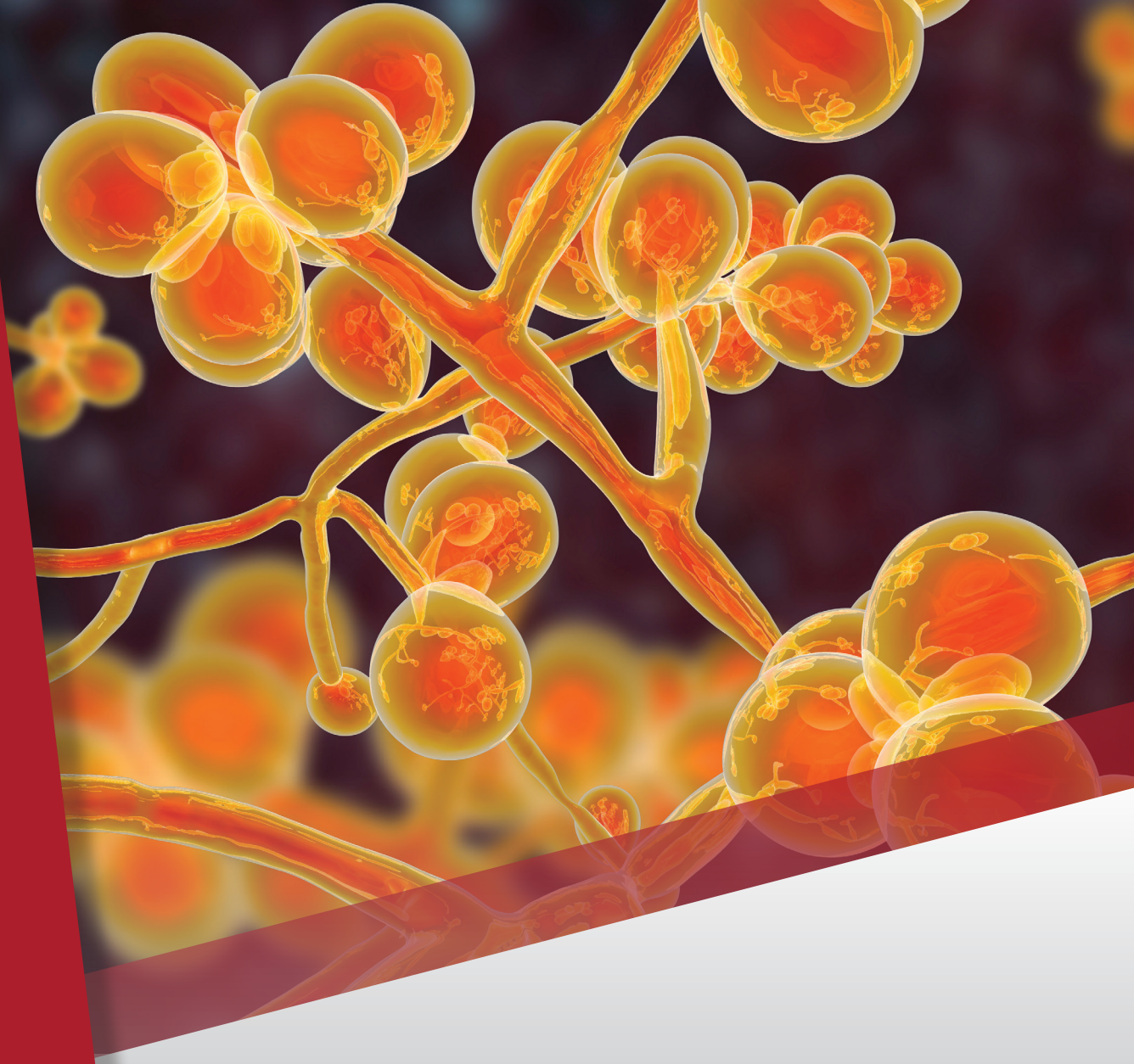
COLLOQUIUM REPORT



One Health: Fungal Pathogens of Humans, Animals, and Plants

AMERICAN SOCIETY FOR MICROBIOLOGY

AMERICAN ACADEMY OF MICROBIOLOGY
RECOGNIZING SCIENTIFIC EXCELLENCE

One Health: Fungal Pathogens of Humans, Animals, and Plants

Report on an American Academy of Microbiology Colloquium held in Washington, DC, on October 18, 2017.

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Introduction

The fungal kingdom includes as many as 6 million species (1) and is remarkable in terms of the breadth and depth of its impact on global health, agriculture, biodiversity, ecology, manufacturing, and biomedical research. More than 600 fungal species are associated with humans, either as commensals and members of our microbiome or as pathogens that cause some of the most lethal infectious diseases (2–4). Individuals with weakened immune systems are the most vulnerable, but otherwise healthy individuals are also at risk from well-known and emerging pathogens, especially in situations in which infection involves a large inoculum. With the global increase in the incidence of invasive fungal infections and the emergence and spread of fungal pathogens resistant to all current classes of antifungals, these organisms pose an acute threat to human health (2–5). The full extent of this threat has not been possible to measure directly because there were no reporting requirements. A signal that matters may be improving came in 2016, when the World Health Organization declared mycetoma, a debilitating tropical fungal affliction of the extremities, to be a Neglected Tropical Disease, thus initiating work on surveillance, prevention, and control. Plans for strengthening the detection and monitoring of, and response to, mycotic diseases as well as implementation of antifungal resistance surveillance in invasive mycosis in the Americas are being developed.

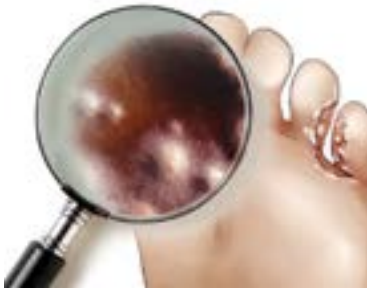
Fungal diseases in humans have been increasing coincident with the advent of revolutionary new medical therapies, including antibiotics, immunosuppressive therapies, and indwelling medical devices. The first descriptions of candidiasis, a systemic yeast infection, were reported in the 1950s after antibiotics eliminated the helpful bacteria in our systems that keep the *Candida* fungus in check. The 1950s also saw the commencement of steroid use, the development of chemotherapy, and the introduction of indwelling catheters that pierce the skin, thereby providing a conduit that defeats skin defenses and enables microbes to cross into the interior. These factors helped fungal pathogens exploit humans as never before; it is remarkable that systemic fungal infections are not more common in humans.

The full impact of fungal diseases in humans is not clear because of the general lack of a requirement for healthcare workers to report fungal infections, noted above. This gap has many serious consequences, among them limited public awareness of fungi and insufficient training about fungi and fungal disease for students in medicine, public health, and microbiology. The complexity of data collection has worked against the creation of large databases to record statistics on fungal

The full impact of fungal diseases in humans is not clear

diseases. The deficit in healthcare professionals cognizant of fungal disease and the absence of readily accessible data on fungal disease adversely impact research on fungal disease. Furthermore, there is recent evidence that the number of fungal species associated with humans is underestimated owing to the fact that many species cannot yet be cultured in the laboratory (6). The resulting ignorance about fungi puts society at significant risk with new fungal pathogens emerging, including those for which none of the current treatment options is effective.

Although many fungi are associated with humans, relatively few are serious pathogens, as human body temperature is a major deterrent to fungal pathogens (7). The fungal kingdom thrives at ambient temperatures found in nature, whereas the normal body temperatures of humans and other mammals are too high for most fungi to invade. As a consequence, fungi—such as the ones that cause athlete's foot, ringworm, and other skin problems—are often found on the outside of the body. Fewer species thrive inside the body under normal conditions. Here, a relatively few, well-adapted fungi cause most human diseases of hosts with an intact immune system. A number of other fungi, however, can cause disease in hosts who are immunocompromised (e.g., those infected by HIV), immunosuppressed (e.g., by medications), or simply waiting for their immune systems to develop. In contrast, fish, bats, amphibians, and snakes have lower body temperatures and are prone to fungal infections. In recent years, there have been an unprecedented number of fungal diseases causing extinctions of wild species, with mass mortalities seen in hibernating bats and amphibians that threaten biodiversity (2).



Fungi that cause ringworm and other skin problems are often found on the outside of the body

Another reason fungal infections are such a serious problem is that they are very difficult to treat. Currently, there are only four classes of antifungal drugs available to treat life-threatening infections (8–10). A limiting factor for identifying new antifungal drugs is the difficulty in finding therapeutic targets for selectively killing the fungi. In contrast to bacterial pathogens, the basic cell and molecular biology of fungi is very similar to that of animals. For example, two of the current drug classes attack a key component of the fungal cell membrane, ergosterol, which is similar to mammalian cholesterol. The underlying similarity between the fungal and animal kingdoms makes it challenging to identify drugs that kill the fungus without causing serious side effects in patients. Researchers are looking for new and innovative strategies to thwart fungal pathogens, but it is a race against time because fungi can rapidly evolve resistance to the drugs we use to kill them. In fact, clinical resistance to every class of antifungal drug has emerged, and multidrug-resistant pathogens are now spreading around the globe (3).

The direct threat posed by fungi to human health, alarming as it is, is exceeded by the indirect effect of fungal diseases of plants that jeopardize food security worldwide. These fungi are responsible for epidemics that kill or reduce yields of the staple crops that feed billions, including rice, wheat, and corn. In addition to killing crops, fungi produce toxins that contaminate food supplies, such as toxins that lead to the development of cancers. Included among these toxins are those with acute effects that have been considered for deployment as biological weapons against humans and crops. Despite this threat, the fungal kingdom is generally neglected when it comes to considering catastrophic risks to humanity (11).

Fungi are also exquisitely responsive to environmental perturbation, which

can exacerbate their deleterious effects. Climate change is altering the global distribution of fungi, and this change will have profound consequences for agriculture (12). The loss of millions of trees from native forests due to fungal diseases (chestnut blight, Dutch elm disease, ash dieback, and many others) constitutes a massive loss of habitat and removes carbon sinks that cannot be fully replaced by replanted forests (13). Urban areas will also be affected when hurricane-associated flooding promotes fungal growth in homes and offices or when windstorms cause outbreaks of human disease caused by soil-borne fungi (14, 15). The adaptability of fungi to new environments is further highlighted by the fact that they have infested the International Space Station (16), and black molds are among the few life forms that have proliferated in the contaminated ecosystems surrounding the Chernobyl nuclear power plant (17).

