

The WHO fungal priority pathogens list: a crucial reappraisal to review the prioritisation

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In October, 2022, WHO published the first fungal priority pathogen list, which categorised 19 fungal entities into three priority groups (critical, high, and medium), for prioritisation of research efforts. The final ranking was determined via multiple criteria decision analysis, considering both research and development needs and perceived public health importance. In this Personal View, we discuss the positioning of the fungal pathogens, namely, *Mucorales*, *Candida* spp, *Histoplasma* spp, *Coccidioides* and *Paracoccidioides* spp, *Fusarium* spp, eumycetoma causative agents, *Talaromyces marneffei*, and *Pneumocystis jirovecii*, while expressing concerns about potential disparities between the WHO fungal priority pathogen list ranking and the actual disease burden associated with these pathogens. Finally, we propose a revised prioritisation list that also considers the regional disparities in the burden of fungal diseases.

Introduction

The rapid, global surge in antibiotic resistance led WHO to release the first bacterial priority pathogen list in 2017, to raise awareness about antimicrobial resistance.¹ In October, 2022, WHO extended this initiative by publishing the first fungal priority pathogen list (FPPL), which used a methodology similar to that used for the bacterial priority pathogen list—a multiple criteria decision analysis approach to guide scientific research efforts on prioritised fungal diseases.^{2,3} This work provides a comprehensive overview of the challenges in fungal disease diagnosis, treatment, and research and development (R&D) goals and presents a list of fungal pathogens categorised into three research priority groups: medium, high, and critical. The process of prioritisation began with systematic reviews and expert opinions, ultimately focusing on 19 fungal pathogens and ten prioritisation criteria (ie, mortality, annual incidence, current global distribution, trends in past 10 years, inpatient care, complications and sequelae, antifungal resistance, preventability, access to diagnostic tests, and evidence-based treatments). Subsequently, intensity levels were established for each criterion and every pathogen (table 1). The final ranking was determined using a combination of discrete choice experiment surveys (which considered R&D needs) and best-worst scaling (which considered perceived public health).

Without denying the crucial value of the WHO FPPL paper, we believe that the priority list described therein does not adequately capture the true burden of some fungal entities and, consequently, the prioritisation that should guide research efforts on these pathogens. In this Personal View, we put forth arguments supporting our concerns about several fungal pathogens and provide a revised list to customise priorities to the region of interest, using WHO regions as a proxy.

Mucorales

Fungi of the order *Mucorales* are part of the high-priority group, with an overall weighted ranking of eight of 19. Despite the growing concern about mucormycosis and a substantial increase in its rate of diagnosis, the real burden

of this disease is yet to be established. Before the COVID-19 pandemic, the incidence of mucormycosis in India was estimated at 140 cases per million of the population, with 195 000 annual cases, approximately 80 times higher than that reported in high-income countries.^{4,5} Following the second wave of COVID-19 in India, there was an unprecedented and worrisome surge in mucormycosis (COVID-19-associated mucormycosis) diagnosis, probably due to the convergence of many predisposing conditions (ie, poor glycaemic control and steroid overuse) in a heavily exposed population.⁶

In India, in view of scarce reliable population-based estimates, a multicentre study found that there was a 2.1-fold increase in mucormycosis diagnosis, from 112 cases in 2019 to 231 cases in 2020, and over 50 000 additional COVID-19-associated mucormycosis cases were reported by November, 2021.^{7–9} Early data suggest a pronounced rise in mucormycosis cases and, with mucormycosis now identified as a notifiable disease in India, more accurate estimates are expected.⁸ The fatality rate for mucormycosis is approximately 38% according to studies performed in India before and during the COVID-19 pandemic, which, in this country alone, could lead to more than 89 000 deaths annually.^{4,10–12} Diabetes, especially with poor glycaemic control, emerges as the primary risk factor for mucormycosis across diverse populations. Before the COVID-19 pandemic, a systematic review of mucormycosis cases mainly from European countries found that 40% of the individuals had diabetes. In India, this percentage was even higher, reaching up to 80% in some observational studies, with a considerable proportion (up to 22%) of individuals with a history of diabetic ketoacidosis.^{4,13} Similar findings were noted in a systematic review of 958 COVID-19-associated mucormycosis cases (80% of patients had diabetes and 10% had diabetic ketoacidosis).¹²

India and the southeast Asia region are witnessing a steady rise in diabetes burden: 74 million cases were reported in India in 2021 (9.6% of the population) and the projections of the International Diabetes Federation indicate a 68% increase in diabetes cases in southeast Asia by 2045. This substantial rise in the predominant risk factor

