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Editorial: The World Health Organization (WHO) Fungal Priority Pathogens List in Response to Emerging Fungal Pathogens During the COVID-19 Pandemic

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Abstract The COVID-19 pandemic, climate change, increased resistance to antifungal drugs, and an increased number of immunocompromised patients have driven a recent global surge in pathogenic fungal infections, including aspergillosis, candidiasis, and mucormycosis. On 25 October 2022, the World Health Organization (WHO) released a list of 19 fungal priority pathogens identified as having the greatest threat to public health. The WHO Fungal Priority Pathogens List represents the first global response to identify and prioritize fungal pathogens and their impact on global public health and to consider the unmet research and development needs. The WHO has grouped the priority fungal pathogens into those of critical, high, and medium priority. This Editorial aims to highlight the importance of identifying and prioritizing fungal pathogens and identifying emerging fungal pathogens and the global factors driving changing patterns of infection.

Keywords: Fungi • COVID-19 • Infection Surveillance • Guidelines • Editorial

In early 2018, an expert panel of leading bacteriologists, virologists, and infectious disease experts convened at the World Health Organization (WHO) headquarters in Geneva [1]. Their aim was to identify pathogens with pandemic potential, but for which no, or insufficient, control measures were in place [1]. In 2018, the WHO list included an entry not seen in previous years [1]. In addition to eight familiar and severe diseases, including Zika, Lassa fever, Marburg virus infection, Ebola, and severe acute respiratory syndrome (SARS), the 2018 WHO list included a ninth potential global threat, identified as Disease X [1,2]. Since 2018, the world has experienced almost three years of the COVID-19 pandemic caused by SARS-CoV-2, but debate continues as to whether COVID-19 or Zika represents Disease X predicted in 2018 [2,3].

However, while the COVID-19 pandemic is still ongoing, and zoonotic viral infections continue to be monitored, fungal coinfections have been increasingly reported in patients with COVID-19, including aspergillosis, candidiasis, and mucormycosis [4]. In some patients with COVID-19, these fungal infections were the main cause of patient morbidity and mortality [4]. There has also been the recent recognition of the global emergence of fungal pathogens of increasing concern. On 25 October 2022, the WHO released its first list of 19 fungal priority pathogens, identified as having the greatest threat to public health [5,6]. The WHO Fungal Priority Pathogens List represents the first global response to identify and prioritize fungal

pathogens and their impact on global public health and to consider the unmet research and development needs [6]. The WHO has grouped the priority fungal pathogens into those of critical, high, and medium priority (Table 1) [6].

Fungal pathogens are a significant threat to public health, possibly driven by the COVID-19 pandemic and increasing resistance to antifungal agents [7,8]. During the COVID-19 pandemic, invasive fungal infections increased significantly in hospitalized patients [7]. Fungal infections have become increasingly common and resistant to treatment with the current four main classes of antifungal agents available and the lack of therapeutic candidates in the clinical pipeline [9]. Most fungal pathogens lack rapid and sensitive diagnostics, and those that exist are not widely available or affordable globally [9]. Invasive fungal infections often affect immunosuppressed or severely ill patients, including those with cancer, HIV/AIDS, post-primary tuberculosis infection, organ transplants, and chronic respiratory disease [6]. The incidence and global range of fungal diseases are increasing due to global warming, increased international travel, and increasing resistance to treatment, which means that the risks of developing more invasive infections in the general population are also increasing [6].

Fungal infections have received little attention, particularly in the past few years, with the burden of fungal diseases, their changing pathogenesis, and antifungal resistance being

Table 1. World Health Organization (WHO) Fungal Priority Pathogens List, 2022 [6].

| Critical priority | High priority | Medium priority |
|--------------------------------|--|---------------------------------|
| <i>Aspergillus fumigatus</i> | <i>Candida glabrata</i> | <i>Candida krusei</i> |
| <i>Candida albicans</i> | <i>Candida parapsilosis</i> | <i>Coccidioides spp.</i> |
| <i>Candida auris</i> | <i>Candida tropicalis</i> | <i>Cryptococcus gattii</i> |
| <i>Cryptococcus neoformans</i> | Eumycetoma (granulomatous *fungal infection of the skin and subcutaneous tissue) | <i>Lomentospora prolificans</i> |
| | <i>Fusarium spp.</i> | <i>Paracoccidioides spp.</i> |
| | <i>Histoplasma spp.</i> | <i>Pneumocystis jirovecii</i> |
| | <i>Mucorales/Mucormycosis</i> | <i>Scedosporium spp.</i> |
| | | <i>Talaromyces marneffeii</i> |

Adapted from: WHO fungal priority pathogens list to guide research, development and public health action. 25 October 2022 [6].