Having enumerated the ways in which fungi can cause devastation, one may wonder whether they make any positive contributions to life on Earth and human civilization. First and foremost, fungi are the Earth's preeminent degraders of organic matter, and more than 90% of plant species form a mutually beneficial symbiosis with fungi (mycorrhizae), in which the plant trades from 3% to 35% of the sugar it makes by photosynthesis for minerals that the fungal partner scavenges from the soil (18–20). Moreover, fungi are invaluable to medicine, as Alexander Fleming famously showed when he discovered penicillin, the first of a phenomenal diversity of medically important secondary metabolites that fungi synthesize. These fungal metabolites have revolutionized patient care and include a multitude of antibiotics, immunosuppressive drugs that inhibit transplant rejection, and drugs that lower cholesterol and reduce the risk of heart disease (21). Fungi are also essential to manufacturing by producing enzymes crucial for fermentation, food production, bioremediation, and biofuel production (18, 22). Among the products that depend on fungi are baked goods, citric acid, soy sauce, and alcoholic beverages, the latter having a global economic value that exceeds that of aeronautics, equals that of automotives, and is eclipsed only by that of petroleum. The fungus most often contributing to this wealth is the microscopic yeast *Saccharomyces*, which also happens to be the best characterized of several fungal model research systems (23), as underscored by four recent Nobel Prizes earned through using this yeast (cell cycle control in 2001, telomeres in 2009, secretion in 2013, and autophagy in 2016).

With human activity, modern medicine, and climate change all intensifying the impact of fungi on global health, agriculture, and biodiversity, it is more crucial than ever to advance our understanding of the fascinating biology of fungi in order to harness their extraordinary potential and evade the devastation they can impose. To tackle this challenge, the American Academy of Microbiology (AAM) convened a colloquium in October 2017, bringing together an international and interdisciplinary team of experts. This meeting transpired a decade after the first of its kind hosted by the AAM. To read the 2007 Colloquium Report "The Fungal Kingdom: Diverse and Essential Roles in Earth's Ecosystem," visit https://www.asmscience.org/content/report/colloquia/colloquia.42. Therefore, this new report from the 2017 colloquium begins by stating the key priorities to address and highlights the remarkable advances in the field inspired by the initial colloquium.

What are fungi?

- Fungi are eukaryotic organisms. Their basic cellular structures are similar to those of human and plant cells but very distinct from those of bacteria.
- Fungi grow in diverse shapes ranging from small yeasts to large multicellular organisms (e.g., mushrooms).
- Most fungi play an important role in nature as saprophytes that degrade organic matter so it can be recycled into new food for growth.
- A small minority of fungi are pathogens that cause disease.

Recommendations

The first AAM colloquium on the Fungal Kingdom was held in Tucson, Arizona, in 2007. We have revisited and updated the recommendations that were included in the report "The Fungal Kingdom: Diverse and Essential Roles in Earth's Ecosystem," many of which have been implemented while others remain prescient challenges that influence our recommendations from the second AAM colloquium on the Fungal Kingdom held in 2017 in Washington, DC, entitled "One Health: Fungal Pathogens of Humans, Animals, and Plants." Below is our new "baker's dozen."

1. **Report and Track Fungal Infections That Cause Disease in Humans, Plants, and Animals.** The full extent of the impact of fungal infections is not appreciated. Thoroughly documenting fungal impact globally and tracking this information would provide a template for understanding disease emergence, range expansion, and impact of drug resistance.

Report and track fungal infections that cause disease in humans, plants, and animals

2. **Conduct a Global Census of Fungal Species.** With respect to pathogenic fungi, many of which are derived from the environment, a global census of environmental fungi and the various locations and species of fungi that exist in nature is a research priority. Continued efforts on a census of this kind are critical to our ability to establish the roles of these fungi in causing diseases in humans, animals, plants, crops, and other perturbed ecosystems.

3. **Conduct a Census of the Fungi In the Human Microbiome.** It is important that researchers conduct a census of the fungi associated with the human body under a variety of conditions. Much progress has been made in emphasizing the need to analyze the fungi in the microbiome (mycobiome) in the context of a variety of human body sites (skin, gastrointestinal tract, oral mucosa, vaginal mucosa, and the lungs) (24, 25). However, examination of the mycobiome and its interactions with both the host and the microbiome and possible contributions to a variety of disease states requires continued research efforts (26).

4. **Support and Sustain the Fungal Genome Databases.** Research involving fungal genomics, including RNAseq-based transcriptomics, is generating enormous and rich datasets, and compiling and storing these data and making them available to the community are imperative

for advances that follow (27, 28). The Fungal Genome Database (FungiDB) (27), supported as part of the broader EuPath Database, and MycoCosm, supported by the Joint Genome Institute (28), require continued support. Databases such as NCBI that store and make available DNA and RNA sequence datasets also require continued support.

5. **Support and Sustain Fungal Culture Collections.** Most research on fungal diseases is carried out on a few well-studied strains. This approach has made it possible to compare results among different laboratories, but it makes it impossible to apply new genetic approaches that exploit the natural genetic variation inherent in populations of pathogenic fungi. Genomic research on model fungi has shown that the genes responsible for any variable trait, including drug resistance and virulence, can be discovered by genome-wide association studies within fungal populations or by reverse ecology studies between them. Applying these approaches to pathogenic fungi depends on access to populations of wild strains kept in culture collections.

6. **Develop New Drugs, Diagnostics, and Therapies.** While some advances have been made in the area of treatment and diagnostics (8, 10, 29), the continued dearth of new antifungal agents and approaches requires continued efforts to develop novel targets and new antifungal drugs, improved diagnostic tests and modalities, and alternative treatment methods such as immunotherapy and antibody-based therapy.

7. **Investigate Mechanisms Leading To Antifungal Drug Resistance.** The widespread global emergence of azole resistance in *Aspergillus fumigatus* has been attributed directly to the widespread use of azoles (also known as demethylation inhibitors [DMIs]) in agriculture (3). In parallel, the emergence of multidrug-resistant *Candida auris* has resulted in difficult-to-manage infections in the hospital setting. There are also increasing reports of infections caused by drug-resistant dermatophytes that are difficult to manage. Studying the ways by which fungi develop drug resistance, and how this trait spreads through environments and populations, is a priority.

Fungal genomics is revealing forces that drive evolution

8. **Enhance and Sustain Training In Fungal Physiology, Classical Mycology, Fungal Genetics and Genomics, and Fungal Pathogenesis.** There is a clear need to train more individuals to address the unique features of this diverse kingdom of pathogenic microbes, including studies on physiology, genetics, phylogenetics, and taxonomy. Courses that emphasize training in mycology, such as the Molecular Mycology course held annually at the Woods Hole Marine Biological Laboratory, require support to sustain their efforts to enhance the training of the next generation of researchers in these areas.

9. **Study Outbreaks To Identify Emerging Fungal Pathogens of Humans, Animals, and Plants.** Over the past several decades, multiple new pathogenic species have emerged, including *Candida auris* in humans, *Batrachochytrium salamandrivorans* (*Bsal*) in salamanders, and multiple new species of plant pathogens. With continued global warming, ecosystem perturbation, and global movement and trade, it is likely that novel fungi will continue to emerge as disease agents. Continued diligence is necessary to identify new and emerging pathogens and then to study these organisms to provide insights relevant to prevention, diagnosis, and treatment (30).

10. **Complete the Genome Sequences of More Fungi and Fungal Populations.** Fungal genomics is revealing forces that drive evolution and contribute to speciation within groups that had been thought to be single species (24, 25, 31, 32). Understanding population structures, as well as gene and trait flow and exchange, is increasingly possible at the whole-genome level. Many fungal genomes remain to be completed using newer long-range sequencing technologies (e.g., PacBio and Nanopore), and novel approaches to enhance annotation both experimentally (RNAseq) and computationally will increase the value of these genomic resources.

11. **Develop New Methods of Preventing Fungal Infections of Plants.** The risk of global azole drug resistance is high due to widespread use of azoles in agriculture (3). New methods to prevent and reduce the impact of fungi in agriculture are needed, such as the ability to spray crops with dsRNA to evoke gene silencing and thereby minimize the impact of fungi on crops and food production.

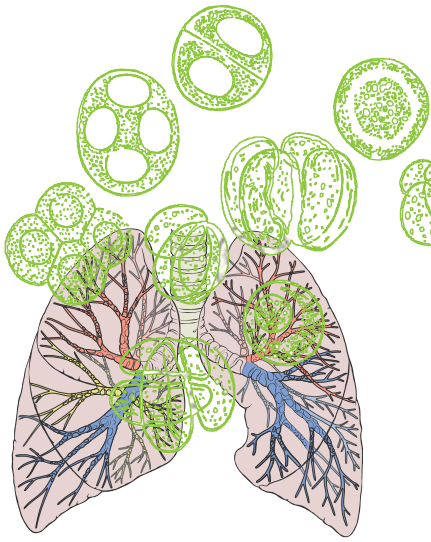
12. **Develop New Approaches to Protect Frogs, Salamanders, Bats, and Other Animals from Pathogenic Fungi.** Ways to treat infected animals, prevent infections, or move animals to safer environments are needed. These approaches may include modifying the skin microbiomes of animals to render them immune or more resistant to fungal infection.

13. **Promote Ways To Bring Diverse Mycologists Together To Develop in Cross-Fertilizing Advances.** While there are similarities among the fungi that infect humans, animals, and plants, there are also vast differences, and different research communities have different perspectives. Supporting ways to bring these diverse communities together will provide insights that advance different areas in a synergistic fashion.

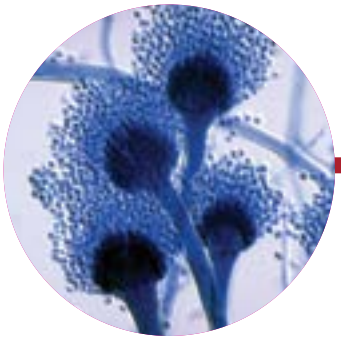
Fungi Cause Human Allergy and Disease

There has been a growing appreciation of the impact of fungi on human health. Humans are routinely exposed to vast numbers of spores and inhale between 1,000 and 10 billion spores on a daily basis. We are also home to fungal species that take residence in distinct parts of our body, including the skin, gut, and other mucosal surfaces. Fortunately, our immune systems generally protect us from fungal diseases. It is clear that people whose immune systems are weakened are much more vulnerable to fungal infections. This vulnerability can result from treatments that intentionally dampen the immune system to prevent rejection of transplants, from side effects of treatments for cancer and other conditions, or from infections or diseases that impair immune function, such as AIDS (33). Fungi can also become more problematic if the normal bacterial residents of the human body are removed, as is the case with antibiotic treatment (34).

There are very different types of fungal infections that depend upon the immune status of the person infected and the kind of fungus. Some infections are superficial in nature, including conditions such as athlete's foot, ringworm, dandruff, and other skin conditions. Fungi can also thrive in the human skin and nails and cause significant damage in this context. Some fungi can cause chronic and devastating localized infections even below the skin. Such infections are more prevalent in tropical regions, as is the case with mycetoma, which was recently classified by the World Health Organization as a Neglected Tropical Disease (35). Systemic fungal infections occur when the fungus spreads throughout the body. These infections often originate either in the lungs, from inhalation of fungal spores, or from commensal fungi that reside within the body. Many of these infections are caused by fungal pathogens of low pathogenic potential that cause disease only when the host is weakened. Some fungal pathogens have the capacity to cause disease even in healthy people without immune suppression, and these are often referred to as primary fungal pathogens. In all cases, invasive fungal infections are life-threatening (33). Most deaths due to fungal infections are caused by a small number of species; the major fungal pathogens of humans are delineated below.



