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Emerging fungal pathogens pose a growing threat to global health

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Abstract
Fungal infections present a formidable global health challenge, affecting over one billion people annually and contributing to significant morbidity and mortality, particularly among immunocompromised populations. This review categorizes key fungal pathogens identified by the World Health Organization into critical, high, and medium-priority groups based on clinical impact and resistance profiles. Critical pathogens, such as *Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus*, and *Candida albicans* pose substantial threats, with multidrug resistance complicating treatment strategies. High-priority pathogens include *Candida glabrata*, *Histoplasma* species, and *Mucorales*, while medium-priority pathogens encompass *Candida krusei*, *Coccidioides* species, and *Pneumocystis jirovecii*. Emerging diagnostic technologies like PCR-based assays and advanced therapeutic approaches are essential in combating these infections. Strengthening global surveillance, enhancing diagnostic capabilities, and optimizing antifungal stewardship programs are critical steps toward mitigating the impact of fungal diseases on public health. Therefore, the objective of this review is to discuss Emerging Fungal Pathogens: A Growing Public Health Concern due to emerging fungal pathogens.

Keywords: Emerging fungal pathogen, immunocompromised patients, morbidity**,** public Health

Introduction
Fungi have become a significant public health issue in developing and developed countries (Pal *et al*., 2014) [15]. Annually, fungal diseases impact about one billion people and result in over 1.5 million deaths (Bongomin *et al*., 2017) [1]. Individuals most at risk are those with underlying health conditions or weakened immune systems, including those with chronic lung disease, prior tuberculosis (TB), HIV, cancer, and diabetes mellitus. Additionally, critically ill patients in intensive care units (ICUs), those undergoing invasive medical procedures, receiving broad-spectrum antibiotics, and taking immune-suppressing medications are at high risk (Bongomin *et al*., 2017) [1]. These vulnerable populations are particularly susceptible to species such as *Cryptococcus*, *Candida*, *Aspergillus*, *Pneumocystis*, *Fusarium*, and *Mucorales*, as well as dimorphic fungi like *Histoplasma* and *Talaromyces* (Oliveira *et al*., 2023) [14].

Important fungal pathogens, such as *Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus*, *Candida albicans*, *Nakaseomyces glabrata* (*Candida glabrata*), *Histoplasma* spp, *Mucorales* (including *Rhizopus* spp, *Mucor* spp, *Lichtheimia* spp, and others), *Fusarium* spp, *Candida tropicalis*, *Candida parapsilosis*, *Pichia kudriavzevii* (*Candida krusei*), *Talaromyces marneffei*, and *Pneumocystis jirovecii* pose a significant public health risk worldwide. The extent of the threat posed by these fungal pathogens is a growing global issue (Parums *et al*., 2022) [20].

To effectively develop strategies for prevention and preparedness, it is imperative to understand the factors that contribute to the emergence and spread of fungal diseases. Changes in the environment, such as climate change, deforestation, urbanization, increased population density, migration, and global travel, can create conditions that favor fungal growth and transmission. For example, deforestation can increase the risk of animal-to-human transmission of fungal infections, and climate change can change the favorable environments in which fungal pathogens can thrive and establish themselves in new regions (Nnadi and Carter, 2021) [13].

Emerging fungal pathogens

Emerging fungal pathogens change the landscape of human mycology. The new emerging pathogens are usually non-pathogenic relatives of existing established pathogens. Sometimes, emerging pathogens are resistant to conventional antifungal therapy and may cause severe morbidity and mortality in immunocompromised patients (Friedman and Schwartz, 2019) [9]. The World Health Organization (WHO) published a fungal priority pathogen list consisting of 19 pathogens, divided into three key groups (Parums, 2022) [20].

