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The WHO fungal priority pathogens list as a game-changer

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Invasive fungal diseases are on the increase globally. The World Health Organization fungal priority pathogens list highlights fungi of critical or high importance to human health and provides pathways for action. The report calls for improved surveillance (diagnostics and antifungal resistance monitoring), research and innovation (implementation research) and public-health interventions.

In late 2022, the World Health Organization (WHO) published the first fungal priority pathogens list — the WHO FPPL[1]. Inspired by the success of the bacterial priority pathogens list — the WHO BPPL — in 2017, the listing of 19 groups of human fungal pathogens that are associated with serious risk of mortality or morbidity seeks to guide research, development and public-health actions against the invasive fungal diseases (IFDs) that they cause. This formal recognition by the WHO brings to the fore a group of infections that have been perennially neglected in terms of the awareness and research funding needed to combat the increasingly destructive diseases that they cause.

Invasive fungal infections cause a range of severe diseases in humans. Although we are all used to the unwanted attentions of superficial fungal infections — athlete's foot, thrush, dandruff, ringworm — we are far less conversant with the burgeoning stable of invasive and chronic fungal diseases. Experienced clinicians fear to discover IFDs in their patients with cancer due to difficulties in initial suspicion, diagnostic confirmation and then successfully treating these infections. For instance, more than half of lung-transplant recipients with invasive aspergillosis are expected to die of the infection and, after tuberculosis, meningitis caused by *Cryptococcus* species is the second leading cause of death in people living with HIV[2]. There is an increasing perception that IFD incidence is rising with the estimated numbers affected being startlingly high; recent assessments suggest that more than 300 million people are affected by serious fungal infections with more than 1.5 million each year thought to die from these diseases[3]. However, and as argued by the WHO FPPL, misunderstanding and poor diagnosis of fungal pathogens by health-care systems, decision makers and funders make it impossible to estimate the global burden of fungal infections with any exactitude and the numbers affected worldwide are likely to be higher than those currently presumed.

Reasons for the likely rise in the burden of IFDs are attributable to a multiplicity of diverse interacting factors. Some of these factors are well understood, such as expanding populations experiencing waning immunity through ageing, the proliferation of modern medical interventions that include immunosuppressive regimes and the persistence of uncontrolled HIV infection. For instance, although the HIV virus was first identified through the increased incidence of *Pneumocystis* fungal pneumonia more than 40 years ago, recent documentation of the high frequency of disseminated histoplasmosis caused by *Histoplasma capsulatum* in Africa, South America and South East Asia in people with AIDS is increasingly recognized as a problem that needs to be urgently addressed because of the common confusion with tuberculosis. However, less well understood are newer risk factors that multiply those populations susceptible to IFDs. We now know that hospitalized patients suffering from respiratory infections are at high risk of fungal coinfections; these include COVID-19-associated pulmonary aspergillosis, influenza-associated pulmonary aspergillosis and chronic obstructive pulmonary disease (COPD). In addition, chronic pulmonary aspergillosis can be mistaken for pulmonary tuberculosis or develop in people successfully treated for these and other pulmonary diseases. These often-lethal combinations of pathogens and lung disease underscore the important role that non-fungal emerging infections have in amplifying the burden caused by clinical mycoses.

Pathogenic fungi that cause IFDs are emerging in their own right driven by eco-environmental changes, with the yeast *Candida auris*, although only described in 2009, now boasting a near-global distribution[4]. Exacerbating the burden of IFD is the attrition of the efficacy of essential drugs through the emergence of antifungal resistance. Owing to the long-term and deep-seated nature of fungal infections in body compartments, often with suboptimal antifungal pharmacokinetics and a lack of fungicidal action, adaptation of the infecting fungus to drug challenge is often followed by high rates of treatment failure[5]. In parallel, the widespread emergence of antifungal resistance in the environment due to opportunistic pathogenic fungi being exposed to agricultural fungicides with the same mode-of-action as clinical antifungals has led to an escalating exposure to infectious inocula that bear pre-acquired resistance[5]. Moreover, the One Health impact of widely used broad-spectrum agricultural fungicides has been argued to have potentiated the emergence of newly emerging fungal pathogens such as *C. auris*[6].