Humans inhale between 1,000 and 10 billion spores on a daily basis



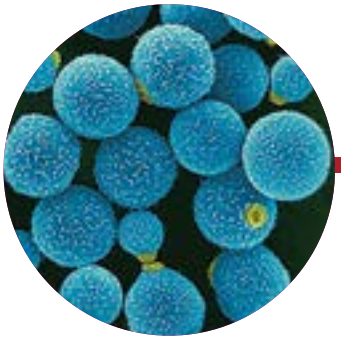
Aspergillus

The genus *Aspergillus* includes several hundred mold species that are found indoors and outdoors worldwide. We are all exposed to *Aspergillus* spores, with air conditioners, compost, and damp buildings providing sources of abundant spores. People generally become ill from *Aspergillus* when they have a weak immune system, damaged lungs, or major allergies (36). Aspergillosis refers to

the group of diseases caused by *Aspergillus*, with the most prevalent diseases being invasive aspergillosis, chronic pulmonary aspergillosis, aspergilloma, and allergic aspergillosis. *Aspergillus* can also be an allergen that causes severe complications for people with asthma, cystic fibrosis, and bronchiectasis, as discussed below. Invasive aspergillosis is most commonly observed in the lungs of severely immunosuppressed individuals but can also spread to other organs and tissues. Invasive aspergillosis has a high mortality rate, 25% to 90% (37). Chronic pulmonary aspergillosis involves long-term infection of the lung and generally affects only people with underlying lung disease. It can manifest as cavities of the fungus in the lungs or even a ball of fungus growing within a cavity (known as an aspergilloma). In certain individuals, strong immune responses to *Aspergillus* infection result in allergic aspergillosis, which is a chronic and debilitating condition that can result in considerable impairment for those affected. *A. fumigatus* is the major species associated with human disease, although these conditions can be caused by other species, such as *A. niger*, *A. flavus*, and *A. terreus*. Current antifungal therapies for invasive and chronic aspergillosis syndromes are often unsuccessful, highlighting the need for new approaches to treat and prevent these infections. Specifically, the recent emergence of triazole-resistant *A. fumigatus* has severely hampered the progress that has been made in treating invasive aspergillosis. In addition to causing human diseases, *Aspergillus* spp. can cause infections in animals, birds, and plants and produce toxins that lead to food spoilage or are carcinogenic.

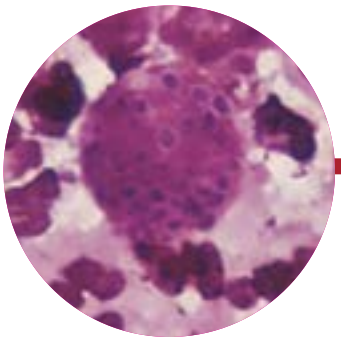
Candida

The genus *Candida* includes more than 20 species of yeasts that can cause human infections. These yeasts generally reside in the gut and on the skin of healthy people, as well as on mucous membranes. When the immune system is weakened or when antibiotics clear out bacteria normally present in the body, *Candida* can overgrow and cause candidiasis (34). When this overgrowth happens in the mouth, throat, or esophagus, it is referred to as thrush. Thrush in the esophagus is among the most common infections in patients with AIDS due to HIV infection. *Candida* overgrowth is also the cause of vaginal yeast infections, which affect ~75% of women at least once in their lifetime and is more frequent in the context of pregnancy, diabetes, antibiotic use, or immune suppression due to steroids or chemotherapy. Hence, *Candida* spp. can cause disease in both immunologically intact and impaired individuals. *Candida* can also escape from the normal places it lives in our bodies and spread, causing life-threatening invasive disease, with about 46,000 cases of candidiasis associated with healthcare facilities in the United States each year (38). When *Candida* spreads to the bloodstream, it is referred to as candidemia and is one of the most prevalent bloodstream infections in North America. Approximately 95% of *Candida* infections in the United States are caused by five species: *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* (39). *C. albicans* is generally the most common cause of candidiasis, but the impact of each species depends on the region of the globe and attributes of the patient population. The mortality rate associated with invasive candidiasis is ~30%, and the CDC now has an Emerging Infections Program to conduct candidemia surveillance. As discussed below, there is a growing concern with emerging *Candida* pathogens, such as *C. auris*, which is often multidrug-resistant, is difficult to identify, and has caused recent outbreaks in hospital settings (40).



Cryptococcus

Cryptococcosis is usually caused by either *Cryptococcus neoformans* or *Cryptococcus gattii* and generally affects the lungs or central nervous system. *C. neoformans* thrives in the environment around the globe and gains entry into humans when spores or desiccated yeast cells are inhaled (41). Most infections with this fungus occur in people with impaired immune systems, especially those with AIDS due to HIV infection. (33, 37, 42). With the introduction of antiretroviral treatments for people with HIV, there was a reduction in the incidence of cryptococcosis in some parts of the world. However, there has been little impact in resource-limited regions where healthcare access is limited and HIV is rampant. Globally, there are approximately 220,000 new cases each year in which *Cryptococcus* spreads to the brain during infection, causing cryptococcal meningitis, and over 180,000 deaths (33, 42). In sub-Saharan Africa, *Cryptococcus* is the leading cause of meningitis in adults. *C. gattii* cryptococcosis is rarer than that caused by *C. neoformans* but has been reported in otherwise healthy people, although those with weakened immune systems or lung conditions are more vulnerable. *C. gattii* resides in soil and in association with some trees in tropical and subtropical environments. Since the late 1990s, *C. gattii* has also been implicated in infections of humans and other animals in British Columbia and the U.S. Pacific Northwest (43).

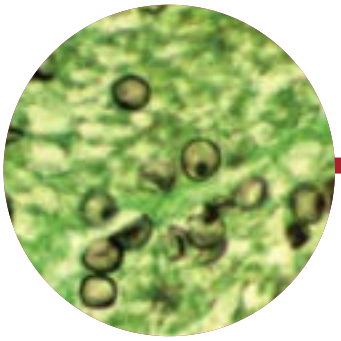


Dimorphic fungi *(Histoplasma, Coccidioides, Blastomyces)*

The dimorphic fungi are characterized by having two morphotypes or shapes. They generally exist as filamentous molds in the environment; at mammalian body temperature, they transition to a spherical yeast form (41). Dimorphic fungi that are major pathogens of humans and other animals include *Histoplasma capsulatum*, *Coccidioides immitis/posadasii*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Emmonsia pasteuriana*, and *Talaromyces marneffei*. Here, we focus on *Coccidioides* and *Histoplasma* as key dimorphic fungal pathogens.

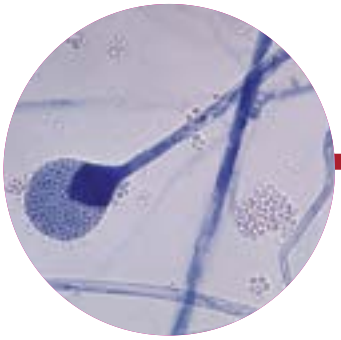
Coccidioides and *Histoplasma* are both capable of causing disease in otherwise healthy humans. When inhaled, spores of both fungi initiate infection. In most cases, both diseases are prevented from leaving the lung by the patient's immune response, which forms granulomas around the fungi (41). At least 10% of the 150,000 U.S. residents infected with coccidioidomycosis annually seek medical treatment for pneumonia, with 1% of these patients requiring life-long antifungal therapy to avoid a fatal outcome, at a cost exceeding $30,000/year (44). *Coccidioides* is endemic in arid zones of the Americas, and coccidioidomycosis is most common in highly populated areas of Arizona and California. The fungus evolved to use small desert rodents as a substrate and has jumped hosts to humans and domesticated dogs and horses (45, 46). Soil disturbance, whether by natural causes or human activity, aerosolizes the spores and leads to infection. Global climate change is certain to alter the distribution of this arid zone fungus. Specifically, *C. immitis* has already been identified in eastern Washington State, far outside of the traditionally defined area where it is endemic (47).

Histoplasmosis is found in the Americas, Africa, India, Asia, Australia, and Europe (48). In North America, it is endemic to the Mississippi and Ohio River Valleys and has evolved to associate with bats and birds, in whose guano it sporulates (49). Disturbance of bat and bird roosts can lead to inhalation of spores and infection. As with coccidioidomycosis, most hosts are unaware of their condition because their immune systems control the infection with granulomas, but a significant percentage seek treatment for pneumonia or flu-like symptoms, and a small percentage require life-long antifungal therapy (41). Although *Histoplasma*, like *Coccidioides*, can cause disease in otherwise healthy hosts, it has a higher incidence in immunocompromised humans and where anti-retroviral therapy is uncommon, as is often the case outside of North America. Mortality in AIDS patients infected with HIV reaches 30%. [https://www.cdc.gov/fungal/diseases/histoplasmosis/index.html].



Pneumocystis

Pneumocystis jirovecii is a fungus that causes serious pneumonia in individuals with weakened immune systems (50). It coevolved with humans and is highly adapted to living in the lungs of healthy people without causing symptoms. Healthy carriers can spread the fungus from one human to another through airborne transmission. *Pneumocystis* pneumonia was rare before the HIV/AIDS epidemic but quickly became an AIDS-defining illness during the 1980s, afflicting approximately 75% of people with AIDS (51). *Pneumocystis* pneumonia remains a frequent opportunistic infection in resource-limited countries and has been increasing in prevalence in patients not infected with HIV, including those with lung disease, inflammatory or autoimmune disease, or cancers of the blood or lymph systems, or those who had received transplants.



Mucormycetes

These molds are found in the environment, often in soil and decaying organic matter, and cause a rare but life-threatening infection called mucormycosis in people with weakened immune systems (41). Extraordinary climactic events, such as tornadoes and tsunamis, can lead to outbreaks as debris can become embedded in skin or eyes. Mucormycetes cause many types of disease, depending on what part of the body comes into contact with the fungal spores from the environment. Pulmonary mucormycosis results from inhalation of spores and is most often seen in people who have received transplants or have cancer or those who have received systemic iron chelation therapy. Rhinocerebral mucormycosis arises in the sinuses and can spread to the brain, most often in people with uncontrolled diabetes. Gastrointestinal mucormycosis is most common in infants and young children following ingestion of fungal spores. Cutaneous mucormycosis can occur following fungal invasion through a skin break caused by surgery, burn, or other trauma and is the most common mucormycosis in people with healthy immune systems (52). Mucormycetes can spread through the bloodstream from the original site of infection, leading to mucormycosis affecting organs such as the brain, spleen, heart, and skin.

