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Commentary

World Health Organization's first-ever release of a fungal priority pathogens list: A reply action proposal for the prevention and treatment of fungal pathogens

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Fungi are widely distributed in the environment, and some are beneficial to medicine, industry, agriculture, and food. For example, *Penicillium chrysogenum, Acremonium chrysogenum,* and *Aspergillus terreus* can synthesize β-lactams, which can be used as drugs [1]; *Aspergillus niger* and *Trichoderma reesei* are well-known industrial enzyme producers [2]. Some fungi, such as *Cordyceps militaris*, are medicinal and edible mushrooms [3]. Fungal pathogens, such as *Candida albicans* and *Aspergillus fumigatus*, can threaten human health [4]. These opportunistic fungal pathogens infect immunocompromised patients, including those infected with HIV/AIDS, those with cancer, hospitalized patients, and organ transplant patients (derived from Centers for Disease Control and Prevention). During the COVID-19 pandemic, the outbreak of mucormycosis in COVID-19-infected Indian patients comprised 71% of new mucormycosis cases globally [5]. Moreover, fungal pathogens may infect post-COVID-19 patients [6]. The mortality of patients infected with fungi is high, and fungal pathogens are distributed in nature with potential resistance to current popular antifungal drugs [7]. *Candida auris* is a common multidrug-resistant fungal pathogen that has caused life-threatening outbreaks in health-care facilities worldwide [8]. *Cryptococcus neoformans* cryptococcosis can cause 41%–61% of deaths in patients, especially in immunocompromised populations, such as those infected with HIV. The annual incidence of cryptococcal meningitis is 250,000 cases and the annual number of deaths is 181,000 [9]. To raise concerns in population and obtain sufficient fungal infection data, the World Health Organization (WHO) released the first-ever fungal priority pathogens list (WHO FPPL) on October 25, 2022 to guide the research, development, and public health action of fungal infections [10].

The WHO FPPL comprises 19 different fungal pathogens divided into three groups: critical-priority, high-priority, and medium-priority [10]. These three groups were determined based on 10 assessment criteria in consultation with the WHO Advisory Group on FPPL and other WHO affiliated staff, including average fungal infection case fatality, complications and sequelae, annual incidence, current global distribution, trends in the last 10 years, inpatient care, antifungal resistance, preventability, availability of diagnosis, and evidence-based treatment. The WHO explained the weight of the prioritization criterion and the generation process of the FPPL. The prioritization process revealed that public health importance, antifungal resistance, major knowledge gaps regarding the global burden of fungal infections and antifungal resistance, and varied fungal pathogens distributions and epidemiologies were essential. Although large-scale cohort fungal infection data remained to be collected and the assessment criteria were limited in the FPPL, the WHO FPPL was the first globally released fungal pathogens list with prioritization. According to the WHO FPPL, improving/establishing effective fungal pathogen surveillance network, enhancing public health interventions, and providing sustainable supports for fungal pathogen infection R&D and innovation should be applied to manage the emergence of fungal infection. The WHO FPPL provides details on the implementation of policy interventions and other suggestions to improve the prevention and treatment of fungal infections.

The WHO FPPL would accelerate the establishment of global antifungal drug resistance gene surveillance system, providing effective prevention and control strategies for fungal pathogen infection. A bacterial antibiotic resistance gene surveillance system has been established and improved globally since the release of the WHO bacterial priority pathogens list in 2017 [11,12]. Currently, antifungal drugs are limited to four classes: azoles, echinocandins, pyrimidines and polyenes, and drug-resistant fungal pathogens are available in clinical and environmental samples [13]. The fungal drug resistance rate is associated with the abuse of some antifungal drugs to control plant fungal pathogens and their inappropriate clinical use in hospitalized patients [14,15]. Thus, the development of a systematic surveillance network for antifungal drug

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resistance genes using an affordable and feasible strategy is a prerequisite for controlling antifungal resistance [16]. Moreover, consideration of One Health is essential for obtaining reliable fungal pathogen information and antifungal resistance pattern distribution for invasive fungal diseases [17]. Gene editing and other cutting-edge technologies used for the diagnosis of COVID-19 are efficient [18] and may pave the way for the diagnosis and detection of fungal pathogens. Moreover, emerging technologies would help reveal the pathogenic mechanisms of fungal pathogens, leading to the discovery of potential fungal pathogens and novel antifungal drugs [19].

The number of antifungal drugs is limited, and the development of efficient novel drug discovery strategy is essential to coping with the potential global epidemic of fungal pathogens. Currently, microbiome strategies have revealed diverse hidden natural product biosynthetic gene clusters in environmental microbiota or human microbiota; however, most of these gene clusters are silent, and their characterization in heterologous hosts is difficult to achieve [20,21]. Improper hosts, toxic products, long biosynthetic gene clusters, and limited precursors have hindered the development of potential antifungal compounds [22]. The integration of metabolic engineering, systems biology, and synthetic biology strategies aided by artificial intelligence allow the purposeful identification of antifungal lead compounds [23,24]. Further pharmaceutical investigation might generate useful clinical antifungal drugs. As fungi are available in the environment and the abundance of fungal pathogens might increase in the future, humans must take necessary steps to avoid being affected by fungi [25]. Insights into environmental fungi can not only identify potential fungal pathogens but also lay the foundation for the recovery of beneficial fungi in daily life. In summary, with the endeavor of the WHO FPPL and the help of cutting-edge biotechnologies, invasive fungal infections can be overcome and a healthy life can be achieved by integrating the One Health approach.

Declaration of competing interest

The authors have declared no conflicts of interest.

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