rare in patients with intact immune systems. Of the more than 5 million different fungal species estimated to exist on Earth, only a few hundred are known to cause mammalian infections. Our primary defense against fungal infection is the warmth of our bodies. In fact, some researchers have proposed that our relatively high body temperatures evolved specifically to avoid fungal infections. Unfortunately, the last century has seen two shifts that may undermine that advantage. First, the average human body temperature seems to be in decline, having dropped by close to one degree Celsius (−0.03°C per birth decade) worldwide over the last century. Second, as the climate changes, fungi seem to be adapting to tolerate higher temperatures. With human body temperatures decreasing while fungal thermotolerance increases, humans' natural defenses against fungal infection diminish. Put in terms of a long-standing and precariously balanced evolutionary arms race, the ability of fungi to attack is growing while natural human defenses are shrinking. It's impossible to forecast how many fungal pathogens could gain the ability to infect humans if these two trends continue.

What we do know is that fungi are amazingly resilient, adaptive, and persistent. They are found even in Earth's most extreme environments. In Antarctica, for instance, they survive winter temperatures that regularly fall below −100°F. Fungi even endured the nuclear meltdown in Chernobyl, where they were exposed to quantities of radiation that killed other life forms. One of the unique attributes of fungi is the ability to produce melanin, a pigment composed of polymers made from the amino acid tyrosine, which shields them from UV radiation, pH stress, and exposure to heavy metals. Melanin also weakens the effectiveness of antifungal medications and helps fungi fend off the aggressive mammalian immune system. Through a process called radiosynthesis, fungi even use their melanin to convert radiation into chemical energy they can use.

Shifting migration patterns and habitat ranges

Around the world, fungi have been disturbingly effective at exploiting the conditions created by increasingly frequent extreme weather events in environments inhabited by humans. Hurricanes and ensuing floods, for example, cause water damage to homes and businesses, which creates conditions that favor mold. Wildfires significantly increase exposure to soil-dwelling fungi, broadcasting fungal spores in the atmosphere for wide dispersal. The dust storms that follow droughts or overfarming also cause soil and microbial aerosolization. All these phenomena may expose vulnerable human populations to more fungal pathogens, some of which may be new to them.

Alterations in temperature and precipitation patterns driven by climate change have also shifted the ranges and flight paths of migratory birds and bats. Both types of animals are effective carriers of fungal pathogens, which they transport in their lungs or on their feet, fur, or feathers. One example of a common bird- and bat-spread fungal disease is histoplasmosis, an infection resulting from inhalation of *Histoplasma capsulatum* spores. The disease, which can cause mild to life-threatening pneumonia symptoms in humans, has significantly expanded northward and eastward in the United States, coinciding with shifts in several migratory routes.

Vulnerable agriculture

What's more, rising global temperatures seem to be enhancing the genetic plasticity of fungal organisms, boosting the speed with which they can adapt to new environments and perhaps their ability to evolve resistance to antifungal drugs.

Agricultural practices have been linked to large-scale fungal outbreaks among crops, making the world's food supply vulnerable to fungal infection. Global agricultural productivity increased substantially following the Green Revolution, in which agricultural scientists engineered crops specifically for high yields. But the lack of genetic diversity in staple crops such as rice and wheat means that the emergence of a single deadly pathogen could have devastating ramifications for the world's food supply. Most of the bananas grown today, for example, come from a single clonal line of the Musaceae family, which is easy to transport, maintains its taste, and provides a high yield. But it is also susceptible to infection by a deadly fungal pathogen known as Fusarium Tropical Race 4, which is currently on the move around the world.

The lack of genetic diversity, plus the evolutionary adaptability of the fungi, are already putting the world's most important foods in jeopardy. Another devastating plant epidemic was chestnut blight, caused by the fungus *Cryphonectria parasitica,* which killed more than 4 billion North American chestnut trees in the early twentieth century. If a similarly efficient and deadly mycosis were to hit the world's main species of grain, it would be calamitous.

Fungi can develop resistance to fungicides when crops are not varied and fungicides that only target a single aspect or mode of action are used to control disease, making future efforts to preserve those agricultural lines more challenging. Furthermore, increased homogeneity in food production at a national level also ties into global trade interdependence. As regional economies focus on monoclonal food production, exporting these foods to new areas that do not typically produce them introduces the potential for the emergence of new fungal pathogens and patterns of resistance.

