Global Catastrophic Threats from the Fungal Kingdom

Fungal Catastrophic Threats

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Contents

Abstract The fungal kingdom poses major catastrophic threats to humanity but these are often unappreciated and minimized, in biological threat assessments. The causes for this blind spot are complex and include the remarkable natural resistance of humans to pathogenic fungi, the lack of contagiousness of human fungal diseases, and the indirectness of fungal threats, which are more likely to mediate their destructive effects on crops and ecosystems. A review of historical events reveals that the fungal kingdom includes major threats to humanity through their effects on human health, agriculture, and destruction of materiel. A major concern going forward is the likelihood that physiological adaptations by fungal species to global warming will bring new fungal threats. Fungal threats pose significant challenges specific to this group of organisms including the potential for intercontinental spread by air currents, capacity for rapid evolution, a paucity of effective drugs, the absence of vaccines, and increasing drug resistance. Preparedness against bio-catastrophic risks must include consideration of the threats posed by fungi, which in turn requires a greater investment in mycology-related research.

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Current Topics in Microbiology and Immunology
https://doi.org/10.1007/82_2019_161

When it comes to biological threats, humanity often has a blind spot for the fungal kingdom. The reason for this has more to do with human perception than a careful risk assessment. In contrast to viruses and bacteria, which have caused historical high-mortality events such as the 1918 influenza epidemic and the Black Death, respectively, humanity has no collective memory of equally devastating events caused by fungi. In fact, humans and mammals are remarkable by their resistance to systemic fungal diseases, a fact that sets them apart from other animals and plants. Human fungal diseases tend to occur in individuals who have impaired immunity or receive heavy exposures of pathogenic fungi and these diseases are not communicable. For example, fungal diseases are common in individuals with advanced HIV infection or medically induced immune suppression as used to prevent rejection in organ transplant recipients. Fungal outbreaks, when they occur, reflect unusual exposures such as histoplasmosis in cave explorers (Lyon et al. 2004) or meningitis in individuals receiving mold-contaminated steroid preparations (Andes and Casadevall 2013). This, in turn, tends to minimize the threat. Fungal diseases are generally not reportable to public health authorities, which compounds the problem of assessing the true burden of mycoses in the human population. However, this essay will argue that such views are shortsighted by exploring fungal threats to humanity, agriculture, and material.

The human blind spot for fungal threats extends to the support given to mycology research, which in turn affects preparedness against a catastrophic threat from the fungal kingdom. Suffice it to say that medical mycology is underfunded relative to other infectious diseases such as tuberculosis and malaria even when the total mortality from fungal diseases, 1.6 million deaths annually, is comparable or greater (Rodrigues and Albuquerque 2018). Cryptococcosis alone ranks fifth among lethal infectious diseases behind AIDS, tuberculosis, malaria, and diarrhea (Rodrigues 2018). When non-lethal fungal diseases such as dermatomycosis are considered, the total burden of fungal diseases affecting humanity rises to over 800 million people (https://www.gaffi.org/). However, there are some encouraging indications that perceptions of the threat from the fungal kingdom are beginning to change. Mycetoma, a devastating fungal infection that cripples millions in equatorial regions was added to the World Health Organization of Neglected Tropical Diseases in 2016. Prominent journals have published articles highlight the fungal threat in recent years (Rodrigues and Albuquerque 2018; Fisher et al. 2018; Brown et al. 2012; Gow et al. 2018) including an editorial titled 'Stop Neglecting Fungi' (2017).

The blind spot does not extend to agricultural experts or plant scientists, who are well aware of the destructive effects on fungal pathogens on crops. In contrast to the paucity of serious fungal diseases among immunologically intact humans, fungi are major pathogens of plants, insects, and ectothermic vertebrates. In fact, today, a few species of fungi are destroying entire ecosystems as amphibians, bats, salamanders, and snakes are decimated by fungal diseases [reviewed in (Fisher et al. 2012)].

