REVIEW

The Impact of Climate Change on Human Fungal Pathogen Distribution and Disease Incidence

Paris Salazar-Hamm[1,2] · Terry J. Torres-Cruz[3]

Abstract

Purpose of Review This review aims to compile the current knowledge on the impact of climate change on human pathogenic fungi. Ongoing surveillance of the fungal lineages described here will be imperative to predict disease burden and geographic expansion.

Recent Findings Emerging infectious diseases are increasing in frequency and impact in response to anthropogenic expedited climate change. The simultaneous global emergence of the multidrug-resistant fungus *Candida auris* has been hypothesized to be intimately related to warming temperatures. Diverse evolutionary pressures, including higher average temperatures caused by climate change and conditioning of pathogens to endothermy, has contributed to antifungal resistance in several fungal lineages. Endemic fungi (e.g., species of *Coccidioides*, *Blastomyces*, and *Histoplasma*) known to be largely constrained by environment and host range are expanding in distribution and increasing disease burden. The COVID-19 pandemic illuminated the vulnerability of human populations to aspergillosis and mucormycosis co-infections. The increasing frequency of extreme weather events presents favorable circumstances for opportunistic fungal infections.

Summary Long-term shifts in temperatures and weather patterns are anticipated to influence emergence, expansion, and virulence of human pathogenic fungi. This includes warming temperatures and stochastic precipitation that may aid in expanding the distribution of several endemic fungal pathogenic lineages and increase disease burden. Here, we review both long-term climate patterns and short-term environmental disruption events that affect dispersal and incidence of human pathogenic fungi. Population growth, urbanization, intercontinental travel, and increased human longevity coupled with progressively damaging climate change effects generate conditions that make communities increasingly vulnerable to fungal pathogens.

Keywords Global warming · Antifungal resistance · Emerging diseases · *Coccidioides* · *Cryptococcus* · *Candida*

Introduction

While certain television shows exaggerate doom from a fungal epidemic, there are notes of truth concerning the emergence and expansion of fungal diseases. Massive population die-offs caused by fungal pathogens are increasing in frequency over the last three decades across the kingdom Animalia. These include white-nose syndrome in bats [1], chytridiomycosis in amphibians [2], sea turtle egg fusariosis [3], snake fungal disease [4], cat-transmitted sporotrichosis [5], and sea star wasting disease [6]. Recent recognition by the World Health Organization (WHO) of fungal priority pathogens acknowledges the reality of emerging, expanding, and more virulent human fungal pathogens [7]. Fungal diseases kill more than 1.5 million and affect over a billion people per year [8]. However, infectious fungi receive less attention than viruses and bacteria since they typically do not derive from dramatic spillover events and are generally not transmissible person-to-person. Severe consequences are expected as novel pathogens are introduced to naïve environments. The objective of this review is to compile the current knowledge on the impact of climate change on human

✉ Paris Salazar-Hamm
psh102@unm.edu

1   Center for Global Health, Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

2   Department of Biology, University of New Mexico, Albuquerque, NM, USA

3   Department of Botany and Plant Pathology, Purdue University, West Lafayette, IN, USA

pathogenic fungi focusing on emergent fungal pathogens, those with expanding distributions, as well as those with climate change induced virulence (Fig. 1).

Climate change represents a global challenge characterized by long-term shifts in temperatures and weather patterns that is aggravated by anthropogenic carbon emissions. It involves heightened temperatures, irregular weather patterns, retreating of global ice sheets, and elevated sea levels [9, 10]. Temperatures are predicted to rise (2–4 °C in the next 100 years) [11, 12]. Drought, heat waves, longer wildfire seasons, extreme rainfall, and stronger hurricanes are expected to be the results of these changes. Climate change can exacerbate the emergence of fungal pathogens that affect humans directly (i.e., clinical disease) and indirectly (e.g., food security, wildlife extinction, and animal health). It can also alter pathogen evolution and host-pathogen interactions leading to an increased risk of fungal disease outbreaks [13]. This may include adaptation to higher temperatures that can consequently lead to shifts in pathogen geographic distribution [14], changes in wind currents and intensity that affect disease burden and range [15, 16], or community-level phenological shifts that alter both pathogen dispersal and distribution [17, 18].