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For the International Diabetes Federation Diabetes Atlas see
https://www.diabetesatlas.org

	Base R&D rank	Public health rank	Combined rank
Critical-priority group			
<i>Cryptococcus neoformans</i>	10	3	1
<i>Candida auris</i>	8	4	2
<i>Aspergillus fumigatus</i>	14	1	3
<i>Candida albicans</i>	13	2	4
High-priority group			
<i>Nakaseomyces glabratus</i> (<i>Candida glabrata</i>)	6–5	6	5
<i>Histoplasma</i> spp	12	5	6
<i>Eumycetoma</i> causative agents	2	9	7
Mucorales	5	8	8
<i>Fusarium</i> spp	3	14	9
<i>Candida tropicalis</i>	11	10	10
<i>Candida parapsilosis</i>	6–5	13	11
Medium-priority group			
<i>Scedosporium</i> spp	4	18	12
<i>Lomentospora prolificans</i>	1	19	13
<i>Coccidioides</i> spp	16	11	14
<i>Pichia kudriavzevii</i> (<i>Candida krusei</i>)	9	17	15
<i>Cryptococcus gattii</i>	17	12	16
<i>Talaromyces marneffei</i>	15	15	17
<i>Pneumocystis jirovecii</i>	19	7	18
<i>Paracoccidioides</i> spp	18	16	19

R&D=research and development. The fungal pathogens are listed according to the combined rank order and grouped into three priority groups (critical, high, and medium) defined by the WHO fungal priority pathogen list paper.⁷

Table 1: WHO fungal priority pathogen list

for mucormycosis portends a potential surge in mucormycosis cases in India and, possibly, throughout the entire southeast Asia region (for instance, the burden of mucormycosis in Pakistan is one of the highest in the region and worldwide, second only to India).¹⁴ This accumulating evidence, in addition to the diagnostic challenges and uncertainties in treatment strategies, further highlights the possible future burden of mucormycosis on health-care systems, particularly in the southeast Asia region, and underscores the need for robust R&D and heightened public awareness. Thus, we believe that the prioritisation of Mucorales at the same level as some *Candida* species, agents causing eumycetoma, or *Fusarium* spp most likely results in an underestimation of the potential threat posed by Mucorales. Finally, although the declining trajectory of the COVID-19 pandemic and potential advancements in medicine or social welfare might bring down these forecasts, the inadequate access to care in such geographical areas will remain a matter of concern.

Candida spp

Bloodstream infections caused by *Candida* spp affect at least 600 000 people every year, with a mortality rate of 30–40%, even in high-income countries. Cases of invasive candidiasis without a positive blood culture (ie, deep-seated candidiasis) exceed 900 000 every year worldwide.^{15–17} Unlike other pathogens on the list, *Candida* spp have been assigned different priority levels based on the species (table 1). This

categorisation does not appear to accurately reflect the key clinical–epidemiological issues arising because of *Candida* spp in recent years. These discrepancies become more pronounced upon examination of the unique characteristics of different geographical regions, thereby necessitating a more focused approach to the prioritisation of *Candida* spp.

Overall, there are fewer diagnostic and treatment gaps for *Candida* infections than for other fungal infections, except in the case of deep-seated candidiasis; in such cases, the sensitivity of blood cultures is approximately 40% and only 20% of cases with a negative blood culture are assumed to be treated.^{16,18} The proportion of *Candida albicans* infections has progressively declined, compared with that of infections caused by *Candida glabrata* (repositioned as *Nakaseomyces glabratus*) and *Candida parapsilosis*, both of which are placed in a lower priority group than *C albicans* (table 1).^{19,20}

The emergence of antifungal resistance in *Candida* species and nosocomial outbreaks of multidrug-resistant *Candida auris* have markedly contributed to the immense attention that the *Candida* genus receives and its high prioritisation. Despite the adverse potency of *C auris*, a systematic review estimated fewer than 2000 deaths worldwide until October, 2019, with echinocandins usually effective against this species.^{21,22}