Emerging fungal threats.
There is additional concern with emerging fungal threats. As a leading example, the CDC has classified *Candida auris* as an emerging pathogen and global health threat. *C. auris* was first reported in 2009 in Japan, and retrospective reviews of *Candida* collections date the earliest strain to 1996 in South Korea (53). This fungus has now been identified in dozens of countries, despite identification requiring specialized laboratory techniques. Risk factors for *C. auris* infections are similar to those for other *Candida* infections, and there is pressing concern as it is often resistant to all of the antifungal drugs commonly used to treat fungal infections. This pathogen has already caused outbreaks in hospital settings and can be transmitted through contact with infected patients or contaminated surfaces, where it can live for several weeks (54). Similarly, the global spread of pan-azole resistance in *Aspergillus fumigatus* is also of great concern as it leaves the medical community with no oral drugs to treat aspergillosis.

Outbreaks of fungal diseases.
Unusual outbreaks of fungal infections are increasingly common (https://www.cdc.gov/fungal/outbreaks/index.html). They typically involve unusual exposures involving large inocula or the introduction of a particular fungus in a susceptible population. These fungal outbreaks are caused by the pathogens discussed above and others (15, 30). There was an outbreak of histoplasmosis in the Dominican Republic in 2015 in which 30 tunnel workers were infected by the fungus, which was likely released from disturbed soil polluted with bat droppings (55). Another outbreak of histoplasmosis occurred in 2013 in a state prison in Illinois in which 78 cases were thought to be connected to disturbed soil

The CDC has classified *Candida auris* as an emerging pathogen and global health threat

There is additional concern with emerging fungal threats

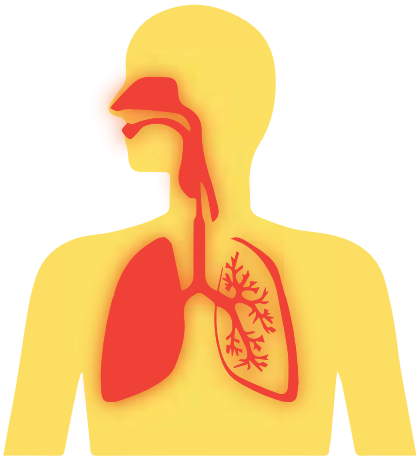
Pathogenic fungi: yeasts and molds

- Pathogenic fungi mainly grow in cell shapes that are referred to as yeasts or molds.
- Yeasts are single-celled organisms that typically divide by budding off a new daughter cell.
- Molds form long filamentous chains of connected cells. Molds also produce small spherical spores. Dissemination of spores in the air is a major route of infection.

polluted with bird droppings. Two additional fungus outbreaks causing coccidiomycosis in prisons were reported in 2013 in California, where installation of solar panels caused another outbreak in 2016–2017. In 2012, a fungal meningitis outbreak affecting 753 individuals in 20 states was attributed to steroid injections that were contaminated with fungus from a compounding pharmacy, and another outbreak of fungal eye infection (endophthalmitis) affecting 43 individuals was also attributed to contaminated injections (56) (https://www.cdc.gov/fungal/outbreaks/index.html). In 2011, there was an outbreak of mucormycosis after a Missouri tornado and an outbreak of blastomycosis in Wisconsin (57, 58).

Allergic fungal diseases.

There is a growing appreciation that fungi are a major cause of allergy and that people who are sensitized to fungi can have severe health complications. Allergic reactions to fungi affect the respiratory tract, as described by the examples below. Airway colonization with *Aspergillus* spp. is common in chronic lung diseases such as asthma and cystic fibrosis and is commonly associated with progressive deterioration of lung function. A subset of patients will develop allergic bronchopulmonary aspergillosis, a severe allergic reaction to antigens produced by *Aspergillus* spp. growing within the airways of these patients. Severe asthma with fungal sensitization (SAFS) is thought to affect at least 1 million people worldwide and is associated with poor asthma control due to sensitivity to many fungi, including but not limited to *A. fumigatus, Penicillium chrysogenum, Cladosporium herbarum, Alternaria alternata, C. albicans*, and *Trichophyton* species. It has also been noted that thunderstorms are associated with an increased incidence of acute asthma attacks, which have been attributed to elevated levels of fungal spores. There is also a plethora of different occupational lung diseases in which specific occupations result in exposure to fungal allergens. Examples include farmer's lung (due to exposure to *Penicillium* in damp hay), wine grower's lung (due to exposure to *Botrytis*), and tobacco worker's lung (due to exposure to *Aspergillus*). Allergic fungal rhinosinusitis (ARFS) affects ~12 million people globally and can occur in response to diverse fungi, including *A. fumigatus*, *A. flavus*, *Bipolaris spicifera, Curvularia lunata*, and *A. alternata*, leading to nasal obstruction, polyps, and impairment in vision. Fungal infections have also been associated with hyperreactive airway disease syndromes, such as asthma, where immune responses to chitin could play a role in pathogenesis (59). Many of the fungi implicated as allergens proliferate in indoor environments. Estimates suggest that fungal growth is visible in 20% to 40% of buildings in Northern Europe and North America, and mold contamination is severely exacerbated following storms and flooding.



Allergic reactions to fungi affect the respiratory tract

Fungal Pathogens of Plants are a Threat to Food Security

Crop-destroying fungi have been a threat to humanity since the agricultural revolution. Diseases caused by fungi and the related oomycetes have led to famines, ruined economies, and blighted landscapes. Although oomycetes, including the devastating *Phytophthora* ("plant-destroyer") *infestans,* are not strictly fungi—their DNA indicates they are more closely related to brown algae and diatoms—they are morphologically and physiologically similar to fungi and have evolved, or gained through horizontal gene transfer (60), many of the same mechanisms for causing disease in plants. Throughout history, this threat was known, and gods were often petitioned that crops be spared (61, 62). More recent history carries examples of the damage that emerging fungal diseases can cause. For instance, Dutch elm disease (*Ophiostoma novi-ulni*) killed millions of mature elm trees, and chestnut blight (*Cryphonectria parasitica*) destroyed billions of American chestnuts (63). Crops have also suffered; epidemics of potato blight (64), wheat steam rust (60), and ergot fungus (65) are among the best documented. Diseases caused by plant pathogens have been increasing in severity and scale since the mid-20th century, and today, emerging fungal diseases challenge global food

Oat crown rust, Minnesota.

Image credit: Dr. Melaniea Figueroa, Senior Research Scientist, CSIRO Agriculture & Food, Australia.

security and ecosystems health in an unprecedented manner (4, 66, 67).

Current threats are manifold. Fungi continue to threaten crops: rice is constantly attacked by the rice-blast disease agent *Magnaporthe oryzae*, causing 12% to 30% crop losses even when fungicides and resistant cultivars are deployed (68). *M. oryzae* recently emerged as a pathogen of wheat in Brazil, Bangladesh, and India (69, 70). However, wheat is most threatened by rust fungi, such as *Puccinia graminis.* New, highly virulent strains of *P. graminis* have overcome the resistance of many commercial wheat varieties and threaten harvests in southern Europe, Asia, and the Americas (71, 72). Although *P. graminis* may re-emerge in the United Kingdom (73), *Zymoseptoria tritici* (wheat leaf blotch) is currently more problematic in such temperate wheat-growing regions. This disease costs the United Kingdom around 3M to 5M € yearly in fungicides and crop losses, despite the use of resistant wheat varieties (74). Trees are also under attack: ash dieback disease, caused by the fungus *Hymenoscyphus fraxineus*, recently emerged in Europe, leaving ash trees threatened in several countries (75), including 90% of the United Kingdom's 90 million trees (75, 76). The future will likely bring new variants of old fungal foes, movement of old adversaries to new crops or areas, and entirely new fungal diseases (4, 67).

Plants are distinct from humans and animals, so it is not surprising that they have developed their own complex defense strategies to protect against fungal pathogens. Once a pathogen has breached the mechanical barrier raised by the plant cell wall, plant receptors trigger signaling cascades that activate plant defense responses (77). Pathogen recognition depends on two classes of receptors. The pattern recognition receptors (PRRs) detect common molecules from fungi and other plant pathogens, such as fungal cell wall components (e.g., glucans) or bacterial surface proteins (e.g., flagellin), which are collectively known as pathogen-associated molecular patterns (PAMPs) (78). These receptors also detect molecules released when a pathogen attacks the host: damage-associated molecular patterns (DAMPs). Meanwhile, another class of sensors known as the NOD-like receptors (NLRs) detect molecules secreted by pathogens to damage the host. Signaling pathways activated by these receptors then trigger defensive responses, including the production of toxic chemicals (e.g., reactive oxygen and nitrogen species) or enzymes that attack the pathogens (77). These are tailored to the pathogen detected; for example, chitinase enzymes are deployed against fungi and oomycetes to destroy cell wall structures (78, 79).

Difficulties in discovering antifungal drugs

- The close evolutionary relationship between humans, animals, and fungi makes it difficult to find drugs that kill fungi without having toxic effects on humans or animals.
- Fungi are quite diverse. This makes it challenging to identify drugs that will inhibit all fungi.
- Fungi have multiple mechanisms for developing resistance to drugs, such as proteins that pump the drugs out of their cells.

Rice is constantly attacked by the rice-blast disease agent Magnaporthe oryzae, causing 12% to 30% crop losses

A novel virulence mechanism employed by plant pathogens has been discovered recently that involves the delivery of small RNAs (sRNAs) into the host plants, which then act to silence genes involved in host plant immunity. Many fungal pathogens, including *Botrytis cinerea*, *Verticillium dahliae*, and *Puccinia striiformis*, have been shown to become more aggressive pathogens by delivering these sRNAs into their host plants to silence immunity genes (80, 81). Other recent studies show that such cross-kingdom use of interfering RNA molecules is bidirectional (82, 83). During the co-evolutionary arms race with pathogens, plants have also adapted to use sRNAs as a weapon. Plants secrete membrane-bound vesicles carrying sRNAs that then enter the fungal pathogen and silence virulence genes to suppress diseases (82).

Factors driving fungal disease Emergence in plants

A variety of factors promote the emergence of fungal disease in plants. As will be described below, some factors are intrinsic to specific fungi, such as the ability to evolve rapidly or to persist and disseminate in the environment. Other factors include the production of unusual ecosystems as a result of intensive agriculture involving monocultures of crops. These factors are being exacerbated by stress on plants due to the effects of climate change.

Fungi have a high evolutionary potential owing to their short generation times and populations large enough to harbor alternative alleles at every locus. As a result, resistance to new fungicides or to new resistant crop varieties can occur in a few seasons. Add to this rapid response the inevitability of genetic exchange among repeated introductions of pathogens and ability of spores to both spread disease and persist in the environment and one can explain the fact that fungi cause most plant disease (67). The virulence genes of some fungal plant pathogens are able to evolve more rapidly because they are present in special genomic regions that are sequestered from essential genes (84–86).

Modern agriculture inadvertently helps fungi cause disease by generating a unique agro-ecosystem conducive to the spread of fungal crop disease (87). Monocultures of a few "elite" crop varieties across wide areas with extended growing seasons provide the perfect environment to select fungi that overcome plant resistance. Fungi exhibit an impressive range of genetic variation, and research has documented ample opportunities for outcrossing, recombination, hybridization, introgression, and horizontal gene transfer (67). In this way, agriculture provides a cradle for the evolution of its own enemies (87).