Pathogenic fungi exist in a broad range of natural habitats. Human pathogenicity has evolved on multiple occasions from non-pathogenic fungi in several major lineages of the fungal tree of life [19••]. Some have well-defined,

known geographic ranges (e.g., *Blastomyces dermatitidis*, *Coccidioides* spp., and *Paracoccidioides* spp.), while others are considered ubiquitous (e.g., *Aspergillus fumigatus*, *Fusarium* spp.). Their distribution may be defined by that of their animal hosts or vectors [20, 21], while the abundance and distribution of soil- or plant-associated fungi depend directly on climatic factors such as temperature and moisture [22]. For example, coccidioidomycosis incidence in Arizona correlates with hot, dry conditions [23••, 24], blastomycosis clusters associate with rainfall after periods of decreased precipitation [25], incidence of *Penicillium marneffei* penicilliosis increases during rainy months [26], and aspergillosis correlates with seasonality in some geographic areas [27]. Environmental disruption is a key factor in the dispersal of pathogenic fungi and their potential to cause infection. There is a link between natural disasters and subsequent human fungal infections in these disaster stricken areas [28]. Pathogenic fungi can be displaced from their natural habitats during a disaster, thus increasing their environmental concentration or introducing them to areas where they would not normally be found. An uptick in fungal spores that may come in contact with injured persons greatly increases opportunities for spurious fungal infections [28] caused by natural events such as dust storms [29], earthquakes [30], tsunamis [31–35], hurricanes [36, 37], and tornadoes [38]. Coccidioidomycosis outbreaks were associated with a severe dust storm in the southern San Joaquin

Fig. 1 Climate change impacts human fungal pathogens. Arrows indicate directionality of effects. Created with BioRender.com
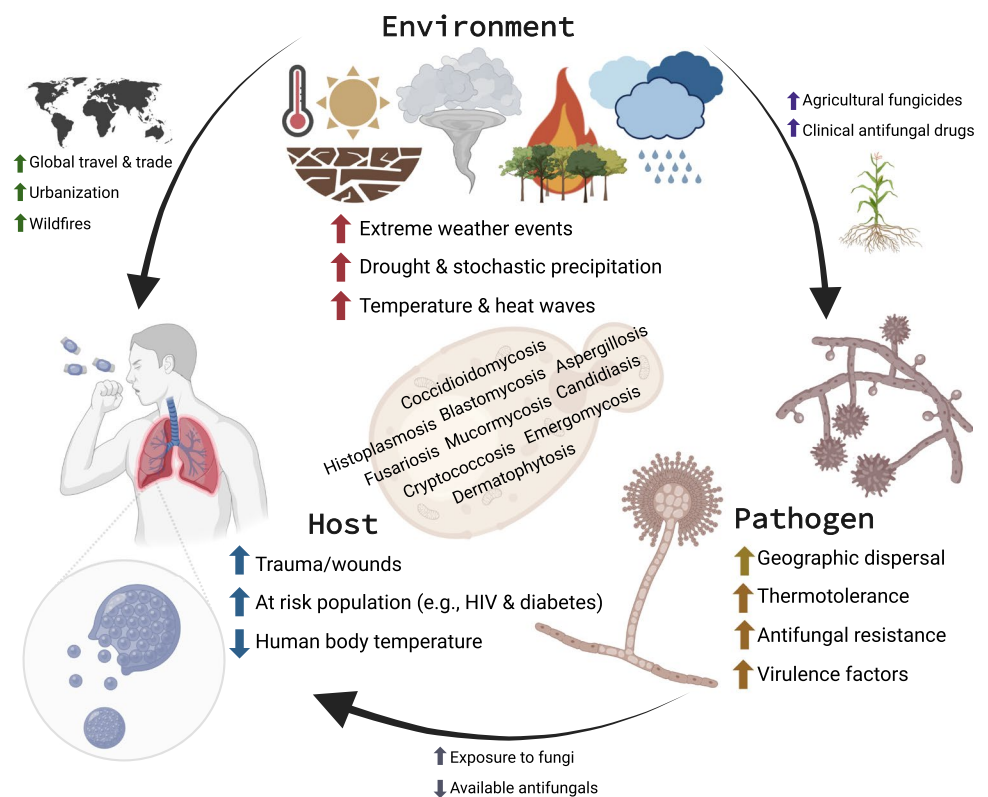
Valley of California in December 1977 [29] and with the January 1994 earthquake in Northridge California, when spores were presumably aerosolized and dispersed by dust clouds [30]. *Aspergillus* has been implicated as an agent of tsunami lung, such as after the 2011 Great East Japan Earthquake and subsequent tsunami where a near-drowning victim, that later died, was found to have disseminated aspergillosis [35]. Persons injured during the 2004 Indian Ocean tsunami showed post-disaster soft tissue mucormycosis [31–33]. Clusters of mucormycosis cases have occurred among 13 persons severely injured on the May 22, 2011, tornado in Joplin, Missouri caused by *Apophysomyces trapeziformis* [38] and 8 patients after the 1985 volcanic eruption in Armero, Colombia, caused by *Rhizopus arrhizus* [39]. Paracoccidioidomycosis infection rates were strongly correlated to the 1982/1983 El Niño Southern Oscillation in Brazil [40]. Unfortunately, current patterns of population growth, urbanization, and human activity coupled with progressively damaging climate change effects create conditions that render communities increasingly vulnerable to these hazards [41].