The pathogens included were ranked, and then categorized into three priority groups; Pathogen category into critical priority group (*Aspergillus fumigatus*, *Candida albicans*, *Candida auris*, and *Cryptococcus neoformans*, Pathogen category high priority (*Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, along With *Fusarium* species, *Histoplasma* species, *Mucorales* species and *Eumycetoma* causative agents, and Pathogen category medium priority (*Candida krusei*, *Coccidiodes* species, *Cryptococcus gattii*, *Lomentospora prolificans*, *Scedosporium* species, *Paracoccidiodes* species, *Pnuemocystis jirovecii*, and *Talaromyces marneffei* (Parums, 2022) [20].

Fungal pathogens in critical priority group

Cryptococcus neoformans is a causal agent of cryptococcal meningitis that affects 194, 000 people, with 147, 000 deaths (Denning, 2024) [6]. Cryptococcosis is the second-leading cause of death in people living with HIV (Zhao *et al*., 2023) [30], but the fungus is also described as capable of causing endocarditis in immunocompetent people (McGuire and Walter, 2022) [11].

Candida albicans: A species that has intrinsic resistance to several antifungals and can cause candidemia that affects 1, 565, 000 people annually, causing 995, 000 deaths, due to its ability to form biofilm on catheters and prosthetic devices (Pathakumari *et al*., 2020; Denning, 2024) [21, 6].

Aspergillus fumigatus is a species that has reemerged as a causal agent of pulmonary aspergillosis associated with COVID-19, influenza, and chronic obstructive pulmonary disease (COPD), with an incidence of 1, 837, 272 cases and 340, 000 deaths (Fisher and Denning, 2023; Denning, 2024) [8, 6].

Candida auris is a newly identified, multidrug-resistant fungal pathogen that poses a significant global health threat (Pal *et al*., 2024) [17]. It was discovered in Japan in 2009 and has since spread to over 50 countries, causing notable outbreaks in healthcare settings worldwide. The fungus is now endemic in various parts of Asia and Africa, where mortality rates from infections have been reported to reach as high as 72% in certain cases (Pal *et al*., 2024) [16]. *Candida auris* emerged simultaneously on three continents and exhibits genetic diversity across different clades: clade I in South Asia, clade II in East Asia, clade III in Africa, and clade IV in South America. It is particularly widespread in Latin America, with clade I identified in Brazil and Chile (Moreno *et al*., 2019; de Almeida Jr. *et al*., 2021) [12, 4] and clade III documented in Argentina (Garcia-Effron, 2023) [10].

Fungal pathogens in high priority group

Candida glabrata is globally distributed commensal yeast that can cause invasive candidiasis, second only to *C. albicans* in incidence. It infects the blood (candidemia), heart, central nervous system, eyes, bones, and/or internal organs. Immunocompromised patients are vulnerable groups for this pathogenic yeast. Echinocandins are the usual treatment option for invasive candidiasis (Denning, 2022) [5].

Candida parapsilosis is an emerging globally distributed yeast that is part of the healthy human and animal microbiome but unfortunately can cause invasive candidiasis in the blood (candidemia), heart, CNS, eyes, bones, and internal organs (Tóth *et al*., 2019) [26].

Candida tropicalis is globally distributed yeast that is part of the healthy human and animal microbiome but unfortunately capable of causing invasive candidiasis (candidemia), in the heart, CNS, eyes, bones, and internal organs). Those with critical illness and decreased host immunity are at risk for this pathogen (Denning, 2022) [5].

Fusarium species are pathogenic filamentous fungi that are distributed globally, but mostly in tropical countries of the world (Pal, 2007) [19]. They primarily infect the respiratory system and the eyes (keratitis) of humans, but they can also spread to the CNS and other organs of the body. Because of their adventitious sporulation, they also cause fungemia. Immunocompromised patients with hematological malignancies or post-hemopoietic stem cell transplantation (HSCT), allogeneic HSCT, acute myeloid leukemia, cytomegalovirus reactivation, and the presence of skin lesions are the risk groups for this infection. The infection is treated by azoles, but the fungi are inherently resistant to most antifungal agents (Parums *et al*., 2022) [20].