Agriculture provides a cradle for the evolution of its own enemies

Climate change is broadening the risks of fungal infection to trees and crops

A species will emerge as a threat only if it is persistent and can disseminate. Crop pathogens must survive between growing seasons until host availability recurs (e.g., by vertical transmission between host generations, wide host range, or resting spores) (67). Spatial travel of spores in the air further allows the invasion of new environments. Rust fungi are adapted to long-distance travel, having spores that spread in atmospheric air currents (88).

Similarly, the fungus causing ash tree dieback produces spores that are able to travel long distances on the wind, partially explaining its unstoppable march across Europe and arrival in the United Kingdom (89, 90). It is important to note that dissemination of the fungus was aided by human activity. Ash dieback spread through the United Kingdom in two ways: from the east, as spores were blown from Europe, and from epicenters within the United Kingdom, each resulting from imported saplings carrying the disease (91). This mode of dissemination represents the biggest anthropogenic risk factor in the emergence and spread of plant disease: trade and transport of infected material (63). Chestnut blight entered North America and Europe from Japan on ornamental trees in 1904 (92). Although the resultant pandemic devastated whole forests across North America, transatlantic trade in chestnut trees and wood continued (92). Such anecdotes highlight a serious problem: that biosecurity, in the sense of keeping a fungus from naïve hosts, is often at odds with commercial interests in the movement of goods that may carry the disease (63). It is one of the great challenges of modern trade to prevent infected shipments, especially when infected plants, seeds, or cuttings are asymptomatic (67).

Climate change is broadening the risks of fungal infection to trees and crops. Fungi are moving towards the poles at 6 to 7 km yearly as the earth warms (93). As climate change opens new regions to particular crops, their fungal pathogens follow them, with agricultural areas becoming gradually more saturated with pathogens over time (94). Prediction of pathogen movement and risk remains difficult and is complicated by many covariates (95). As well as such gradual spread, fungi may spread during extreme weather events. A crop pathogen that illustrates the devastating potential of such events is bacterial citrus canker. Efforts to eradicate this pathogen from

A consequence of the spread of fungi is that pathogens invade naïve ecosystems

Florida were abandoned following the "year of the four hurricanes" (96). It is easy to see how parallel events could occur in fungal pathogens.

A consequence of the spread of fungi is that pathogens invade naïve ecosystems. Thus, host species may lack defenses and there may be little or no competition. Furthermore, where pathogen species barriers were maintained by geographic separation, hybridization may provide a genetic bridge, allowing virulence or fungicide resistance genes to be shared. This type of genetic exchange occurred between causal agents of different epidemics of Dutch elm disease (97).

Darker fungi are more common away from the equator (98). Melanin-producing microbes, as many fungi are, have the capacity to harness solar radiation for heat, a property that could allow them to contribute to climate change through trapping heat and warming their environments (98, 99).

Impact of fungal plant diseases

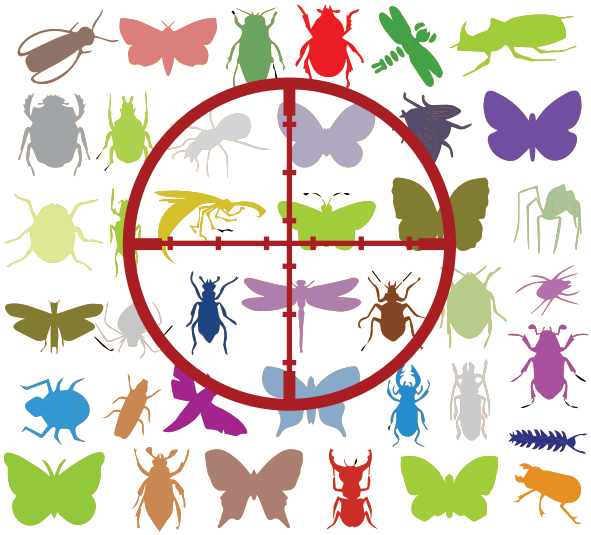
It is easy to understand the direct agricultural and economic consequences of fungal crop disease. For example, costs associated with *Septoria tritici* blotch disease are twofold: yield loss and fungicide treatments (74). Losses can be extreme. For example, a soybean rust epidemic cost Brazilian farmers $2 billion from 2001 to 2003 (100). These impacts are felt first by farmers and are most direct in subsistence farming. Where there is heavy reliance on a few crops, the result of crop disease can be a humanitarian crisis (64). For example, the wheat stem rust strain Ug99 causes up to 100% crop losses in Uganda and other parts of Africa and the Middle East. Its spread into India threatens food security there, as well (101). Even when there is no risk of famine, diversity of diet can be threatened. Fusarium wilt of banana attacks the clonally propagated Cavendish cultivar, which is grown almost exclusively for export and is a significant food staple for certain populations. Loss of Cavendish banana crops is unlikely to precipitate a crisis in local food supply, although the economic consequences may be severe for those whose livelihood depends on the cultivation of bananas (102, 103). Doubtless, consumers elsewhere will feel the loss of an affordable, nutritious food.

There are also indirect effects of fungal plant disease that propagate through ecosystems with potentially disastrous consequences for other species. Following chestnut blight, dead trees were largely replaced by oak, whose leaves, unlike those of chestnut trees, do not degrade easily in water. Thus, nutrient availability and productivity decreased in affected aquatic environments (104). The loss of chestnut fruits caused a decline in squirrel populations; woodpeckers, meanwhile, enjoyed plentiful deadwood (105, 106). The threatened European ash supports around 40 species, 6 of which live only in association with this tree (107, 108); its decline will inevitably affect the ecosystem. With damage to ecosystems, we inevitably see loss of ecosystem services. Trees like chestnut, elm, and ash are excellent carbon sinks, and their loss not only removes this function but eventually leads to the release of the stored carbon. Without the Dutch elm disease epidemic, it is estimated that elm trees would have taken up an extra megaton of CO_2; American chestnut trees might have absorbed 35 megatons (4). Dutch elm disease and ash dieback have both changed the British landscape forever, while in the American Appalachians, the seas of white chestnut blossoms are no more (63). Such losses cannot be measured, but are felt.

A soybean rust epidemic cost Brazilian farmers $2 billion from 2001 to 2003

Fungal Pathogens of Animals Are a Threat to Biodiversity

The animal kingdom is widely colonized and often infected by fungi; it is safe to say that no fungus-free animal exists. However, animal physiology produces extreme environments for fungi, and most animals are able to control fungal infections when they occur (109). As a consequence, fungal diseases in mammals are often associated with the animal host manifesting lowered immunity, either through preexisting infections (such as HIV/AIDS) or through suboptimal health (such as aging). These conditions open the host niche to parasitism by a wide variety of saprophytic environmental fungi that can cause opportunistic infections across most animal species when they become immunocompromised; these infections are normally not transmissible (109). However, pathogenic fungi have also evolved specific mechanisms to infect animals and are able to use the host to amplify their infectious propagules; these are known as zoophilic fungi.



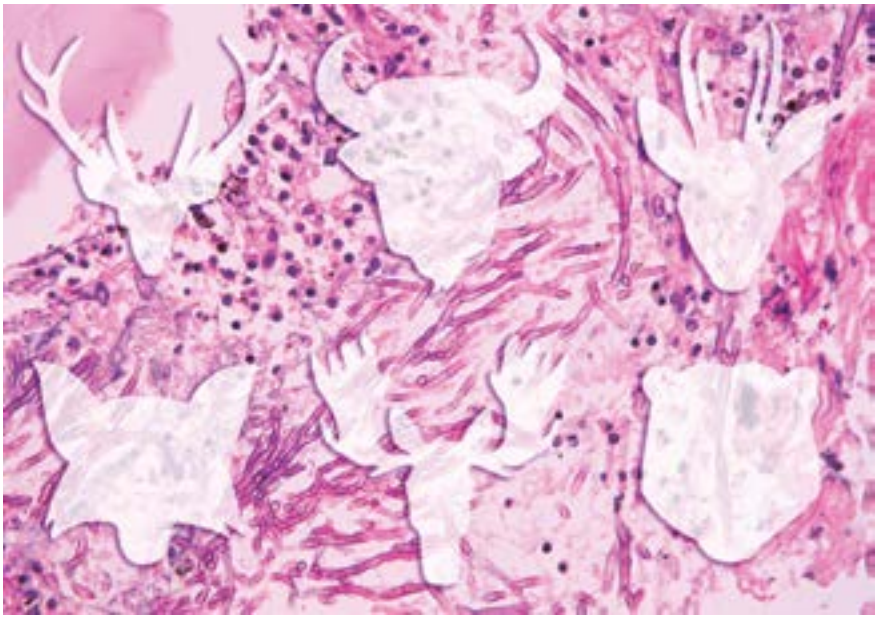
There are more than 700 species of "entomopathogenic fungi" known to infect insects

Zoophilic fungi exhibit a dualistic life cycle whereby both the environment and the host can be used to generate infectious propagules. Examples include *Pseudogymnoascus destructans*, which causes bat white-nose syndrome (WNS), and dimorphic fungi—such as *Coccidioides immitis* (which causes coccidioidomycosis) or *Histoplasma capsulatum* (which causes histoplasmosis)—that infect a broad spectrum of vertebrate hosts (110, 111). It should be noted that, in many cases, the life cycles and relative importance of environment-to-host versus host-to-host transmission have yet to be fully elucidated for fungal infections of animals. In contrast, it is clear that human-to-human transmission readily occurs with *Candida* species, *Pneumocystis*, dermatophytes, *Malassezia*, and microsporidia. We do know that treatment of infections caused by zoophilic fungi is very difficult owing to the existence of environmental reservoirs of infection that act as long-lived sources of inocula. When combined with the difficulty of treating wild species, attempts to treat zoophilic fungal infections of animals must overcome almost insurmountable hurdles.

The vast majority of species in the animal kingdom are invertebrates, mainly insects, and these are widely infected by fungi, which are important

regulators of insect populations (112). Known as "entomopathogenic fungi," there are more than 700 species (with many more yet to be discovered) known to infect insects. These fungi have evolved highly specialized mechanisms to invade and parasitize their invertebrate hosts. Discovered by Alfred Russel Wallace (1823–1913) during his explorations in the tropics, species of *Ophiocordyceps* are known to produce insect "zombies" through manipulation of host behavior in order to ensure their own transmission. Across montane regions of Asia, the fruiting bodies of *O. sinensis* that emerge from parasitized ghost moth caterpillars are valued herbal remedies that can command high prices, leading to an increasing scarcity of this fungus. Early research by Agostino Bassi (1773–1856) on the "muscardine disease" that devastated the French silkworm industry led to the discovery of *Beauvaria bassiana*, the first report of any animal disease caused by a microbe. Subsequently, this fungus and other species of entomopathogenic fungi have been investigated widely as commercial biopesticides against insect pests as diverse as locusts, mosquitoes, aphids, and beetles.