Emerging Fungal Diseases

For the purpose of this review, we consider emerging fungal diseases to be those that have been reported to cause human disease in the last 30 years, have arisen in new geographic locations, or have become increasingly problematic with their emergence being attributed to climate change effects, such as candidiasis, fusariosis, mucormycosis, and emergomycosis. Not discussed at length here, but of growing concern, are a number of uncommon disease-causing fungi such as filamentous basidiomycetes [42] and fungi-causing entomophthoromycosis (e.g., conidiobolomycosis and basidiobolomycosis) [43].

Candidiasis

Synergies between temperature (thermal adaptation to warming climates) and fungicide exposure have been invoked to explain the rapid worldwide emergence of multidrug-resistant *C. auris* in humans, following its discovery in Japan in 2009 [44, 45, 46••]. Pathogenic lineages of this fungus emerged independently on three continents simultaneously (i.e., Asia, Africa, and South America) [45], and it is suggested to have emerged in part as a result of widespread use of antifungal drugs [47]. *Candida auris* isolates are broadly resistant to antifungals, severely limiting treatment options [45]. This *Candida* species is also capable of growing at higher temperatures than most of its close relatives while it preferentially colonizes the cooler skin (e.g., ears), facts consistent with a recent acquisition of thermotolerance [46••].

The few *C. auris* isolates from environmental origin available are significantly different from clinical isolates as they are more susceptible to antifungal agents and grow slowly at 37 and 42 °C [48]. Although human-induced climate changes could be responsible for the continuous narrowing of the thermal restriction zone for *C. auris*, other factors (e.g., migration, pollution, and high population density) may explain its persistence and acquisition of antifungal resistance [49].

Fusariosis

Various species within *Fusarium* [50, 51] cause local or invasive fusariosis, generally involving immunosuppressed individuals but occasionally immunocompetent patients [52–54]. In healthy individuals, observed fusariosis includes onychomycoses, skin infections, and keratitis. *Fusarium* keratitis develops from trauma to the eye, contact lens wear, and use of corticosteroids [55–57], with trauma being the typical predisposing factor and occurring in 40–60% of patients [56]. Meanwhile, in immunocompromised individuals, deep local and disseminated infections are observed [58]. *Fusarium* conidia can travel significant distances, making them efficient at dispersal [55]. Some species cause infections worldwide, but endemic regions are tropical and subtropical [54, 59]. Members of the *F. solani* species complex (FSSC) are the most common (i.e., *F. falciforme* and *F. keratoplasticum*) and most virulent human pathogens, followed by the *F. oxysporum* and *F. fujikuroi* species complexes (FOSC and FFSC, respectively) [52, 58, 60]. The prevalence of fusaria in the environment has been connected to plumbing systems and soils. FFSC, FOSC, and *F. dimerum* species complexes are highly represented in sink drain biofilms. The same top six multi-locus sequence types (MLSTs) are found in sink drains and clinical isolates [61], and four FSSC haplotype groups have been particularly associated with human infections [62]. *Fusarium* spp. can also affect humans indirectly as many of them are mycotoxigenic and can cause devastating diseases, producing trichothecenes and fumonisins [63]. The response of mycotoxigenic fungi to climate change could induce shifts in their geographical distribution and the pattern of mycotoxin occurrence [64•]. Mycotoxin production in *Fusarium* is highly influenced by climatic conditions; for example, mycotoxin contamination in maize has been connected to extreme levels of precipitation [65]. Mycotoxin contamination is expected to increase as an effect of climate change [66].