1 The Fungal Kingdom

The fungal kingdom is enormous, with an estimated 5 million species (Blackwell 2011). This kingdom is tremendously diverse and includes species ranging from mushrooms to microscopic organisms such as *Saccharomyces cerevisiae*. Fungi are generally considered auxotrophs, such that their major role in the biosphere is that of being decomposers of plant and animal matters. However, there is some evidence that fungi can harvest electromagnetic energy for nutrition (Dadachova et al. 2007; Robertson et al. 2012), which could allow them with a capacity to synthesize their own food and this could have significant implications for exobiology and their potential to threaten materiel. Among the large phylogenetic relationships, animals and fungi are each other's closest relatives (Baldauf and Palmer 1993). A practical consequence of this close relationship is that it is more difficult to find metabolic differences to exploit in making antifungal drugs. Hence, although there are relatively few fungal species that are pathogenic to humans, fungal infections, when they occur, tend to be chronic and difficult to treat.

One of the remarkable characteristics of fungi is their metabolic capacity to produce secondary metabolites. Many of our current drugs such as penicillin, statins, and anticancer drugs are secondary metabolites of fungi. However, the same machinery also produces compounds that are harmful to animals such as mycotoxins. The mycotoxins are a diverse lot of compounds that includes cancer-causing aflatoxins, the neurotoxin ergot alkaloids and the amatoxins found in poisonous mushrooms (Peraica et al. 1999). Some mycotoxins such as T-2 have considerable weapon potential (Paterson 2006) and were implicated in the "yellow rain" episode in Southeast Asia (Rosen and Rosen 1982; Mirocha et al. 1983), although the veracity of this conclusion has been questioned (Ashton et al. 1983). On the other hand, there is strong evidence that aflatoxins were developed by the Iraqi bioweapons program prior to the First Gulf War (Davis 1999). Contamination of grains with trichothecene-type mycotoxins produced by *Fusarium* spp. caused an epidemic mycotoxicosis with 60% mortality during a 1932 outbreak in the USSR (Peraica et al. 1999). From the viewpoint of considering catastrophic threats from the fungal kingdom, it is noteworthy that they are major pathogens of plans and non-mammalian animals, as well as sources of compounds with significant toxicity.

2 On the Nature of Fungal Catastrophic Threats

Fungal pathogens differ from such communicable pathogens as viruses in that do not need a host to survive. Most pathogenic fungi are environmental organisms capable of surviving in the environment without a need for a host. For example, the chytrid responsible for worldwide amphibian declines has caused the extinction of several species of frogs and yet survives in infected lakes even when its hosts are decimated. This non-dependence of hosts for survival means that selection pressures that could attenuate virulence will not necessarily apply. In addition, non-dependence on their hosts for survival means that fungal pathogens can drive a species to extinction.

The nature of the fungal threats differs depending on the possible targets and we will consider three major target categories: humans, agriculture, and materiel.

Humans. None of the currently known human pathogenic fungal species is likely to pose a catastrophic risk to humans unless there is a severe decline in the immunity of the population, as happened in certain groups with HIV infection or unless the fungal species is weaponized in some fashion to deliver overwhelming innocula and/or weaken the immune response. Of course, the emergence of a new fungal species with pathogenic potential for immunocompetent humans would be an unforeseen threat. Many new pathogenic fungi are reported yearly, but these tend to be isolated cases in association with severe immune deficiencies or unusual exposures. Nevertheless, recent years have witnessed the emergence of *Candida auris* as a major nosocomial pathogen, which appeared suddenly in 2009 without a yet identifiable origin (Forsberg et al. 2018). Although fungal pathogens are not usually considered as biological weapons for use against humans, some species have significant weapon potential (Casadevall and Pirofski 2006). As early as 1961, one authority wrote that "the fungi seem to be ideal warfare agents in many ways, such as ease of handling, ease of dissemination, resistance to damage by explosives, production of severe but temporary illness in most cases, ability to cause temporary, or permanent infection of local areas depending on the organism selected" (Furcolow 1961). The military had noted the high infectivity of *Coccidioides* spp., a fact that could have contributed to the designation of this organism as the sole fungal species in the original select agents list (Casadevall and Pirofski 2006).