Out of the enormous diversity of fungal species that inhabit Earth, only around 625 have been reported to cause infection in vertebrates, and many of these are case reports. This number implies a relative paucity of pathogenic fungi for vertebrate hosts, consistent with the view that they are a challenging niche for fungi to invade (109). Vertebrate resistance to fungi may be a function of having both innate and acquired immunity, with the latter lacking in invertebrate animals and plants. However, several fungal species have acquired recent notoriety as causing emerging infectious diseases (EIDs) owing to the recent appearance of virulent fungal infections of animals. These fungal EIDs have led to mass die-offs, population declines, and, in some cases, complete species extinctions. Worldwide trends have shown that fungal EIDs in both animals and plants are occurring globally, are increasing through time as a proportion of disease alerts for all pathogens, and



Fungal infections can be highly lethal in wildlife, with rates of mortality approaching 100%

are having a greater impact on host population sizes when compared against other classes of pathogens (4).

The factors that underlie contemporary increases in fungal diseases of wildlife are multifactorial and relate to the following key biological features. First, fungal infections can be highly lethal in wildlife, with rates of mortality approaching 100%. Second, fungi can often survive independently outside of their host as durable spores in the environment, with the consequence that rates of infection and dispersal remain high even when hosts become scarce. This survival has contributed to the rapid emergence of fungal EIDs across intercontinental distances. Third, while host specialization can occur in pathogenic fungi, many species are generalists, with broad host ranges. This generalist behavior can lead to sustained transmission within complex communities that drives high rates of disease in the most susceptible species. Fourth, as noted above, fungi are genetically diverse due to their ability to undergo genetic recombination, hybridization, or horizontal gene transfer, as well as gain and loss of regions as small as genes or as large as chromosomes (113). Genotypes selected for traits that make them good pathogens can then spread as clones and cause widespread, devastating disease (3, 4).

A plague on frogs and bats

In recent decades, two emerging fungal diseases, chytridiomycosis in amphibians and WNS in bats, have driven rapid losses in biodiversity. The fungi underlying these infections exhibit a combination of features that explain their notoriety as pathogens.

Chytridiomycosis is caused by the fungal species *Batrachochytrium dendrobatidis* (*Bd*) and *B. salamandrivorans* (*Bsal*). The former was discovered in 1998 (114) and is thought to have emerged during the first half of the 20th century (115), causing a panzootic that now parasitizes all continents that contain amphibians (116). *Bsal* was discovered in 2013 (117), and both species of chytrid are known to have been spread by human trade from their endemic range in South Asia (115, 118). These chytrids have evolved an impressive arsenal of virulence factors in order to infect amphibians, which likely explains their extremely high virulence and transmissibility in host species

that do not share a long history of coevolution. Following its emergence, *Bd* contributed to the decline of at least 6.5% of known amphibian species, representing the greatest documented loss of biodiversity attributable to any pathogen and placing *Bd* among the most destructive invasive species (119). While *Bd* is known to infect more than 500 amphibian species, the host range infected by *Bsal* is more limited, mainly to caudates (salamanders and newts). Nonetheless, due to its extremely high virulence in these species, uninfected regions of the world that contain high caudate biodiversity (currently North America and Europe) have instigated import bans on certain amphibian species as a biosecurity measure to contain the further spread of *Bsal* (120).

WNS is a skin infection of bats caused by the fungal species *Pseudogymnoascus destructans* (*Pd*) (121). The first evidence of emergence of this wildlife disease stems from a photograph of a hibernating bat exhibiting characteristic clinical signs in a cave near Albany, New York, in February 2006 (122). Unusual mortality among hibernating bats caused by WNS was first reported the following winter (also in New York), and by 2018, WNS had been confirmed in 11 North American species of bats across 33 U.S. states and 7 Canadian provinces (123). Since the emergence of WNS, millions of North American hibernating bats have died as a result of this disease, and mortality in hibernacula can exceed 90%. *Pd* is a psychrophilic fungus with growth limited to temperatures below 20°C, making it ideally suited to infect bats during hibernation, when core body temperature approximates that of the surrounding environment (124). As the disease progresses, hibernating bats suffer a progression of physiological disturbances, including respiratory acidosis, electrolyte imbalance, and increased energy usage, leading to behavioral perturbations that contribute to poor body condition and death (125). Following broader investigations of bat fungal skin infections, the previously unknown pathogen *Pd* was found to also infect and be tolerated by hibernating bats throughout regions of Europe, China, and Mongolia (126, 127). Genetic analyses of *Pd* isolates from North America, Europe, and Asia support the recent introduction of *Pd* to North America from Europe, followed by long-distance expansion by clonal reproduction (128). As no bat species are known to migrate between Eurasia and North America, human activity, such as global travel or trade, is the most likely means by which *Pd* was originally introduced to the northeastern United States. As for chytrid fungi and other epizootic fungal infections, global biosecurity will be key to preventing further spread of known pathogens and new introductions of novel pathogens.

By multiple metrics, global incidence of EID is on the rise (4). While historically there has been a focus on zoonotic diseases that emerge from wildlife reservoirs, there is now increasing recognition that infectious disease presents a major threat to wildlife conservation (129). Unlike pathogens that may require a viable population of animal hosts for their own survival, zoophilic fungi have the capability to either parasitize a host or persist in the environment. Zoophilic fungal pathogens also have broad host ranges, representing a particular threat to wildlife, with the potential to drive species or populations to extinction. Enhanced public and political attention to high-consequence fungal diseases of wildlife, such as chytridiomycosis and WNS, has been an important first step towards developing a collective strategy to more effectively detect and respond to this unprecedented conservation challenge.

Infectious disease presents a major threat to wildlife conservation

Broad Host Specificity of Fungi: Transkingdom Pathogenesis

Fungal pathogens are unusual in their ability to cause disease in phylogenetically distant hosts. For example, *Cryptococcus* spp. and *Aspergillus* spp., among others, are able to cause disease in animals, plants, and protozoa, making them pathogenic microbes of the kingdoms Animalia, Plantae, and Protista. Within a kingdom, such as Animalia, these organisms can cause disease in very different species. In this regard, *Cryptococcus* spp. are reported to cause disease in mammals, insects, and worms, each with very different immune defense mechanisms. To put this ability into perspective, it is worthwhile to consider how unusual it is compared to other groups of pathogenic microbes. For example, none of the 10 most common causes of bacterial plant disease is an animal pathogen, although some enterobacteria can cause disease in both plants and animals. Similarly, viral and protozoal organisms that infect multiple hosts, such as influenza virus and *Plasmodium* spp., limit their range to animals. Hence, the host range of some pathogenic fungi is unmatched by other species and suggests that the capacity for generalized virulence implies different types of pathogenic strategies.

Mallorcan Midwife toad Alytes muletensis *mortalities.*

Image credit: Jaime Bosch

The fungal kingdom is enormous and encompasses millions of species. It is a major source of pathogens for plants and nonmammalian animal species but, as noted above, there are relatively few fungi that cause disease in mammals owing to their high body temperature and adaptive immunity. In contrast, ectothermic vertebrates have only adaptive immunity. This concept is highlighted by the experience with WNS in bats, which are susceptible during the torpor of hibernation but not during summer months when they are endotherms. One of the concerns with global warming is that higher ambient temperatures will lead to the adaptation of fungal species with pathogenic potential to warmer temperatures and defeat the thermal exclusionary zone that currently protects mammals against many potential fungal pathogens (130). Hence, the medical importance of fungal pathogens could increase dramatically in the decades ahead (130).

In contrast to viral and bacterial communicable diseases that rely on hosts for microbial survival, some fungal diseases are remarkable in that they can drive susceptible species to extinction. For example, chytridiomycosis in amphibians has already resulted in the extinction

of dozens of frog species (131). Likewise, WNS in bats is likely to lead to the extinction of several North American bat species (132). WNS is a communicable disease between individual bats, suggesting that the lack of communicability of some human fungal diseases is likely to be a function of host resistance rather than a limitation in host-to-host spread for pathogenic fungi.

Despite the tremendous importance of fungi to the ecology of the earth and as pathogenic species that can disrupt ecosystems, the fungal kingdom is understudied. The remarkable resistance of humans to invasive fungal diseases, which are in general not communicable, has resulted in their not being reportable; as a result, we lack reliable epidemiologic information regarding their burden on humanity. Even less information is available on fungal diseases of animals. Recently, this situation has attracted more attention, with a major microbiological journal taking an editorial position arguing that the fungal kingdom should not be ignored (133). Fungal research receives a fraction of the resources available for other pathogens despite a prevalence of millions of cases of mycotic diseases each year that are responsible for tremendous mortality and morbidity (134–136). One consequence of this neglect is that mycological fields tend to be small, such that for some major pathogenic fungi there are only a few scientists studying aspects of their life cycle and pathogenesis. Small fields often mean that progress is slow, and thus the development of cellular and molecular tools can lag, further slowing progress relative to other pathogenic microbes. The combination of limited funding, small fields, and underdevelopment of research tools can hinder the recruitment of new scientists to some fields, which results in a vicious cycle that perpetuates the situation. Despite this hurdle, the international mycology community is remarkably vibrant and has managed to make great progress by fostering cooperation and collaboration across continents, problems, and fields.

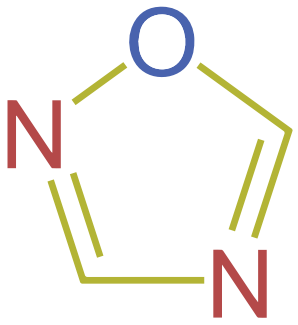
Fungal diseases are very difficult to treat in all hosts. In humans and animals, disseminated fungal diseases are usually fatal unless treated. In general, fungal diseases tend to be chronic and kill the host slowly relative to many bacterial diseases. Fungal diseases require prolonged courses of antifungal drugs for cure and can be incurable in some immunocompromised hosts. Complicating the treatment of fungal diseases is the fact that there are relatively few classes of antifungal drugs, of which the major types are the polyenes, azoles, and echinocandins. A major difficulty in identifying new antifungal drugs is that animals and fungi are each other's closest relatives, which means that there are relatively few differences in cellular physiology and metabolism to be exploited in drug design. Prevention of fungal diseases relies largely on the use of prophylactic antifungal therapy for those at high risk. Notably, there are no approved vaccines against fungal pathogens.

Fungal diseases are very difficult to treat in all hosts

Hibernating bats exhibiting clinical signs of white-nose syndrome, January 2008, Morris Cave, Vermont.