Mucormycosis

Fungi in the order Mucorales—including species of *Rhizopus*, *Lichtheimia*, and *Mucor* [67]—are environmentally ubiquitous and can cause life-threatening invasive

infections [68]. Associations between weather patterns and mucormycosis have been hypothesized [69–71], suggesting that warm and dry conditions contribute to mucormycosis clusters [72]. The sporangiospores of Mucorales are small and can be aerosolized and dispersed under favorable atmospheric conditions which vary from high humidity to xerophytic conditions depending on the taxa [73]. Traumatic skin injury and inhalation or ingestion of spores can lead to invasive mucormycosis [74], usually in patients with diabetes mellitus or who are severely immunocompromised [67]. Mucormycosis cases have been reported after natural disasters, such as causing necrotizing fasciitis in victims of the 2004 Indian Ocean tsunami [31] and the 2011 Missouri tornado [38]. Invasive pulmonary mucormycosis is a recognized secondary complication of COVID-19 [75, 76] and has been reported in combination with pulmonary aspergillosis, especially in COVID-19 critically ill patients in the intensive care unit [77, 78].

Emergomycosis and Emmonsia-Like Pathogens

In 1994, an Italian woman with advanced HIV disease and widespread cutaneous lesions was diagnosed with an atypical disseminated mycosis, caused by the dimorphic fungus *Emergomyces africanus* [79]. As a result of advancements in molecular identification procedures, *E. africanus* is now linked to at least 86 patients with disseminated mycoses with advanced HIV in South Africa [80, 81]. The genus *Emergomyces* includes five species causing emergomycosis systemic fungal infections in immunocompromised persons, and such emergomycoses have been documented on at least four continents [81]. Detections in soil [82] suggest this saprophytic fungus as an opportunistic pathogen taking advantage of the increasing immunocompromised population and human global travel. Characterization of the lung mycobiome in non-human hosts indicates great diversity of close relatives of *Emergomyces* (e.g., *Blastomyces*, *Emmonsia*, and *Emmonsiellopsis*) [83], many of which have been reported as emerging fungal pathogens causing disease in immunocompromised hosts [84].

Expanding Geographic Distributions

Shifts in global temperature patterns represent an opportunity for environmental fungal pathogens to colonize new geographical areas, expanding their range [85, 86]. Most fungi grow at ambient temperatures; however, only a limited number of species are known to grow well above 37 °C [87]. It is possible that the environment contains large numbers of fungal species with pathogenic potential that are currently non-pathogenic to humans due to their inability to grow at mammalian temperatures [46••]. Higher ambient temperatures, caused by climate change, could lead to selection of fungi with higher thermal tolerance allowing them to breach the mammalian thermal restriction zone [46••] and defeating the protection that was previously granted by endothermy [22].

A selected number of fungi have adapted to shapeshift in multiple environments triggered by changes in temperature (dimorphism). These fungi live as hyphal networks in the environment but shift to a yeast phase for immune evasion upon inhalation of spores by a potential host. Although each fungus possesses its own unique ecology, a number of these are endemic pathogens with defined ranges [88]. In addition to gradual warming and stochastic precipitation that directly affect soil temperature and moisture, geographic expansion of these fungi may be indirectly affected by the distribution of their reservoir hosts or vectors.