Agriculture. In contrast to mammals, fungi are major pathogens for plants and the susceptibility of human plant food staples to fungal diseases means that fungal pathogens represent a tremendous threat to agriculture. Threats to agriculture that disrupt the food supply for humans or domesticated animals could rise to the threat level of potential global catastrophic threats if the food supply is diminished, with resulting famine and social instability. Several fungal species have been developed as agents of biological warfare including *Puccinia graminis tritici* (stem rust of wheat) (Rogers et al. 1999). Certainly, a simultaneous outbreak of fungal pathogens on major food crops such as wheat, corn, and rice would have a devastating effect on human and domestic animal food supplies. Today, the world's bananas are being threatened by *Pseudocercospora* spp. (Churchill 2011). Since the major consumer strain of banana is maintained by grafting, breeding-resistant crops is not an option, and there is concern for a catastrophic decline in this food staple, which will reduce a major source of calories for humanity and income for subsistence farmers (Churchill 2011). The Irish potato famine of the mid-1840s stands out as a singular catastrophic event where a plant pathogen destroyed a food staple crop for a population. The pathogen responsible for the Irish potato famine, *Phytophthora infestans,* was considered a fungus until recently, given its morphological similarities to fungi (Goodwin et al. 1994), but was re-classified as oomycetes based on genomic analysis (Cooke et al. 2000). Despite the taxonomic change, this event serves to illustrate the catastrophic risks posed to agriculture by fungal pathogens.

Materiel. Although microbial destruction of equipment and materiel is not usually a consideration when evaluating biological risks to humans, human dependence of technology raises the possibility that fungal destruction of material can develop into a global catastrophic risk. Fungal deterioration of military equipment in the tropics was a major problem during theSecond World War. Fungi are known to contaminate spacecraft (Vesper et al. 2008), where they have been associated with damage to instruments. Mold contamination of human habitats can contribute to health problems and make them uninhabitable. The flooding of New Orleans after the Katrina and Rita hurricane led to mold contamination of homes resulting in high levels of mycotoxins (Centers for Disease Control and Prevention (CDC) 2006; Rao et al. 2007). Some of the molds that contaminated homes damaged after Katrina are reported to induce developmental defects in flies (Inamdar and Bennett 2015) although it has been difficult to establish an association between mold contamination and specific health effects in humans (Barbeau et al. 2010). Molds have been implicated in sick building syndrome where fungal products have been proposed to impact the health of human occupants (Straus 2011).

3 Some Considerations Specific to Fungal Threats

Trans-kingdom pathogenic potential. Several pathogenic fungi are remarkable in their host range. In contrast to many viral and bacterial pathogens that have a relatively narrow host range, fungi like *Aspergillus* and *Fusarium* spp. can cause disease in hosts of different kingdoms. For example, *Fusarium oxysporum* causes banana wilt in plants and severe infections in immunocompromised humans. This is important because it illustrates the potentially destructive capacity of this group of organisms. In general, most fungi with pathogenic potential for plants and ectothermic animals are not pathogenic for humans and mammals because their high basal temperatures create a thermal restriction zone (Robert and Casadevall 2009; Bergman and Casadevall 2010). Hence, the relative paucity of fungal species that are pathogenic to humans despite the enormous size of the fungal kingdom may be a result of the combination of high temperature and adaptive immunity. In fact, I have suggested that the remarkable resistance of mammals to fungal diseases is itself a product of selection by fungi at the end of Cretaceous when a fungal bloom may have kept down the reptiles favoring the mammals (Casadevall 2005; Casadevall 2012a).

Genetic flexibility and rapid evolution. Most fungal pathogenic species are capable of rapid evolution, which confers the capacity for rapid changes in phenotypes associated with virulence and drug susceptibility. The fact that most species are capable of both asexual and sexual reproduction means additional opportunities for gene exchange and recombination. The pace of fungal evolution can be so rapid that for organisms such as *C. neoformans*, which is capable of causing chronic infections lasting months if not years, new genetic variants can emerge during infection consistent within host adaptation and microevolution (Chen et al. 2017).

From the catastrophic risk perspective, the ability of fungal species to change rapidly introduces concerns about the emergence of more pathogenic strains and increasing drug resistance.