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Human migration

The migration of people into sparsely populated areas that already host fungal pathogens poses a growing threat to public health, too. For example, housing pressures have driven many Californians to move to the Central Valley, where a common soil-dwelling fungus called Coccidioides causes valley fever. More people are infected each year as frequent droughts make the area hotter, drier, and more hospitable to the fungus. In addition, increased construction and other human activity stir up the soil, releasing the long-active spores into the air. Older residents with less robust immune systems are especially vulnerable to the worst effects of valley fever.

Supporting disease surveillance systems

The crisis is deadly serious. However, several steps can be taken to reduce the public's vulnerability to the shape-shifting capability of fungi. First, fungal pathogens don't stick to one domain, so researchers must likewise look across agriculture, forestry, and health care to battle them. Improvements in the detection and monitoring of fungal pathogen activity requires taking a One Health approach to look across these multiple domains and understand how changes to agriculture or forestry may affect health. Adapting farming and forestry methods could reduce vulnerability to fungal pathogens. Likewise, it is necessary to regulate the use of fungicides to prevent fungi from becoming resistant and potentially spreading to humans, livestock, or other animals. And, as a crucial final line of resistance, more research is urgently needed to find effective novel antifungal drugs and treatments.

The public health community should adopt a One Health approach to fungal disease surveillance. This approach, currently focused on viral and occasionally bacterial pathogens, attends to the complex interplay of human, animal, and environmental factors in determining the course (and mitigation) of public health threats. While some surveillance systems do attend to agricultural pathogens, including some that track crop-threatening fungi, most of these efforts today focus on food scarcity rather than human health.

To be effective, surveillance programs must strengthen their tracking of fungal pathogens in humans, animals, and plants. Furthermore, researchers must integrate those new systems with existing epidemiological efforts, which now primarily consider other kinds of human infection, into a comprehensive early-warning system to alert public health officials of emerging hot spots for fungal pathogens. This will help ensure early detection of emerging or spreading drug-resistant fungi before they cause significant health problems. Finally, scientists should work to understand how the effects of climate change may shift the epidemiology of endemic fungal pathogens into new environments and contribute to the emergence of novel fungi.

Given researchers' limited understanding of whether and how widespread fungicide use affects antifungal resistance in clinical settings, more research on local resistance patterns in the environment is also needed. Similarly, better understanding of how fungi evolve to tolerate fungicides can illuminate how fungicide use may contribute to antifungal resistance in humans.

There is no question that regulating fungicide is a complex task. It requires a tricky balance between preserving crop yields today while preventing devastating antifungal resistance tomorrow. A coordinated and collaborative approach between governmental agencies that regulate human and agricultural health and those that prevent environmental degradation is necessary to develop strategies for mitigating antifungal resistance while also protecting agricultural and economic interests. Some encouraging steps are already underway to promote these conversations with key stakeholders.

Lastly, the current array of treatments for fungal infections requires development. Identifying antifungal candidates that work in new ways—and transforming them into effective and deployable interventions—must also be a priority. This remains a particular challenge in the field of antimicrobial drug development, as "last line" drugs are purposely reserved for crises or when commonly prescribed treatments have failed, making these expensive-to-develop drugs a poor return on investment for pharmaceutical companies. Overcoming this financial paradox requires that government agencies provide financial incentives and streamline regulatory hurdles for such research.

The challenges in the treatment of fungal disease remain immense. The scientific and public health communities must coordinate efforts to increase public awareness, boost researchers' understanding of pathogen spread, and develop comprehensive eradication efforts. Addressing the many health threats related to this complex nexus of anthropogenic factors through collective, cross-disciplinary action must start immediately.

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***Angel N. Desai** is an associate professor of medicine in the Division of Infectious Diseases at the University of California, Davis. She is a member of the New Voices in Sciences, Engineering, and Medicine program at the National Academies. **George R. Thompson III** is a professor of medicine at the University of California, Davis, School of Medicine with a joint appointment in the departments of Medical Microbiology and Immunology and Internal Medicine, Division of Infectious Diseases. He serves on the Coccidioidomycosis Study Group Board and as chair of the Mycoses Study Group Education Committee, and is the president-elect of the Mycoses Study Group.*