Image credit: Michael Chu

Measures to Treat or Halt The Spread of Fungal Pathogens



Azoles are the most commonly used antifungal class

Strategies to control Fungal infections of humans

Licensed antifungal agents. Current licensed antifungals for systemic treatment of medically relevant fungi are limited to four classes: azoles, polyenes, echinocandins, and 5-flucytosine (5-FC) (8–10). Azoles inhibit the synthesis of the fungus-specific membrane sterol ergosterol, while amphotericin B, the only polyene licensed for systemic use, binds to ergosterol, sequestering this essential sterol and also forming pores in fungal plasma membranes (9, 137). Amphotericin B is the first-line agent for mucormycete infections, cryptococcal meningitis, and severe infections with dimorphic fungi and is a second-line agent for *Aspergillus* infections. Azoles are the most commonly used antifungal class and are first-line therapy for *Aspergillus* infections and uncomplicated dimorphic fungal infections. As oral agents, they are commonly used as step-down therapy for *Candida*, cryptococcal, and mucormycete infections. Intravenous echinocandins are molecules that inhibit the synthesis of the β-1,3 glucan component of the cell wall and are first-line therapy for *Candida* infections. 5-FC is a prodrug that is converted by fungal cytosine deaminase into 5-fluorouracil (5-FU), which inhibits RNA synthesis. 5-FC use is restricted to adjuvant therapy with amphotericin B for cryptococcal meningitis.

Although the availability of new oral azoles with broad activity against different species has improved therapeutic options to treat invasive fungal infections, the mortality of invasive aspergillosis, mucormycosis, and rare mold infections in immunocompromised patients remains unacceptably high (37, 39, 136). Furthermore, drug-drug interactions (with azoles) and toxicity (with amphotericin B and 5-FC) often limit the use of these agents in populations at high risk for fungal disease, such as organ transplant recipients.

While intrinsic resistance to azoles and polyenes has long been observed in a number of *Candida* and *Aspergillus* species, the two most common pathogenic species in these genera, *C. albicans* and *A. fumigatus*, are intrinsically susceptible to these antifungal classes. Of concern, rates of acquired antifungal resistance are rising in both of these species (138). Resistance of *C. albicans*—a natural component of the human biome—has been linked to prior exposure to antifungal agents and person-to-person transmission. Induction of efflux pump expression, overexpression of Erg11 (the target of azole antifungals), and point mutations within *ERG11* have been the most commonly described molecular mechanisms underlying *C. albicans* azole resistance. Acquired resistance of *A. fumigatus* due to prior azole treatment is limited to individual patients with chronic invasive aspergillosis, as this organism is not a commensal of humans and is not spread from person to person. A

similar range of resistance mechanisms has been described in this population, including efflux pumps and amino acid substitutions within the *Aspergillus* azole target enzyme Cyp51A. More alarming, however, is the emergence of *A. fumigatus* azole resistance in azole-naïve patients. As described above, this trend was associated with the use of azole antifungals as fungicides in agriculture and the selection for azole-resistant strains in the environment, which can then be inhaled by humans (3). Environmentally acquired azole-resistant *A. fumigatus* strains share similar mutations within the promotor and coding region of *cyp51A* that lead to both overexpression of the target enzyme and decreased affinity for azoles. Infections due to these strains have now been reported worldwide, leading to calls to limit the agricultural use of azole antifungals.

The pipeline of new antifungal Therapeutics. There is some room for optimism, however. A number of new antifungal agents with activity against existing and novel targets are in late pre-clinical and clinical trials (8–10). Building on the success of the echinocandins, two new β-glucan synthesis inhibitors with activity against *Candida* and *Aspergillus* are currently undergoing clinical evaluation. Rezafungin (CD101) is a long-acting echinocandin that can be administered once weekly. Ibrexafungerp (SCY-078) is a triterpenoid that inhibits β-glucan synthesis and, unlike echinocandins, can be given orally. Both agents have low rates of drug-drug interactions and excellent safety profiles. However, neither is active against mucormycetes.

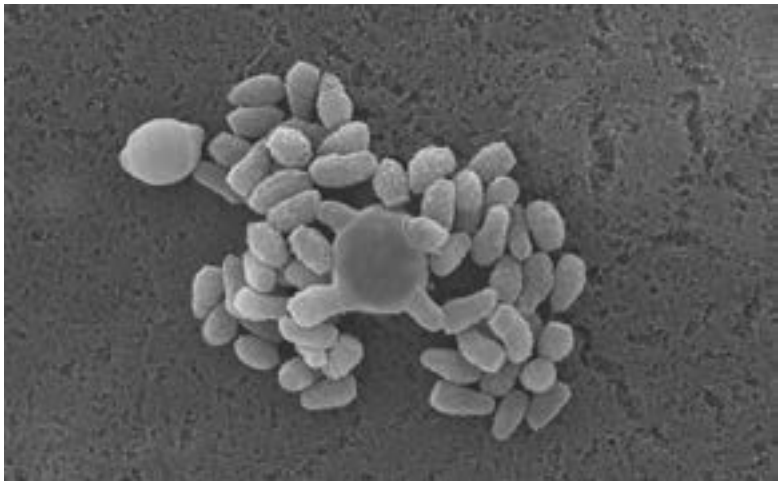
Several agents with novel mechanisms of action are currently in clinical trials. Olorofim (F901318) is a first-in-class agent that targets fungal dihydroorotate dehydrogenase, a critical step in pyrimidine synthesis with activity against *Aspergillus* and the rare mold *Scedosporium*. APX001 is a prodrug that is converted by serum alkaline phosphatase to its active form and inhibits Gwt1 and glycosyl phosphatidylinositol (GPI) synthesis, leading to the inability to anchor proteins within the fungal cell wall and disrupting a range of cell wall functions. APX001 has activity against most medically relevant fungi, including *Candida*, *Aspergillus*, mucormycetes, and other rare molds. VL-2397 is a natural product isolated from *Acremonium* with activity against *Aspergillus*. The mechanism of action of this compound is not known, but its selectivity for fungal cells derives from the fact that it is taken up by the fungal siderophore transporter Sit1, which is absent from mammalian cells. The role of these agents in the treatment of fungal infections awaits the results of full-scale clinical trials to evaluate their tolerability and efficacy against a range of human fungal infections.

Fungal vaccines. The fact that infection by fungi, such as *Coccidioides* or *Histoplasma*, leads to immunity for further infection, coupled with the high mortality and morbidity associated with fungal infections, has led to an interest in the development

A number of experimental fungal vaccines have proven effective in immunocompromised animals

Many populations at risk for fungal infections are immunocompromised

of fungal vaccines. However, there are several challenges in the design of a fungal vaccine that must be overcome (139–141). Many populations at risk for fungal infections are immunocompromised and therefore may respond poorly to vaccination or lack the immune effectors required for vaccine-mediated immunity. Conversely, inappropriate immune responses to fungi risk unwanted chronic inflammatory reactions to commensal or inhaled fungi that we encounter naturally. Similarly, fungal antigens have been implicated in allergic diseases, such as asthma, and worsening of atopic conditions with fungal vaccine antigens is a concern. However, these challenges are not insurmountable. High-risk populations can be vaccinated prior to the initiation of immunosuppression, and a number of experimental fungal vaccines have proven effective in immunocompromised animals. Passive administration of monoclonal antibodies to fungal antigens may provide another approach. Passive antibody therapy with a monoclonal antibody to *C. neoformans* capsular polysaccharide was shown to be safe and reduced antigen in patients with AIDS (142). Unfortunately, this therapy was not pursued due to the inability to find an industrial partner, but it established the first attempt to use monoclonal antibody therapy in humans. The use of antigens that are specific to fungal forms unique to invasive infection, such as yeast antigens in dimorphic fungi or hyphal antigens of *Candida* or *Aspergillus*, has the potential to avoid unwanted immune reactions to fungal antigens to which we are normally exposed. This approach has been used with an anti-*C. albicans* vaccine currently in clinical development, in which the hypha-specific Als3 protein is used as the antigen. That vaccine has shown promise in initial clinical trials (143). Use of formalin-killed spherules of *C. immitis*, the morphologic form found during human infection, has also been explored. Although the efficacy of this vaccine in early clinical trials was disappointing, other vaccines using heat-killed or attenuated fungi have been reported to mediate protection against *Aspergillus*, *Blastomyces*, *Cryptococcus*, and *Candida* infection in preclinical models, suggesting that this approach may still hold promise.



Scanning electron microscopic (SEM) image of Cryptococcus deneoformans basidium *sporulation during unisexual reproduction..*

Image credit: Ci Fu and Joseph Heitman, Duke University, and Valerie Lapham, North Carolina State University Center for Electron Microscopy.

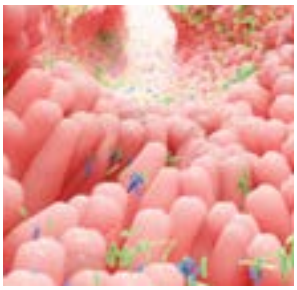
Looking to the future, recent advances in our understanding of the glycan composition of fungal cell walls suggests that there are a range of polysaccharides specific to fungal hyphae or other morphologies found during infection. These glycans provide a number of possibilities for the development of glycoconjugate vaccines with highly defined antigens specific to invasive fungal infection. Such vaccines have proven highly effective in the prevention of bacterial diseases but remain largely unexplored in fungi.

Immunomodulatory therapies. The observation that invasive fungal infections are rarely observed in immunocompetent hosts highlights the potential of immunotherapies for the prevention and treatment of fungal infection. A wide variety of strategies to augment antifungal immunity has been explored in preclinical models of infection (144). Broadly, these approaches can be divided into molecular and cellular therapies. Some examples of these approaches are highlighted below.

Cell-based therapies rely on the administration of modified immune cells to prevent or treat infection. Proof-of-concept preclinical studies have demonstrated the potential of this approach in the treatment and prevention of infections due to multiple fungal pathogens. Notable examples include early reports of dendritic cell vaccines to prevent fungal infection and more recently the treatment of *Aspergillus* infections by adoptive transfer of T cells expressing a chimeric receptor containing pattern-recognition sequences from the C-type lectin dectin-1, which recognizes fungal β-glucans (145).

A wide variety of cytokines and other immunomodulatory biologic agents have been evaluated for their ability to modify infection. Proinflammatory and Th1-type cytokines such as tumor necrosis factor alpha and interferon gamma are critical in the defense against a wide variety of fungal pathogens. Preclinical studies have suggested that administration of these and similar cytokines can improve the outcome of experimental fungal infection, but clinical trial data are lacking or equivocal with respect to human populations. More recently, the use of anti-PD1 and anti-CTLA-4 antibodies (checkpoint inhibitors) has been explored (146). These agents reverse T-cell exhaustion and have shown dramatic activity in the immune control of advanced-stage melanoma and other cancers. Preclinical and early clinical data suggest that these molecules may be effective in augmenting T-cell immunity against a wide range of fungal pathogens; again, clinical trial data are not yet available.

Other innovative strategies to Control fungal infections. Beyond conventional antimicrobial and immune therapy, a number of other strategies to control fungal infection have been explored. These include the use of mycoviruses to attenuate fungal virulence, therapeutic microbial enzymes to degrade fungal biofilms or cell wall structures, and the use of siderophore conjugates as Trojan horses for the delivery of toxic or antifungal molecules specifically to fungal cells (147, 148). Looking to the future, one area in need of further study is the role of the microbiome in governing resistance to fungal infections (24, 25). Multiple studies have linked the composition of the human microbiome to significant alterations in immunity. The importance of the microbiome and the effects of microbiome manipulation on the susceptibility to fungal infections are areas in need of further exploration.