C parapsilosis is gaining recognition as a challenging pathogen, with characteristics that justify high prioritisation. *C parapsilosis* is a major cause of life-threatening candidaemia in individuals at high risk, such as those admitted to intensive care units or premature neonates. This pathogen has strong biofilm-production capabilities, which endow it with tolerance to echinocandins. However, the primary concern lies in the progressive spread of fluconazole-resistant strains of *C parapsilosis*, which are capable of initiating hospital-based outbreaks with elevated mortality rates. Controlling these outbreaks demands substantial efforts in terms of infection control.^{20,23} The prevalence of fluconazole resistance in *C parapsilosis* varies widely across geographical regions and health-care facilities, with higher rates observed particularly in southern Europe, South America, and South Africa, where these strains show fluconazole resistance rates exceeding 20%.^{20,23,24} Epidemiological studies of strains from Asia, Europe, and America, have found that the rate of fluconazole resistance is much lower for *N glabratus* (6–12%) and, especially, for *C albicans* (<1%).^{20,24,25} Moreover, evidence also indicates that biomarkers for *Candida* infections, such as serum β -D-glucan, might show a lower sensitivity for candidaemia caused by *C parapsilosis* and *C auris* than for candidaemia caused by other species.²⁶ These attributes elevate the threat level for *C parapsilosis* to a standing similar to that for *C auris*, despite *C auris*' higher priority than that of *C parapsilosis* in the FPPL. Meanwhile, the ranking of *C albicans* most likely overestimates its actual threat.

Histoplasma spp

Histoplasmosis is caused by two different species—*Histoplasma capsulatum* var *capsulatum*, which is considered

endemic to the Ohio and Mississippi river valleys in the USA and to central America and South America; and *H capsulatum* var *duboisii*, which is found only throughout much of Africa, where it overlaps with other *Histoplasma* species. However, for both species, there is increasing evidence to suggest that the exact geographical distribution is largely unknown, with *H capsulatum* var *capsulatum* also widespread in Asia and the Indian subcontinent, and new foci of autochthonous disease observed in North America, Africa, and Europe.^{27–32} A retrospective study conducted in the USA among more than 45 million Medicare beneficiaries between Jan 1, 2007, and Dec 31, 2017, reported 79 749 cases of histoplasmosis in 94% (48 of 51) of the US states, with an incidence of more than 100 cases per 100 000 person-years in 92% (1806 of 1971) of US counties.³³ Moreover, the estimate of 71 450 cases annually for disseminated histoplasmosis in people with AIDS is considered uncertain because of scarce data from Africa and southeast Asia.¹⁶ The inadequate diagnostic capacity in these regions, together with a low clinical index of suspicion, leads to the underdiagnosis and underreporting of histoplasmosis, both among immunocompetent and immunocompromised hosts.^{34–36} For instance, the implementation of *Histoplasma* antigen testing in Brazil led to a 53.8% increase (from 78 cases using classical methods to 120 cases using urinary antigen testing) in the diagnosis of histoplasmosis among people living with HIV.³⁵ Finally, the insufficient access to appropriate antifungal therapies (especially liposomal amphotericin B) in many areas with a high histoplasmosis burden and the poor drugs pipeline for this mycosis call for an upgrade of the ranking for *Histoplasma* spp in the FPPL.

Fusarium spp and eumycetoma causative agents

Infections caused by *Fusarium* spp, especially invasive disease, are uncommon and most individuals affected are highly immunocompromised (especially individuals with prolonged and pronounced neutropenia). A study on patients who underwent haematopoietic stem-cell transplantation found that the incidence rates of infections caused by *Fusarium* spp do not exceed 6% (and are usually much lower, around 1–3%).³⁷ Infections caused by *Fusarium* spp pose a substantially lower global threat than mucormycosis or candidaemia caused by *C parapsilosis*, *N glabratus*, and *Candida tropicalis*, which have been assigned the same priority group, even after considering two factors—first, the optimal treatment strategy for individuals with fusariosis remains unclear because of a scarcity of randomised clinical trials and the fact that patients recover from the infection if they have immune reconstitution; second, the number of patients with predisposing factors to fusariosis will probably increase in the future, due to an increased use of therapy involving depletion of T immunity.³⁷

Eumycetoma is a deep tissue chronic infection with a largely unknown global incidence. Morbidity (but not mortality) associated with eumycetoma is a major concern for the following reasons: low-income and middle-income

countries are the most affected, evidence-based treatment guidelines are scarce for the condition, and relapse after treatment is common. The prioritisation for eumycetoma causative agents in the FPPL is driven by a higher R&D rank, but in our opinion, this ranking is not fully justified if we consider the clinical burden of eumycetoma infections, especially in terms of mortality, compared with those of mucormycosis, histoplasmosis, or candidaemia.³⁸