Origin of virulence. With the exception of *Candida* spp. and dermatophytes, the overwhelming majority of human pathogenic fungi live in an environment where they are usually involved in degrading plant matter. Hence, in contrast to most viral, bacterial and protozoal pathogens infection by pathogenic fungi comes not from other hosts but directly from the environment. This raises the question of why do organisms that have no need for an animal host seem to have the capacity for mammalian virulence. Studies from several laboratories over the past two decades have implicated amoeba in the origin of virulence for environmental pathogenic fungi. The uncanny resemblance between amoeba- and macrophage-*C. neoformans* interactions suggested that such virulence factors as the capsule, melanin synthesis, and phospholipases were important for fungal survival after amoeba predation (Steenbergen et al. 2001). Similar observations were made with other pathogenic fungi such as *Aspergillus, Histoplasma,* and *Sporothrix* spp. (Steenbergen et al. 2004). According to this view, the capacity for virulence in soil pathogenic fungi emerges stochastically from interactions with third-party agents such as ameboid predators (Casadevall 2012b), with the majority of environmental fungi being unable to cause disease in mammals because of their thermal restriction zones caused by endothermy.

Prevention. Prevention of fungal disease is possible in individuals at high risk by the administration of antifungal agents prophylactically. The development of relatively non-toxic antifungal therapy in the form of oral azoles such as fluconazole has provided an effective option for preventing fungal disease high-risk individuals such as transplant recipients and those with advanced HIV infection. The availability of these effective oral drugs would provide a means for preventing disease in populations at risk from a natural or intentional release of pathogenic fungal spores. In contrast, there are no licensed vaccines available for any major human fungal pathogen. Numerous experimental vaccines that have shown efficacy in animal models of fungal disease but with the exception of a vaccine to prevent recurrent vaginal candidiasis (Edwards et al. 2018), none are close to clinical development. Azoles are also used in agriculture for the treatment and protection of crops.

Drug resistance. One of the characteristics of human fungal diseases is that these are often chronic and require prolonged antifungal drug therapy, which creates conditions for the selection of drug-resistant strains (Fisher et al. 2018). This combined with the widespread use of antifungal agents in agricultural settings has been associated with the emergence of resistance in many pathogenic fungi, including some like *Aspergillus* spp. that are acquired directly from the environment (Abdolrasouli et al. 2015; Chowdhary et al. 2013). Increasing drug resistance among human and plant pathogenic fungi means that this has to be an important consideration in a global catastrophic event involving pathogenic fungi.

Intercontinental spread. In contrast to viral and bacterial threats that usually require transport in infected hosts for dissemination across continents, fungal spores can disseminate and spread by air currents (Brown and Hovmoller 2002). Fungal spores comprise a large percentage of the particulate matter suspended in the air and the spore composition shows seasonal fluctuation (Frohlich-Nowoisky et al. 2009). The capacity for intercontinental spread by air currents is of significant concern for the emergence of pathogenic fungi for it implies that such outbreaks are not likely to be contained by the usual disease-control measures as quarantine and isolation.

Global warming and fungal diseases. The finding that the majority of fungal species cannot tolerate mammalian temperatures indicates that endothermy is a major source of protection against mycotic diseases (Robert and Casadevall 2009). In the early twenty-firstst century, there is strong evidence that the planet is warming as a result of the anthropomorphic release of greenhouse gases such as CO_2. Hence, there is the concern that as the ambient temperature increases some fungi with pathogenic potential will adapt to the higher temperatures, which will allow them to survive at mammalian temperatures (Garcia-Solache and Casadevall 2010). Experimental fungal evolution has demonstrated that fungi can rapidly adapt to higher temperatures (de Crecy et al. 2009). Analysis of temperature tolerances in a fungal collection as a function of time suggests that basidiomyces are already adapting to global warming by becoming more thermotolerant (Robert et al. 2015). If this occurs, humanity could witness the emergence of new pathogenic fungal species (Garcia-Solache and Casadevall 2010).