Coccidioidomycosis

Coccidioides, causing coccidioidomycosis (Valley fever), is predicted to be intimately influenced by climate change due to its strong correlation with both temperature and precipitation [23••, 89]. A seasonal pattern of wet followed by dry conditions has been linked to increased coccidioidomycosis incidence across the Southwestern United States [90–93]. Disturbance of dry arid soils caused by high winds or human activities can cause arthrospores to become airborne and inhaled by humans or animals. Spurious natural events can also cause an increase in coccidioidomycosis cases. Unrelenting wildfires in the Western United States have increased significantly in size and frequency over the last 30 years [94]. Smoke contains pollutants harmful to human health as well as viable aerosolized microbes, including fungal conidia that can travel up to hundreds of miles on air currents [95]. Wildfires in California have been broadly correlated to an increase of coccidioidomycosis cases by 20% in the month following smoke exposure [96•]. Additionally, firefighting involves soil-disturbing activities which have been linked to outbreaks of coccidioidomycosis [97]. The distribution of *Coccidioides* is patchy in the environment and is thought to be dependent on rodent reservoirs that have low-level lung infections [83]. Climate indirectly influences dispersal of *Coccidioides* as small mammal hosts respond to their habitat, including water and nutrient availability. Upon death, decaying hosts provide keratinaceous materials for the fungus to metabolize and proliferate [21]. Additional thermotolerance to extreme desert temperatures by species of *Coccidioides* [98] may allow continued proliferation. A pivotal study by Gorris and colleagues estimated that approximately 47.5 M people in 217 counties spanning 12 states live in the coccidioidomycosis endemic region of the United States. This study further estimates that, due to climate warming, by the year 2100, the endemic region of

this disease in the USA will more than double in size, affecting 17 states, with the number of cases rising by 50% [85].

Blastomycosis

The environmental niche of *Blastomyces*, causing blastomycosis, is still largely unknown. However, *Blastomyces dermatitidis* has been isolated from moist soil and organic matter in the Mississippi and Ohio River Valleys and around the Great Lakes (USA) [99, 100]. Recent transient environmental detections of *B. dermatitidis* post-flood in Hennepin County Minnesota, a low-endemicity county [101], support the long suspected connection of blastomycosis proliferating after flooding events [102, 103]. Blastomycosis is demanding greater attention due to novel disease-causing species (i.e., *B. helicus* and *B. gilchristii*) [104, 105], worsening disease severity [106], and cases expanding beyond the previously defined endemic range [107].

Histoplasmosis

Histoplasma, the causal agent of histoplasmosis, has a global distribution; but the disease is more burdensome in the African and American continents [108]. The radiation of *Histoplasma* dates to between 3 and 13 million years ago [20]. Nevertheless, climate change arguably has and will continue to influence its rate of expansion. Reports of clinical cases of histoplasmosis in extreme latitudes in Canada [109] and Argentinian Patagonia [110] could be related to new favorable environments for the fungus and/or for its animal vectors. Bats are considered the major reservoir and dispersers. Besides bats, *Histoplasma* has been detected in a diverse number of wild mammals (e.g., primates, mustelids, and procyonids) [111–113], as well as domesticated animals (e.g., equines, canines, and felines) [114, 115]. A tight association with vertebrates suggests that mammals play an important role in the speciation and dispersal mechanisms of *Histoplasma*. Range, population size, mortality rate, and reproductive success of vertebrate vectors are likely to be affected by climate change [116], which may in turn affect the ecology and evolution of *Histoplasma* spp.

Cryptococcosis

Cryptococcosis, a fungal infection mainly affecting the lungs or central nervous system, is primarily caused by *Cryptococcus neoformans*. This fungus has a cosmopolitan distribution and can be found in soil, on decaying wood, in tree hollows, or in bird droppings [117]. While *C. neoformans* primarily infects immunocompromised individuals, another causative species, *C. gattii*, can infect healthy individuals [118]. Previously thought to be limited to tropical and subtropical regions of South America, Africa, Asia, and Australia,

locally acquired *C. gattii* outbreaks were first recognized in the late 1990s in the Pacific Northwest (USA) and Europe [119]. Expanding suitable habitat (e.g., eucalyptus trees) and anthropogenic dispersal [120] will only lend to expanding ranges with global warming [121•, 122]. The range expansion of *C. gattii* may be particularly concerning due to highly virulent clonal lineages [123, 124].

