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Will invasive fungal infections be The Last of Us? The importance of surveillance, public-health interventions, and antifungal stewardship

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1. Introduction

The video game-turned-HBO show ‘The Last of Us’ is a fanciful representation of a zombie apocalypse caused by a fungal infection. Although *Ophiocordyceps*, the ‘zombie fungi’ featured in the show, do not infect vertebrates, the show serves as a reminder that many fungi can cause life-threatening invasive fungal infections (IFIs). *Candida* and *Aspergillus* species are the most common and well-known causes of IFIs, but at least 300 species of opportunistic human pathogenic yeasts and molds exist.

Each year, IFIs are responsible for over 1.5 million deaths globally and, in the United States alone, impose health-care costs ranging from five to seven billion dollars [1,2]. During the COVID-19 pandemic, rates of death from fungal infections have increased [3], and the burden of IFIs is poised to grow given the expanding population of patients living with

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Author contribution statement

Roxana M. Rodriguez Stewart, Shawn R. Lockhart, and Jeremy A. W. Gold substantially contributed to the conception and design of the review article and interpretation of the relevant literature. Tom Chiller and D. Joseph Sexton revised the review for intellectual content.

Declaration of interest

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immunosuppressive conditions (e.g. solid organ and stem cell transplantation), increasing antifungal resistance, and potential climate-change related expansion of the geographic ranges in which pathogenic fungi live. Despite the morbidity and mortality associated with fungal infections and their growing public health importance, we still have much to learn about their diagnosis and management. In this review, we discuss gaps and global disparities in fungal laboratory capacity including antifungal susceptibility testing, the paucity of fungal surveillance, and the importance of antifungal stewardship, all against the backdrop of increasing antifungal resistance and a limited armamentarium of antifungal therapies.

2. Diagnostic testing and laboratory capacity

Patients who develop IFIs frequently have complex medical comorbidities, and the clinical manifestations of IFIs are often nonspecific, making diagnosis challenging [4]. Rapid identification of fungal infections is critical to ensure early treatment and prevent severe disease and deaths. Laboratory diagnosis of fungal diseases can involve microscopic examination, culture, antigen or antibody testing, and several molecular assays [4]. Although automated systems exist that can identify certain yeast species, no automated systems exist for the identification of filamentous fungal isolates. Therefore, laboratories depend on personnel with expertise in phenotypic identification of fungi. Because IFIs are uncommon compared with bacterial and viral infections, dedicated clinical mycology sections are generally only maintained in large tertiary medical centers. Smaller facilities often must send out fungal isolates to reference or public health laboratories for identification, a process that frequently causes diagnostic delays and increased cost.

Clinical microbiology laboratories serve as the front line for disease detection, including IFIs. However, establishing mycology laboratories can be challenging in developing countries given limitations in infrastructure, funding, and personnel with fungal expertise. Identifying laboratory deficiencies and expanding laboratory capacity through diagnostic assay development, education, and training are crucial for strengthening a country’s public health surveillance and response to fungal diseases. Even in settings with governmental or nongovernmental organization support for clinical diagnosis and testing of bacterial and fungal diseases, fungal laboratory diagnosis is often ignored [5]. The inability to diagnose IFIs, which depends in large part on laboratory testing, can lead to these infections going untreated, often resulting in death, or treated empirically, which can lead to misuse and overuse of antibacterial and antifungal medications, a driver of antimicrobial resistance [6]. Increasing clinical awareness of fungal diseases in at-risk populations is the first step in highlighting the importance of advancing laboratory testing capacities through diagnostic assay implementation and increased personnel training. This would lead to improved accuracy and turnaround time of results, resulting in proper diagnosis and a decrease in empiric treatment.