Invasive fungal infections after natural disasters. Fungal infections following natural disasters can add to the initial calamity (Benedict and Park 2014). Coccidioidomycosis can follow earthquakes, which presumably reflects spore aerolization following shaking of soils (Schneider et al. 1997). Similarly, an outbreak of coccidioidomycosis was reported after a dust storm (Pappagianis and Einstein 1978). Recently, a cluster of soft tissue cases of mucormycosis, caused by *Apophysomyces trapeziformis*, followed a severe tornado in Joplin, MI, in individuals with skin injuries who were not immunocompromised (Austin et al. 2014). Aspiration of water during natural disasters such as tsunamis can cause a pneumonitis called “tsunami lung” and several fungal species have been associated with this condition [reviewed in (Benedict and Park 2014)] as well as occasional cases of systemic fungal infection (Kawakami et al. 2012; Nakamura et al. 2013). Although in the episodes alluded above only a few individuals have suffered serious mycotic diseases, their occurrence highlights a fungal threat that can complicate geological and atmospheric catastrophic events.

4 Summary

The well-being of humanity is dependent on the health of many ecosystems that are vulnerable to fungal diseases. Today, the fungal kingdom poses major catastrophic risks to humanity through the ability of certain fungal species to affect the health of people, animals, and plants. While human fungal epidemics comparable to an influenza pandemic are unlikely from known fungal pathogens due to the remarkable resistance of mammals to pathogenic fungi, this situation could change with the emergence of new fungal pathogens. In this regard, the alarming appearance of drug-resistant *Candida auris* in recent years is a warning bell that like viruses, new pathogenic fungi can appear without warning. Certainly, the destruction of bats in North America by white-nose syndrome shows that mammals are not immune to epidemic fungal diseases. Today, perhaps the greatest threat from the fungal kingdom is their potential destruction of crops or ecosystems needed for human sustenance and health, any disruption of human food supply would have catastrophic effects on our species and its complex societies.

Some catastrophic events associated with fungal or fungal-like diseases

Risk	Event	Organism	Comment/reference
Mass casualties	10th Plague visited on Egypt	*Aspergillus* or *Penicillium* spp.	Similarities to mycotoxicosis have been noted (Schoental 1984; Bennett and Klich 2003)
Mass casualties	Plague of Athens	*Fusarium* spp.	The cause of the Plague of Athens described by Thuycides remains uncertain. At least one authority has suggested that it was caused by mycotoxins (Schoental 1995)
Mass casualties	Epidemics of ergotism in Middle Ages	*Claviceps purpurea*	As many as 40,000 people died in the Aquitaine region of France in 944–945 CE from consuming contaminated grains (Schiff 2006). Epidemics of ergotism were a common occurrence until modern times
Mass delusion	Salem witch trials	*Claviceps purpurea*	Ergotism was suggested as the etiology for some of the accusation and proceedings (Caporael 1976), although others have argued against this hypothesis (Spanos and Gottlieb 1976)
Mass starvation	Irish potato famine	*Phytophthora infestans*	Considered a fungus until recently (Goodwin et al. 1994), this organism is now considered an oomycetes (Cooke et al. 2000)
Mass casualties	Alimentary toxic aleukia	*Fusarium* spp.	Episode in USSR during 1930 that affected >10,000 with 60% mortality (Peraica et al. 1999)
Ecosystem damage	Worldwide amphibian declines	*Batrachochytrium dendrobatidis*	Chytrid fungus has led to worldwide amphibian declines (Lips 2016)
Ecosystem damage	White-nose syndrome in bats	*Pseudogymnoascus destructans*	Disease emerged in North America in 2006 resulting in catastrophic declines in certain bat species (Blehert 2012)

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Risk	Event	Organism	Comment/reference
Ecosystem damage	Salamander declines	*Batrachochytrium salamandrivorans*	Chytrid fungus killing salamanders of Europe (Stegen et al. 2017)
Food staple destruction	Banana declines	*Pseudocercospora* spp.	Banana crops threatened by fungus that causes black leaf streak disease (Churchill 2011)
Mass casualties	Steroid medication contamination	*Exserohilum rostratum*	Contamination of steroid medication led to fungal disease in hundreds of individuals (Lockhart et al. 2013; Chiller et al. 2013)
Materiel damage	Mold growth in flooded homes	Numerous species	Homes flooded after hurricanes often have to be abandoned due to intractable mold growth

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