Histoplasmosis is caused by three variants of *Histoplasma capsulatum*: *Histoplasma capsulatum* var. *capsulatum*, which is widely distributed and infects humans and various animal species (Pal, 2007) [19]; *Histoplasma capsulatum* var. *duboissii*, causing African histoplasmosis found in baboons and humans in Africa (Pal, 2007) [19]; and *Histoplasma capsulatum* var. *farciminosum*, responsible for epizootic lymphangitis primarily affecting horses in Ethiopia (Rebuma *et al*., 2024) [24]. The disease can occur sporadically or in epidemic form, leading to morbidity and mortality in susceptible individuals. Sporadic cases have been reported from over 60 countries worldwide, including India. In the USA alone, approximately 25, 000 cases of histoplasmosis are diagnosed annually. Individuals engaged in soil-related activities are at higher risk of severe disease manifestations. *Histoplasma capsulatum* has the potential to infect various organs, including the skin, lungs, brain, eyes, adrenal glands, heart, liver, spleen, nasal passages, and gastrointestinal tract (Pal *et al*., 2021) [18].

Mucorales species comprise a diverse order of pathogenic molds found worldwide, including *Rhizopus* spp., *Muco*r spp., and *Lichtheimia* spp., among others. These fungi can infect humans through the inhalation of spores, leading to mucormycosis. Typically, *Mucorales* infections affect the lungs and sinuses initially but can spread to involve the eyes, central nervous system, and gastrointestinal tract (Pal, 2007) [19]. Fungal invasion can also occur through skin injuries, burns, or other trauma, increasing the risk of subcutaneous mucormycosis. Invasive mucormycosis is a severe disease, with mortality rates ranging from 23% to 80% in adults and up to 72.7% in pediatric patients (WHO, 2022) [29].

Eumycetoma is a deep tissue infection caused by fungi commonly found in soil and water that enter the body through skin breaks (Pal, 2007) [19]. Causative agents of

eumycetoma include *Madurella* spp., *Falciformispora senegalensis*, *Curvularia lunata*, *Scedosporium* spp., *Zopfia rosatii*, *Acremonium* spp., and *Fusarium spp*., although comprehensive microbiological data are limited. This infection predominantly affects impoverished populations and can lead to numerous complications and long-term effects. Many eumycetoma patients, up to 60–80%, experience significant disruptions to their daily lives, and high amputation rates, reaching 39%, have been documented. Risk factors include occupations involving farming, male gender, and younger age groups (11–30 years), (WHO, 2022) [29].

Fungal pathogens in medium priority group

Candida krusei a member of the human microbiota, can transition into opportunistic pathogenic yeast capable of invading mucosal surfaces. It can cause various infections, such as oropharyngeal candidiasis, esophageal candidiasis, vulvovaginal candidiasis, and cutaneous candidiasis. Critically ill and immunocompromised patients are particularly susceptible to serious nosocomial infections from this pathogen (Denning, 2022) [5].

Coccidioides species are dimorphic fungi found primarily in the Americas, existing as molds in the environment, especially in soil. Upon inhalation of fungal cells, *Coccidioides* spp. can infect humans [19]. Coccidiomycosis typically begins in the lungs but can spread to involve the central nervous system, bloodstream, bones, and other organs. There is no documented human-to-human transmission. While healthy individuals can be affected, those who are immunocompromised due to conditions like cancer, hematopoietic stem cell transplantation (HSCT), or organ transplantation are more vulnerable. Risk factors include people of African descent, particularly African-Americans, advancing age (over 40-60 years old), specific occupations, and exposure to environmental dust and soil (WHO, 2022) [29].

Cryptococcus gattii is pathogenic yeast with a global distribution, primarily found in environments, such as soil and certain trees in tropical and subtropical regions worldwide. Infection occurs through the inhalation of spores, leading to cryptococcosis. Initially affecting the lungs, cryptococcosis can progress to involve the central nervous system (cryptococcal meningitis), bloodstream (cryptococcaemia), and other organs. Unlike *C. neoformans*, there is no documented human-to-human transmission of *C. gattii*. Invasive cryptococcosis caused by *C. gattii* is a serious infection traditionally observed in immunocompetent hosts (WHO, 2022) [29].