One area in need of further study is the role of the microbiome in governing resistance to fungal infections

Strategies to control Fungal infections of plants

Two control methods have been traditionally deployed in the fight against plant-pathogenic fungi: the breeding of inbred disease resistance (R) genes into crop plants and the widespread spraying of antifungals. Recently, some new approaches are being explored.

Host-induced gene silencing (HIGS). Recent studies have shown that plant cells can produce specialized types of RNA molecules that traffic to pathogen cells to turn off virulence functions. This phenomenon has made it possible to control fungal and other eukaryotic pathogens by expressing fungal gene-targeting sRNAs or double-stranded RNAs (dsRNAs) in crop plants. These artificial sRNAs are sent from crop plants to pathogens and silence essential growth and virulence genes, a phenomenon called host-induced gene silencing (83, 149–152). For example, transgenic barley plants expressing dsRNAs targeting the fungal pathogen *Blumeria graminis* development gene that encodes 1,3-β-glucanosyltransferase (*GTF1*) or effector genes *Avra10* and *Avrk1* displayed significantly reduced disease symptoms caused by *B. graminis* (153). Similarly, *Arabidopsis* and tomato plants expressing *Botrytis cinerea DCL1/2*-targeting sRNAs have significantly reduced gray mold disease symptoms (83). sRNAs are one of the major mobile signals for cross-kingdom RNA interference and are transferred from host cells to pathogens in host-induced gene silencing. Such sequence-based RNA interference strategies could be adapted easily to control multiple pathogens simultaneously by targeting essential virulence genes from different pathogens (83). For example, transgenic plants expressing sRNAs that target the essential virulence genes *DCL1* and *DCL2* from both *B. cinerea* and *V. dahliae* exhibit enhanced resistance/tolerance to both fungal pathogens (83).

It is highly desirable to develop new methods of disease control without generating GMOs

Spray-induced gene silencing for disease control. One of the limitations of cross-kingdom RNAi and host-induced gene silencing is that it requires stable genetic transformation, which is not yet possible for many economically important crops. Additionally, the public has concerns about genetically engineered crops, commonly known as genetically modified organisms (GMOs). It is highly desirable to develop new methods of disease control without generating GMOs or requiring extensive use of chemicals.

One promising new avenue relies on uptake of external RNAs from the environment that block expression of virulence functions. An example of this phenomenon is "environmental RNAi," which has been observed in *C.*

elegans and several nematodes and insects (154) but not yet in mammals. It was not clear until recently that plants and fungi could take up RNAs from the environment. However, the fungal pathogen *B. cinerea* is capable of taking up specialized RNA molecules from the environment (83), which makes it possible to use strategies involving dsRNAs or sRNAs that target pathogen genes directly for disease management. Indeed, spraying *B. cinerea DCL1/2*-targeting dsRNAs or sRNAs on the surface of fruits, vegetables, and flowers significantly inhibits gray mold diseases (83). Spray-induced gene silencing (SIGS) is also effective for disease control in monocots (155), which represent some of the most important crop species. It has also been shown that spraying dsRNAs that target *Fusarium graminearum* cytochrome P450 lanosterol C-14α-demethylase (*CYP51*) genes significantly reduced disease symptoms on barley leaves (155). These RNAs that target pathogen genes serve as a new generation of fungicides that are effective for both dicot and monocot crop species (152).

Recent advances in nanoparticle technology have improved the potential applications of spray-induced gene silencing for plant protection. Naked dsRNA and sRNA treatments can protect plants from microbial pathogens for 5 to 8 days after spraying (83). A recent study indicates that the duration of protection against viral infection was extended to more than 20 days when dsRNAs were incorporated into layered double hydroxide (LDH) clay nanosheets called BioClay (156). Because these nanoparticles and the RNAs within them are nontoxic and easily degradable, this technique is an environmentally conscious method that improves the efficacy of plant disease management.

Spray-induced gene silencing provides safe and powerful plant protection, not only on preharvest crops (155, 156) but also on postharvest products (83). Fruits, vegetables, grains, and decorative plants are subject to postharvest attack by microbial pathogens during processing, transportation, and storage (157). Furthermore, pathogens often produce toxic chemicals while proliferating on postharvest products. For example, fungal pathogens such as *Aspergillus*, *Penicillium*, and *Fusarium* produce mycotoxins on postharvest grain

One Health perspective

- The use of the same types of antifungal drugs on crop plants and humans raises the risk of the development of drug resistant strains that are refractory to antifungal therapy.
- Fungal diseases in animals have broad impacts. For example, a fungal infection killing bats in North America blocks the bats' role as pollinators and in eating insects, both of which impact agricultural production of crops for humans.
- Commercial trade can introduce fungal pathogens into new areas. In particular, global trade in pets (e.g., reptiles) can spread fungi to new areas that are not adapted to the foreign fungal species. The consequent disruption of ecosystems has broad effects.

products. Some mycotoxins are considered carcinogenic and can pose a serious threat to consumers' health (158). Controlling postharvest diseases using a new generation of sustainable and eco-friendly RNA-based fungicides can help reduce the yield loss as well as prevent the accumulation of toxic chemicals produced by pathogens.

Fungicides. Towards the end of the 19th century, sulfur and copper products, such as Bordeaux mixture (a combination of copper sulfate and lime), were first sprayed in the vineyards of France to protect grapes from fungal attack. In addition, mercury-based fungicides (organomercurials) became fashionable but quickly disappeared from use due to their broad toxicity to mammals. In the 1940s, the potential for synthetic and more complex fungicides in crop protection was realized and a wide range of nonsystemic products was introduced, some of which are still in use. These nonsystemic chemicals adhere to the leaf surface and show strong antifungal activity, thus preventing the fungi from entering the host. The discovery in the 1960s of systemic fungicides, which can spread to different sites in the plant, had a strong impact on cereal production and heralded a major shift in fungal disease control in general. Since then, the global fungicide market has grown continuously, being valued at 11.23 billion USD in 2014 and projected to reach 16.3 billion USD by 2023 (stastica.com).

The global fungicide market is projected to reach $16.3 billion by 2023

The number of different classes of fungicides available for preventing plant pathogen outbreaks is much broader than was described above for antifungal drugs used to treat humans. Although several lack clearly defined modes of action on the fungal cell, the most important chemistries fall into a few groups that target mitochondrial function, the cytoskeleton, or enzymes in ergosterol biosynthesis. Most widely used fungicides target a single fungal enzyme or protein, thereby blocking a vital cellular process in the fungal cell. Among these single-target-site fungicides are: (i) the azoles, which block ergosterol biosynthesis similar to the azole drugs used to treat human pathogens and account for ~30% of sales worldwide, and (ii) the strobilurins, also known as QoI inhibitors, which ablate the electron transfer chain in mitochondrial respiration and hold ~22% of the sales market (159). It is worth noting that our current pathogen management strategy also depends on a few multisite fungicides such as mancozeb and chlorothalonil. Despite their widespread use, the precise modes of action of these fungicides remain elusive.

In spite of some success in identifying fungicides for treating fungal pathogens of plants, there

are many challenges in their effective use for agriculture. One unintended consequence is that broadly acting fungicides can kill off beneficial soil fungi that form symbiotic relationships with plants and benefit their growth. Also, under favorable conditions, the pathogenic fungi can reproduce rapidly (i.e., short generation times) to produce prolific numbers of spores that disseminate to other plants. Moreover, fungi frequently change their genetic content and thus are able to adjust rapidly to changes in the environment (113). These characteristics make the control of fungi problematic, particularly in "modern" agriculture (i.e., since the late 20th century Green Revolution). Here, the widespread planting of vast monocultures of genetically uniform crops, guarded by single-target-site fungicides and inbred disease resistance genes, has provoked the emergence of genetically altered pathogens. These emergent strains are resistant to fungicide treatment and have overcome the inbred resistance genes. For example, since azole resistance was first noted in a plant-pathogenic fungus in 1981 (160), it has become a widespread phenomenon in agriculture (3). As described above, this resistance has also crossed over to being a major concern for human health as the agricultural use of azoles has been linked to the development of *Aspergillus* strains that are resistant to the azole drugs used in human patients, which limits one of the only therapeutic options for treating these infections. Resistance against newly introduced fungicides can occur within two years, as exemplified by target site mutations emerging in fungal strains following treatment with particular strobilurins (159). Our understanding of the mechanisms underpinning the development of resistance remains fragmentary.

Concluding Remarks

Despite the fact that fungi play many beneficial roles both in the Earth's ecosystem and human industry, a subset of fungi causes devastating diseases in plants, animals, and humans. The goal of this report is to raise awareness that these fungal threats are being exacerbated by a convergence of different forces. As detailed above, climate change is causing increased stress on plants and animals that makes them more susceptible to fungal infections, and in addition climate change is reducing the thermal exclusion zone that normally serves to protect animals from fungi. Global commerce, including the pet trade, endangers local plants and animals by introducing foreign species of fungi to which they are not adapted. Changes in medical care are increasing the population of patients who are highly susceptible to fungal infections, and this problem is worsened by the fact that our limited arsenal of antifungal drugs is being undermined (or compromised) by the emergence of drug-resistant strains of fungi, in some cases attributable to antifungal agents in agriculture. By highlighting the convergence of these forces in this report we aim to raise awareness of scientists and policy makers concerning these established and emerging fungal threats to global health and food security. First among the baker's dozen of recommendations listed above that should be taken is facilitating the reporting of fungal diseases. Only when the true extent of fungal disease is appreciated can enthusiasm be generated for acting on the other 12 recommendations.

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Recommendations

- Report and Track Fungal Infections That Cause Disease in Humans, Plants, and Animals
- Conduct a Global Census of Fungal Species
- Conduct a Census of the Fungi in the Human Microbiome
- Support and Sustain the Fungal Genome Databases
- Support and Sustain Fungal Culture Collections
- Develop New Drugs, Diagnostics, and Therapies
- Investigate Mechanisms Leading to Antifungal Drug Resistance
- Enhance and Sustain Training in Fungal Physiology, Classical Mycology, Fungal Genetics and Genomics, And Fungal Pathogenesis
- Study Outbreaks To Identify Emerging Fungal Pathogens Of Humans, Animals, and Plants
- Complete the Genome Sequences of More Fungi and Fungal Populations
- Develop New Methods of Preventing Fungal Infections of Plants
- Develop New Approaches to Protect Frogs, Salamanders, Bats, and Other Animals from Pathogenic Fungi
- Promote Ways To Bring Diverse Mycologists Together To Develop in Cross-Fertilizing Advances

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This report is based on the deliberations of experts who gathered to discuss a series of questions developed by the steering committee. All participants had the opportunity to provide feedback, and every effort has been made to ensure that the information is accurate and complete. The contents reflect the views of the participants and are not intended to reflect official positions of the Academy or of American Society for Microbiology.

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