Acquiring Antifungal Resistance and Virulence Factors

Antimicrobial resistance (AMR) is a complex global health challenge, not restricted to particular regions or countries but rather proliferating on every continent. Antifungal resistance usually leads to prolonged treatment and hospital stays, as well as a heightened need for expensive and highly toxic second-line antifungals. The WHO fungal priority pathogens list (FPPL) details antifungal resistance as the highest weighted criterion in determining priority [7]. While AMR in bacteria is propagated by commensal and environmental organisms exchanging extrachromosomal plasmids via horizontal gene transfer, selection for AMR genes and alleles in fungi is generally constrained to within species boundaries; therefore, resistance to antifungals usually evolves *de novo* for each species [125]. Despite these constraints, evolutionary pressures, including higher average temperatures expected under climate change, conditioning pathogens to endothermy [22], and overuse and dependency on the few available antifungal agents [126, 127], have resulted in antifungal resistance in several fungal lineages. The WHO's most recent global research agenda for AMR in human health states that *Candida auris*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* are of critical importance [128].

Antifungal drug resistance or tolerance in these fungi is acquired in a variety of ways depending on the antifungal mode of action. For example, azole antifungals inhibit synthesis of the essential membrane component ergosterol. Resistance to azoles can result from mutations in *ERG11* homologs, which encode for an enzyme supporting ergosterol production, or from mutations that lead to increased efflux of the drug from the fungal cell [129]. The latter appears to be particularly important in *Candida* species, while in *C. neoformans*, overexpression of efflux pumps caused by chromosomal aneuploidy and hypermutation seems to be the main mechanism. Echinocandins, a second class of antifungals, inhibit 1,3-β-D-glucan synthase (*FKS1* and *FKS2*) [130]. Mutations in this gene cause antifungal resistance in *Candida* and *Fusarium*, while hypermutation in species of *Cryptococcus* generates resistance to pyrimidine analogues [125]. However, few studies have explored the extent to which climate changes directly

influence the occurrence, directionality, and significance of synergistic interactions between temperature and antifungal resistance.

Climate and environmental pressures have selected for a multitude of additional virulence factors (e.g., thermotolerance, melanin production, and resistance to oxidative stress) that result in successful fungal pathogens. Heat acclimation is thought to be influenced by the availability of new habitats, global climate change, and encountering new hosts [131]. Decreasing human body temperatures [132] make humans even more vulnerable to colonization of thermotolerant pathogens. The capacity for thermotolerance is interspersed among Ascomycetes and Basidiomycetes, suggesting that it may have emerged independently several times in evolutionary history. However, there are certain phylogenetically related taxa, such as cryptococci [133] and aspergilli [134, 135], that have maintained this ability. This phenotype may be due to mutations in heat shock proteins activated in response to changes in temperature that regulate cellular processes associated with morphogenesis, antifungal resistance, and virulence by triggering a wide array of cellular signaling pathways [136]. Fungal thermotolerance is a complex process with diverse manifestations (reviewed in [137]) which requires further study.

Aspergillosis

Aspergillus species are ubiquitous, saprophytic fungi with airborne conidia. *Aspergillus fumigatus* is the main causative agent of human aspergillosis, which can establish a lung infection when the immune system is compromised [138]. The conidia of *A. fumigatus* are distinguished by melanin pigmentation which is thought to defend the genetic material from the adverse effects of ionizing radiation in the environment [139]. Oral triazole antifungal drugs (i.e., itraconazole, voriconazole, and posaconazole) are usually effective against *A. fumigatus* and are used as therapy in management and prophylaxis of invasive aspergillosis [140]. However, azole resistance has emerged in *A. fumigatus* isolates from Europe, Asia, Middle East, and Africa [141–143], likely acquired at least in part from the agricultural use of azoles [144]. High rates of patient mortality are observed when treatment of invasive aspergillosis fails on azole-resistant strains [145–147]. The frequency of azole-resistant *A. fumigatus* is elevated in high-temperature environments such as composts [148–150], greenhouses [151], and tropical countries [152]. Heat shock inducing ascospore germination in high-temperature azole-containing habitats can serve as evolutionary accelerators with increased selective pressure on recombination [153] suggesting the occurrence of synergistic interactions between temperature and antifungal resistance [154].