In response to a systemic lack of engagement with this deepening public-health crisis, the WHO used a multi-step approach to prioritization across the spectrum of global mycoses. After assembling an international expert mycology group, the initial fungal pathogens of concern were selected, without ranking. Systematic reviews related to each pathogen's frequency and antifungal resistance incidence were conducted. Ten semi-quantitative criteria were then agreed as the basis for prioritization including incidence or prevalence of disease caused by that pathogen and its geographic range, mortality, complications after treatment, diagnostic and treatment availability, transmissibility and outbreak potential and antifungal resistance concern. An international discrete choice experiment conducted among more than 300 practitioners and diagnostic laboratorians then ranked each pathogen. This was followed by a best/worst scaling survey of

relative public importance among more than 40 mycology experts to prioritize the same pathogens. These results were merged, and the final ranking produced three groups: fungal pathogens of critical, high and moderate importance.

Deemed of critical importance were *Candida albicans*, *Aspergillus fumigatus*, *C. auris* and *Cryptococcus neoformans*, followed by *Candida glabrata*, *H. capsulatum* and the several fungi causing mucormycosis or mycetoma. *Fusarium* spp., *Candida tropicalis* and *Candida parapsilosis* were deemed to be of high importance. Numerous recommendations flowed from this exercise, highlighting three priority areas for action: surveillance; research and development and innovation; and public-health interventions. Based on the WHO recommendations, strategies to reduce the global burden of fungal diseases include the improved surveillance of fungal diseases, necessitating affordable access to diagnostic tools as close to the patient as possible; targeted support for research and development and innovation to accelerate the implementation of new antifungal drugs and improved diagnostics; and enhanced health systems to secure equitable access to evidence-based therapy, diagnosis, resistance detection and antifungal stewardship.

So why is the WHO FPPL a game-changer? Forewarned is forearmed, and mycological capability in public health and research is sorely lacking in many regions and countries[7]. Global and national policy changes to address the many fungal pathogens of both critical and high importance are called for. Medical, biomedical, pharmacy and public-health training programmes are falling short in their recognition and inclusion of IFDs. By increasing awareness, data and evidence generation should follow, and doing so will show where strategic investment is best targeted. Investment need not be focused on long-distance goals, and public-health gains are readily achievable through more equitable distribution of the existing diagnostics and antifungal armamentarium; for instance, ensuring wider availability of antifungals such as liposomal amphotericin B and flucytosine as well as rapid cryptococcal antigen assays in regions where the burden of HIV–AIDS is highest are essential steps towards tackling the global burden of cryptococcal infection[8].

The potential of research and development to attack and solve pressing problems was shown by the unprecedented speed in developing an mRNA vaccine against SARS-CoV-2 in less than a year. Yet, for every pathogen on the FPPL, the WHO records "No vaccine is available". However, fungal vaccines are achievable and if we can raise a vaccine against the fungus *Pseudogymnoascus destructans* causing white-nose syndrome in bats[9], does the fact that there are no licensed vaccines against human IFDs not underscore a clear failure in biomedical science? Further, where gains have been achieved through the development of new mode-of-action antifungal drugs such as the new antifungal Olorofim active against aspergillosis, the parallel development of agricultural fungicides that target the same biochemical pathway threaten to spin the roulette wheel of environmental resistance another turn[10]. From this perspective, the key contribution of the FPPL may well be to shine a light into those dark neglected corners of health care where IFDs prey, and where this unmet public-health issue urgently needs to be addressed.

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Competing interests

M.C.F. has been paid for talks on behalf of Gilead. D.W.D. and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company that is developing Olorofim, and share options in TFF Pharma. D.W.D. acts or has recently acted as a consultant to Pulmatrix, Pulmocide, Biosergen, TFF Pharmaceuticals, Pfizer, Omega, Novacyt, Rostra Therapeutics, MucPharm and Cipla. D.W.D. sat on the Data and Safety Monitoring Board for a SARS-CoV-2 vaccine trial and chairs a Data Review Committee for Pulmocide. In the past 3 years, D.W.D. has been paid for talks on behalf of Hikma, Gilead, BioRad, Basilea, Mylan and Pfizer. D.W.D. is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group, and recently joined the One World Guideline for Aspergillosis.