Lomentospora prolificans is a globally distributed opportunistic pathogenic mold capable of causing invasive infections, known as invasive lomentosporiosis, affecting various organs, including the respiratory system, bloodstream, and central nervous system. These infections are frequently fatal, particularly in critically ill and immunocompromised patients, such as those with cancer. The mortality rate from invasive lomentosporiosis ranges from 50% to 71% in adults and is around 50% in immunocompromised children (WHO, 2022) [29].

Scedosporium species are opportunistic pathogenic molds found worldwide. They can cause invasive infections, known as invasive scedosporiosis, primarily affecting the respiratory system but also involving the bloodstream, central nervous system, and other organs. These infections can be systemic and potentially fatal. Risk factors for scedosporiosis include malignancy, hematopoietic stem cell transplantation (HSCT), and severe immunosuppression. Mortality rates associated with scedosporiosis can reach up to 42-46% in both adults and children (WHO, 2022) [29].

Paracoccidioides species are dimorphic fungi endemic to Central and South America, primarily residing in the soil (Pal, 2007) [19]. Upon inhalation or skin penetration by fungal spores from the environment, *Paracoccidioides* spp. can infect humans, causing paracoccidioidomycosis. This disease predominantly affects the lungs, mucous membranes, and skin, with the potential to spread to lymph nodes and other organs of the reticuloendothelial system. Many individuals infected with *Paracoccidioides* spp. remain asymptomatic. Importantly, there is no documented human-to-human transmission of paracoccidioidomycosis (WHO, 2022) [29].

Pneumocystis jirovecii is an opportunistic fungal infection primarily affects those with impaired immune systems, especially those living with HIV/AIDS. Diagnosing, treating, and avoiding Pneumocystis pneumonia require an understanding of its pathogenicity (Weyant *et al*., 2021) [28]. The host's immunological status has a major impact on the severity of *Pneumocystis jirovecii* infection. Pneumocystis pneumonia develops when an immunocompromised person, such as someone living with HIV/AIDS, has a weakened immune system that permits the fungus to spread unchecked. Both humoral and cell-mediated immune responses are thought to be involved in the immunological mechanisms that regulate *Pneumocystis jirovecii* infection, even though these mechanisms are not well understood (Charpentier *et al*., 2021) [3]. Human-to-human transmission of *Pneumocystis jirovecii* is possible and occurs through respiratory droplets (Vera and Rueda, 2021) [27].

Talaromyces marneffei is a dimorphic pathogenic fungus found in the environment (e.g., soil, decaying wood) and causes the disease talaromycosis. It primarily infects the host's lungs (respiratory system) due to spore inhalation and spreads to the CNS, blood, and other parts of the human body. Critically ill and immunocompromised patients (HIV/AIDS, cancer) or organ transplant patients are the vulnerable groups for invasive talaromycosis (Parums *et al*., 2022) [20].

Clinical significance

Fungi play a crucial role in numerous clinical disorders affecting both humans and animals globally (Pal, 2007) [19]. In humans, significant fungal infections include.

Candidiasis that is caused by *Candida* species, commonly affecting the skin, nails, and mucous membranes (Pal, 2007) [19]. Several species of *Aspergillus*, primarily impacting the respiratory system are responsible to produce aspergillosis (Pal *et al*., 2014) [15]. Cryptococcosis, a life-threatening mycosis, is caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, leading to severe lung and central nervous system infections. *Histoplasma capsulatum* is the etiological agent of histoplasmosis that primarily affecting the lungs but capable of spreading to other organs [18]. Pneumocystis pneumonia is caused by *Pneumocystis jirovecii*, a serious infection primarily affecting immunocompromised individuals, such as those with HIV/AIDS, characterized by severe respiratory symptoms including coughing, shortness of breath, and fever (Rajendra Santosh *et al*., 2021) [23]. In animals, fungal infections also

commonly affect the skin, hair, and nails of various species, including cats, dogs, and livestock (Seyedmousavi *et al*., 2018) [25].