Cryptococcosis

Cryptococcus neoformans is the highest-ranked fungal pathogen in the FPPL [7] and considered a global threat to human health [155]. It regulates caspofungin resistance via posttranscriptional regulation of cell wall biosynthesis genes [156] and flucytosine conversion through transposon mutagenesis [157]. It is also common for *C. neoformans* to overexpress the drug target and efflux pumps caused by chromosomal aneuploidy and hypermutation [125]. Fluconazole resistance in *C. neoformans* is attributed to chromosome duplication (aneuploidy) of chromosome 1 which harbors genes *ERG11* and *AFR1* [158] as well as mutations in the *ERG11* gene [159, 160]. A mutation in *CDC50* (encodes the β-subunit of membrane lipid flippase) mediates echinocandin resistance by preventing drug uptake [161].

Cryptococcal species maintain several virulence factors that have evolved over long periods of evolutionary time selected by environmental pressures. Melanin production provides protection for multiple species of *Cryptococcus* from environmental stressors including antifungal compounds, oxidants, UV light, macrophages, and extreme temperature [162]. *Cryptococcus gattii* preferentially expresses melanin at 30 °C [133] compared with 37 °C for *C. neoformans* [163]. While *C. neoformans* is frequently isolated from pigeon guano, the niche of *C. gattii* remains uncertain; thus, it is unclear what environmental pressures are influencing this phenotype. Although thermotolerance is established in multiple species of *Cryptococcus* [133], thermotolerant strains of *C. laurentii*, which normally do not grow at 37 °C, have been associated with disease in extremely immunosuppressed hosts [164]. This may be an indicator that the ability to grow at or above 37 °C may induce pathogenicity in currently benign fungi.

Fusariosis

Fusariosis infections are also challenging to treat due to multidrug resistance [51, 55, 165], further complicated by increased incidence of such infections [166] and the lack of research on developing new therapeutic options for treatment. There is low investment from the pharmaceutical industry for drug development to combat fusariosis [167]. Current treatment and prophylactic agents include amphotericin B, voriconazole, and posaconazole [168]. However, *Fusarium* spp. have intrinsic resistance to echinocandins [51] and azoles [169]. AMR is a risk factor associated with the use of fungicides in the environment [170]. Azoles are the most commonly used group for pathogen control as well as for treatment of human infections, making it an increasing concern for the potential development of resistance [170]. Additionally, *Fusarium* has mechanisms that contribute to resistance acquisition to most antifungal agents, like changes

in amino acid sequences and overexpression of genes that encode efflux pumps [171].

Candidiasis

The increasing use of azoles for treatment of superficial and systemic infections by *C. glabrata* has resulted in selection and emergence of resistant isolates and an increase in infections by other non-*albicans* species [172]. Multiple drug resistance mechanisms have been found in the *C. glabrata* complex for resistance against azoles, polyenes, and echinocandins. These mechanisms include the overexpression of drug transporters, gene mutations that alter thermotolerance, induction of hypervirulence due to increased adhesion factors, biofilm production, and modifications in vital enzymes that produce cell wall proteins that prevent the activity of drugs designed for its inhibition [173]. Low susceptibility to antifungal therapies available is associated with a higher mortality rate [174].

Candida auris is resistant to fluconazole and has variable susceptibility to other azoles, amphotericin B, and echinocandins [45]. Multidrug resistance and high associated mortality rates make this pathogen an emerging global threat that is difficult to eradicate from hospitals despite intense infection-prevention strategies [45, 47, 175, 176]. The Centers for Disease Control (CDC) has documented that cases of *C. auris* increased in the USA from 329 in 2018 to 1012 in 2021 [177]. Although accurate data are lacking with respect to antifungal prescription practices, anecdotal evidence suggests an increase in the use of triazoles and other antifungals in recent years. In South Africa, *C. auris* seems to have emerged more rapidly in private hospitals where echinocandin use is higher than in public hospitals [178]. Increased use of azole antifungals in surgical ICUs is suspected to have caused a shift in the prevalence of *Candida* species toward the more difficult-to-treat pathogens, particularly *C. krusei* and *C. glabrata* [179, 180].