Many institutions lack access to essential diagnostic tools to identify fungal infections. For example, the current gold standard for fungal diagnosis is culture and most European laboratories (99%) can process isolates for culture-based testing, but this figure drops to 89.5% for Asian laboratories and 78% for Latin American and Caribbean laboratories [7-9]. While no similar survey data exist for Africa, we know that South Africa is the

only country on the continent with a mycology reference laboratory [10]. Although several countries, including Nigeria and Kenya, are actively increasing their fungal laboratory capacity, diagnostic capacity for fungal infections is lacking in the majority of countries in Africa. Availability greatly declines when assessing other more complex methods for fungal identification, such as MALDI-TOF and molecular methods, or antifungal susceptibility testing. Even in Europe, laboratory capacity for fungal diagnostics greatly varies depending on gross domestic product. In Latin America and the Caribbean, only 9% of diagnostic centers reach the minimum standards for fungal laboratory diagnostic capacity as defined by the European Confederation of Medical Mycology [8,9]. A survey conducted in seven Asian countries assessing laboratory practices for diagnosis of fungal infection showed many laboratories in Indonesia, the Philippines, and Thailand have almost no access to advanced diagnostic tests [7]. To our knowledge, no fungal laboratory capacity assessments have been conducted in other areas of the world. These examples highlight the disparities of fungal diagnostic testing around the world.

Lagging even further behind our ability to diagnose fungal infections is our ability to perform antifungal susceptibility testing (AFST). Publications from both the United States and the United Kingdom highlight the paucity of laboratory ability to perform AFST [5,11]. While yeast susceptibility testing is available in just over half of UK laboratories, only a handful perform mold AFST [5]. In the United States, fewer than a dozen clinical laboratories perform mold susceptibility testing [5,11]. Only a handful of countries around the world have tried to perform comprehensive susceptibility testing for yeasts, but no country has a comprehensive program for the susceptibility testing of molds [12].

Several efforts to improve laboratory capacity for fungal diagnostics nationally and internationally are underway. The Fungal Diagnostics Laboratories Consortium (FDLC), composed of clinical mycologists, was recently created to facilitate and support research and assay development, commercialization, clinical validation, and laboratory implementation of diagnostic assays [11]. The Centers for Disease Control and Prevention (CDC)'s Antimicrobial Resistance Laboratory Network (AR Lab Network) provides enhanced monitoring of antimicrobial resistant pathogens by building laboratory capacity to detect certain antimicrobial-resistant pathogens, increasing diagnostic testing potential and tracking of antifungal resistance.

CDC has established a platform for fungal genome data comparison called FungiNet. This platform is currently being rolled out across the world for countries that are interested in international data sharing. Increased fungal sequencing capacity results in more robust genomic surveillance for fungal diseases, including rapid detection of pathogenic strains, monitoring for prevalence of fungal pathogens in a population, and determining their geographical distribution.

3. Fungal surveillance and antifungal resistance

Antifungal resistance is a growing global public health concern. Worldwide, azole resistance is increasing in *Aspergillus fumigatus, Candida parapsilosis*, and *Candida tropicalis* [13,14]; terbinafine and azole resistance is increasing in dermatophytes like *Trichophyton indotineae*

and *Tricophyton rubrum* [15]; and certain strains of *C. auris* have acquired multidrug- and pan-resistance [16]. Unfortunately, because very few countries have effective surveillance for fungal diseases and limited laboratory capacity to detect resistance, the global burden and impact of resistance is unknown. Historically, no coordinated global surveillance for fungal diseases has existed. There have been attempts to estimate the global burden of fungal disease, but most of the data have been based on crude estimates and extrapolated data from a limited number of countries [2,17]. While these estimates provide some useful data, they generally do not represent resource-limited settings where the basic tools to diagnose fungal diseases are not available, and often do not include antifungal resistance. The rising rates and geographical spread of antifungal resistance, as suggested by limited studies and surveillance, underscore the critical importance of including IFI-causing fungi, such as *C. auris* and *A. fumigatus*, in existing surveillance programs [18]. In the United States, a subset of state public health laboratories in the AR Lab Network is building capacity to detect and monitor antifungal resistance for notable fungal antimicrobial-resistant threats, including *C. auris*, other *Candida* species, and *Aspergillus fumigatus*. Although these efforts are relatively new, they were helpful in tracking increased spread of *C. auris* during the COVID-19 pandemic [19].