* Fungal causes of eumycetoma include *Madurella mycetomatis*, *Aspergillus spp.*, *Nocardia spp.*, *Fusarium spp.*

unknown [6]. However, the recently developed WHO Fungal Priority Pathogens List has now identified critical, high, and medium priority fungal pathogens ranked on their public health impact and/or risk of emerging antifungal resistance (Table 1) [6]. The WHO report aims to collate evidence regarding the response to treatment of the priority fungal pathogens, including preventing antifungal drug resistance [6]. There are three primary actions recommended by the WHO: investing in innovation, research, and development; improving laboratory capacity and the ability to undertake infection surveillance; and improving public health interventions for fungal infection prevention and control [6]. The most important criteria for allocating research and development include antifungal resistance, patient mortality, evidence-based treatment, access to diagnostics, annual incidence, and infection complications and sequelae [6].

Table 1 summarizes the 19 priority fungal pathogens categorized as critical, high, and medium priority [6]. The WHO critical priority group currently includes *Aspergillus fumigatus*, *Candida albicans*, *Candida auris*, and *Cryptococcus neoformans* [6]. *Candida albicans* and *Candida auris* are invasive fungal pathogens that can cause outbreaks with high mortality in healthcare facilities and are resistant to major classes of antifungal drugs [10]. Invasive *Aspergillus fumigatus* is a deadly infection with a 50% mortality rate [11]. *Cryptococcus neoformans* and *Cryptococcus gattii* are invasive spore-forming yeasts with a high mortality rate following infection [12]. In 2020, following reports of the first cases of COVID-19-associated azole-resistant pulmonary aspergillosis, a consensus diagnosis and management statement was developed by experts, and supported by international mycology societies [13]. The 2020 European Confederation for Medical Mycology and

International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria recommended that first-line therapy be either voriconazole or the triazole antifungal, isavuconazole [13]. If azole resistance is identified, liposomal amphotericin B is recommended [13].

Some new fungal species are believed to have emerged due to climate change. For example, *Candida auris*, which is in the WHO critical priority group, is a new fungal pathogen that has emerged since 2009 and has now spread globally, with reports of infections from every continent [14]. *Candida auris* has a possible nonhuman environmental reservoir and dispersal by birds [14]. This fungal pathogen is now of concern in healthcare settings in patients with comorbidities and is resistant to antifungals and disinfectants [14]. Recently, four major genomic clades have been identified, associated with specific geographic regions: clade I, South Asia; clade II, East Asia; clade III, South Africa; and clade IV, South America [14]. Clade II infects the ear only, whereas the other clades have caused invasive and systemic infections [14].

The WHO high priority group includes eumycetoma, also known as Madura foot, which can be caused by *Madurella mycetomatis*, *Aspergillus spp.*, *Nocardia spp.*, and *Fusarium spp.* [15]. Several fungi of the order *Mucorales* cause life-threatening infections, predominantly in patients with impaired immunity [16]. Clinically important species include *Lichtheimia corymbifera*, *Mucor circinelloides*, and *Rhizopus microsporus* [15]. *Mucorales/Mucormycosis* is a WHO high priority fungal pathogen that is an aggressive fungal disease of patients with poorly controlled diabetes mellitus, comorbidities, and immunosuppression [17]. During the COVID-19 pandemic, Egypt, Iran, and the states of Gujarat and Maharashtra in India have reported

increased cases of mucormycosis [17]. The most common type observed is the rhino-orbital-cerebral form of mucormycosis [18]. Some cases of invasive mucormycosis have required extensive surgical excision and debridement due to poor responses to antifungal agents [17,18]. More than 4,000 patients with COVID-19 in India died due to mucormycosis during the second wave of the COVID-19 pandemic in 2021 [18]. Because of the recent prevalence and mortality due to mucormycosis in India, national clinical guidelines have been developed to diagnose, track, and manage this fungal infection, including the Code Mucor guidelines and registry of COVID-19-associated mucormycosis in India [18,19].

Fungal infection has been an under-recognized component of antimicrobial resistance, and infection rates have been affected by global environmental change and expanding high-risk populations [20]. Also, pathogenic fungi that infect humans are evolving resistance to systemic antifungal drugs [7,20]. Risk reduction strategies should aim to minimize the emergence of resistance in pathogenic fungi by reducing environmental causes,

improving infection surveillance and diagnostics, controlling transmission, and developing novel therapeutics through improved research and development [20]. Predictions for a possible future Disease X could include fungal organisms.

Conclusions

The COVID-19 pandemic, climate change and changes in human and animal habitation, increased resistance to antifungal drugs, and an increased number of immunocompromised patients have driven a recent global surge in pathogenic fungal infections. On 25 October 2022, the WHO released the Fungal Priority Pathogens List, identifying 19 critical, high, and medium priority fungal pathogens. Recognition of the global public health impact of fungal infection may raise clinical awareness, address unmet research needs on antifungal agents, and improve infection surveillance to rapidly identify emerging fungal pathogens.

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