Dermatophytosis

Cutaneous mycoses are among the most common fungal infections worldwide. Dermatophytic fungal species of *Microsporum*, *Epidermophyton*, and *Trichophyton* cause infections of the skin, nails, and hair [181]. Transmission may occur through contact with humans or animals or indirect contact with fomites. During the past decade, an epidemic of severe, antifungal-resistant tinea has emerged in South Asia because of the rapid spread of *Trichophyton indotineae*, partly owed to the misuse and overuse of topical antifungals and corticosteroids [126]. Severe infections prove to be resistant to conventional antifungals, including allylamines (terbinafine and naftifine) conferred by point mutations in the squalene epoxidase (*SQLE*) gene and

azoles (itraconazole and fluconazole). While the expansion of clinical cases has mainly been attributed to global travel, temperature and humidity are also critical to dermatophyte growth. In rabbit farms, the presence of dermatophytes was significantly higher in animals held under conditions with higher temperatures (> 20 °C) and with humidity ranging from 62 to 65% [182]. The range of *Microsporum canis* is limited by altitude, suggesting that the fungus may be constrained in the soil by temperature and moisture [183].

Conclusions and Future Directions

Anthropogenic induced climate change may provide fungal pathogens with opportunities to expand their distribution and develop antifungal resistance and other virulence factors. But additional considerations such as the increasing number of immunocompromised hosts, limited antifungal therapies, and an absence of fungal vaccinations compound the emergence, persistence, and expansion of these fungal pathogens. Fungal infections tend to be overlooked, and increased awareness by health care providers, public health professionals, and community members is necessary. The impacts of climate change are predicted to become more severe as global temperatures continue to rise and as climate change contributes to greater frequency and severity of extreme weather events. Very few fungi are obligate to human hosts (i.e., *Pneumocystis* spp.), while the majority have an environmental phase (e.g., saprobic, endophytic, or aquatic) where they certainly will be impacted by changes in the climate and weather. Despite ongoing research on human fungal pathogens, more work is needed to bridge the gaps between scientists investigating ecology and evolution and physicians diagnosing and treating patients. Advancements in genomics increase opportunities for translational medicine, such as determining resistance profiles and rise of pathogenic strains.

Myriad research questions remain unanswered in this field, from basic biology and ecology of these fungal pathogens to applied clinical research. Further studies are needed to validate hypotheses associated with the emergence of certain fungal pathogens (e.g., *Candida auris*) and determining the environmental niche of them (e.g., *Blastomyces*, whose environmental niche is still undetermined). We have summarized the limited current knowledge of how climate change may affect human pathogenic fungi. Yet, a large knowledge gap remains. We encourage studies on (1) the occurrence, directionality, and significance of synergistic interactions between temperature and antifungal resistance [154]; (2) the development of new therapeutic options for treatment, including a higher investment from the pharmaceutical industry for drug development to combat fungal diseases; (3) detailed range expansion of natural reservoirs

and surveillance data; and (4) the effects of the interaction between multiple fungal diseases on the same patient (e.g., invasive pulmonary mucormycosis reported in combination with pulmonary aspergillosis in COVID-19 patients in ICU) [77, 78].

Improvements in surveillance and increased education about fungal infections is of paramount importance to alleviate underreporting and delayed diagnosis in order to further accurately understand range expansion and disease burden. For example, although the National Notifiable Diseases Surveillance System (NNDSS) tracks cases of coccidioidomycosis in 26 states (52%), neither histoplasmosis nor blastomycosis is currently a nationally notifiable condition [184]. This detailed incidence and distribution data would be invaluable for its use in disease epidemiology and forecasting. Computational models have been successfully developed for infectious human disease forecasting, such as for dengue viruses [185] and West Nile virus [186], but have rarely been implemented for fungi. Coordination between biologists, mycologists, and epidemiologists along with health officials in each region is needed to further advance in this field and get ahead of the potential challenges climate change effects will have on fungal pathogen distribution expansion and disease incidence.

Declarations

Competing interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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●● Of major importance.

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