Given the paucity of laboratories performing AFST worldwide, this is a leading diagnostic gap. The World Health Organization (WHO) is making an effort to incorporate fungal pathogens into their existing surveillance system, the Global Antimicrobial Resistance and Use Surveillance System (GLASS), the first global collaborative effort to standardize antimicrobial resistance surveillance [20]. Recognizing that one of the major limitations in addressing the threat of antifungal-resistant fungi is a lack of surveillance data at the global level, GLASS started an early implementation protocol in 2019 for the inclusion of *Candida* spp., to support countries in strengthening or building their national fungal surveillance for invasive *Candida* infections. The WHO, in partnership with international subject matter experts, next created the Fungal Pathogen Priority List (FPPL). The FPPL has the objective of increasing research and development, improving surveillance, and informing public health interventions for historically neglected fungal pathogens [21]. Access to diagnostic testing and antifungal resistance were two of the criteria evaluated when deciding on the inclusion and ranking of various types of fungi in this list.

In the United States, the (CDC) uses the National Notifiable Disease Surveillance System (NNDSS) and the National Healthcare Safety Network (NHSN) to standardize national surveillance. While the NHSN is generally concerned with healthcare-associated infections, the NNDSS collects national data for only two fungal pathogens, *Coccidioides* and certain cases of *C. auris*. Several fungal pathogens, including *C. auris*, are included in CDC's list of nationally notifiable diseases, but notifying CDC of these cases is not mandatory. Although these efforts allow for better tracking of fungal infections and antifungal resistance, they do not come close to the surveillance mandated for bacterial and viral pathogens.

4. Antifungal stewardship

Antifungal stewardship (AFS) focuses on coordinated interventions to monitor and direct the appropriate use of antifungals to achieve the best clinical outcomes and minimize

antifungal resistance [22]. Antifungal stewardship may improve patient outcomes, reduce treatment costs, and decrease the emergence and spread of antimicrobial resistance around the world [23]. Antifungal stewardship is inextricably linked to diagnostic testing as part of a comprehensive fungal disease management system [24]. The Mycoses Study Group Education and Research Consortium has developed a set of recommendations for enhancing AFS that center around increasing personnel training, diagnostic testing, antifungal susceptibility testing, disease reporting, and patient monitoring [23]. There are few systemic antifungal classes available to treat IFIs, with only two approved classes containing antifungals effective against molds. Antifungal stewardship efforts are becoming increasingly critical, with a growing number of antifungal agents in phase 2 and phase 3 clinical trials, which include three new classes, essentially doubling the treatment options [25]. As these new antifungals are rolled to our armamentarium, a comprehensive plan for improving laboratory capacity, judicious use of antifungals, and susceptibility testing should become part of a comprehensive stewardship program to provide optimal, timely treatment.

5. Conclusion

IFIs are a growing threat to public health, and the lack of emphasis given to these pathogens has led to improper diagnosis, inadequate treatment, limited surveillance, and increased antifungal resistance. Enhancement of laboratory capacity around the world is critical to prevent disease and deaths caused by fungal infections. The development of quicker and more reliable diagnostic tools, expansion of training programs, and adequate funding could help achieve this goal. The incorporation of fungal pathogens into already existing surveillance programs will likely improve tracking of fungal infections and the spread of antifungal resistance, both nationally and internationally, to guide public health activities. Emphasizing antifungal stewardship to educate the healthcare community about proper antifungal usage can aid in curbing antifungal resistance. By improving laboratory capacity, public health surveillance, and antifungal stewardship, we will better understand the burden of invasive fungal infections, mitigate the development of antifungal resistance, and maybe even prevent a fungal zombie apocalypse.

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