Diagnostic techniques

To achieve an even earlier and more precise diagnosis, new methods for the detection of fungal elements in tissue samples (e.g., PCR-based techniques, serological tests) and fungal identification (e.g., matrix-assisted laser desorption/ionization time-of-flight analyzer technology) are now available in adjunction to traditional methods (microscopic examination of clinical samples, histopathology, and culture). PCR-based methods targeting specific fungi are now used to detect several fungal pathogens directly from clinical samples. Real-time PCR uses fluorescent dyes to enhance specificity through either a nonspecific DNA binding dye, SYBR green, or a specific fluorescently labeled probe directed to a target sequence. Since one (or more, in the case of multiplex PCR) specific pathogen is targeted, it is possible to work on 'contaminated' samples. These techniques are very 'clinical-friendly' since they are presented as 'panels' (e.g., a PCR panel for seizure episodes in cats to detect the main agents responsible for neurologic infections, *Cryptococcus*, *Toxoplasma*, and *Neospora*), (Peano, 2022) [22].

The use of serological tests (e.g., the search for wall fungal components, such as beta-glucan) may be a precious tool to diagnose and monitor the therapy response in a variety of diseases (e.g., disseminated aspergillosis in dogs; avian aspergillosis). Direct microscopy retains its importance as a quick and inexpensive tool to 'intercept' a fungal infection. It also allows for observing the cellular population involved in the immune response and finding other pathogens. It is helpful to interpret the results of more advanced tests (culture, PCR). The sensitivity of microscopic exams varies with the individual agent, the source and quality of the specimen, and the skills and experience of the laboratorian. Diagnosis of an invasive fungal infection by direct microscopy and histopathology may require the use of biopsies of deep tissues, which may pose a risk for the patient. Often, it does not allow fungal identification (Peano, 2022) [22].

Treatment approach

Antifungals are commonly used drugs for the treatment and prophylaxis of most fungal infections (Carmona and Limper, 2017) [2]. Amphotericin B is a natural product of *Streptomyces nodosus.* It is effective for most clinical isolates of *Candida* spp. and *Aspergillus* spp., *Cryptococcus neoformans*, endemic mycosis, *Zygomycetes*, and brown-black molds (Drew, 2016) [7]. Triazoles are the preferred agents for the treatment and prevention of invasive aspergillosis in most patients and many endemic mycoses. Echinocandins are usually preferred among other antifungals for their activity against *Candida* spp. Fluocytosine is generally used in combination with amphotericin B to treat refractory *Candida* infections and cryptococcal meningitis (Pal, 2007; Carmona and Limper, 2017) [19, 2].

Conclusions and recommendations

Fungal infections continue to be a major global public health concern, affecting groups that are already at risk and creating difficult diagnostic and treatment decisions. Effective management of these infections is made more difficult by the advent of fungal diseases that are resistant to drugs and even resistant to multiple drugs. The World Health Organization has classified important fungal pathogens into three priority groups: critical, high, and medium. The focus of this research is on these pathogens, emphasizing their epidemiology, clinical relevance, and mortality rates.

Based on the above conclusion the following recommendations were forwarded:

- For fungal epidemics to be promptly detected and reported, surveillance systems must be strengthened worldwide.
- Investing in sophisticated diagnostic tools, like serological tests and PCR-based assays, can help identify fungal diseases accurately and on time.
- Antifungal stewardship strategies must be put in place in healthcare settings to maximize the use of antifungal drugs, prevent the emergence of resistance, and enhance patient safety and clinical results.
- Using a One Health approach to treat fungal illnesses that integrates the viewpoints of animal, environmental, and human health.

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