Coccidioides and Paracoccidioides spp

Coccidioidomycosis is caused by two dimorphic fungi—*Coccidioides immitis*, which is mostly found in California and Arizona, with more recent evidence of its presence in Utah and Washington as well; and the newly designated *Coccidioides posadasii*, which is distributed not only in the southwestern states of the USA but also in parts of central America and South America.^{39–41} Climate change appears to be an important cause for the expansion of the endemic areas of coccidioidomycosis observed in the USA.^{42,43} However, the geographical distribution of coccidioidomycosis is far from exhaustive, since it is not a notifiable disease yet in 24 US states and in Latin America (except Argentina). Although previous estimates of coccidioidomycosis in the USA are of approximately 150 000 new annual infections,⁴⁴ there is evidence of an eight-fold increase in incidence (from 5.3 to 42.6 cases per 100 000) in a timeframe of 14 years (1998–2011).⁴⁵ Moreover, data from Medicare recipients in the USA showed that 40% (339 of 839) of the counties had an incidence of more than 100 cases per 100 000 person-years with a total of 37 726 cases.³³ Finally, the latest estimates (2019–21) indicate a total annual incidence of 30 043 severe forms of coccidioidomycosis in the Americas, with 2042 annual deaths.¹⁶ In the case of paracoccidioidomycosis, a neglected systemic fungal infection endemic to some countries in South America (Brazil, Argentina, Colombia, Ecuador, Venezuela, Paraguay, Bolivia, and Peru) and central America (Mexico) that affects mainly rural workers,^{46,47} a recent survey points to poor availability of diagnostic tools.⁴⁸ Of late, owing to molecular studies, the classic taxonomic classification of *Paracoccidioides*, which considered *Paracoccidioides brasiliensis* as the unique species responsible for human disease, has been changed by including numerous cryptic species (*Paracoccidioides loboii*, *Paracoccidioides americana*, *Paracoccidioides lutzii*, *Paracoccidioides venezuelensis*, *Paracoccidioides restrepiensis*, and *Paracoccidioides cetii*).⁴⁹ This change complicates the diagnosis of paracoccidioidomycosis, since two of these species are uncultivable (*P loboii* and *P cetii*) and the considerable genetic differences among these species have major implications for the serological diagnosis of the disease.^{47–50} In Brazil, which reports 80% of the paracoccidioidomycosis cases in Latin America, the incidence of the disease is 9–40 cases per 100 000 inhabitants in hyperendemic areas; however, once again, paracoccidioidomycosis is not a notifiable disease in the Americas, which hinders an estimation of the actual magnitude of its epidemiology. Although paracoccidioidomycosis-related mortality is generally low

(average annual mortality rate=1.45 deaths per million inhabitants), the disease frequently occurs in a chronic form characterised by clinical sequelae in almost 50% of the affected individuals (despite treatment) and late relapse that can be observed even 5 years after an apparent cure.⁴⁷

Lomentospora prolificans and *Scedosporium* spp are rare moulds associated with invasive fungal infections in immunocompromised hosts, known to trigger nosocomial outbreaks from ambient air contamination.⁵¹ In terms of the incidence and mortality rate, both coccidioidomycosis and paracoccidioidomycosis surpass the (scant) statistics of diseases caused by *L. prolificans* and *Scedosporium* spp, whose ranking is strongly biased by their R&D rank (first position for *L. prolificans* and fourth position for *Scedosporium* spp); nonetheless, the public health perception for *L. prolificans* and *Scedosporium* spp is the lowest among all fungal pathogens (table 1). The major knowledge gaps in terms of the epidemiology, diagnosis, and treatment of infections by *L. prolificans* and *Scedosporium* spp has probably driven their evaluation in the FPPL, resulting in an inappropriate final ranking, to the disadvantage of *Coccidioides* spp (fourteenth position) and *Paracoccidioides* spp (which close the list), and the other pathogens in the medium-priority group.

Talaromyces marneffei

T. marneffei, a dimorphic fungus endemic to southeast Asia, southern China, India, and Indonesia, poses a substantial threat in individuals with cellular immunity defects (eg, people living with HIV and individuals undergoing transplantation).⁵² Although the exact incidence rates are unknown, in endemic countries, more than 17 000 cases of *T. marneffei* infections are expected to be diagnosed among people living with HIV each year, with exceedingly high mortality (up to one-third of the affected patients).^{53,54} In China, in 2019, the number of people living with HIV was estimated to be 784 000, of whom 60% were not receiving antiretroviral therapy and 4951 had talaromycosis (with 3163 cases in 12 provinces).⁵⁵ However, estimates indicate that 23 117 cases of HIV-associated *T. marneffei* infections will be diagnosed in China by 2050. Moreover, in China, talaromycosis mortality rate doubles when the diagnosis is delayed, reaching 100% when the diagnosis is missed.⁵⁶ In a review published in 2018, *T. marneffei* has been ranked as the third-most feared fungal infection in the world, but in the WHO FPPL, this dimorphic fungus is considered of medium priority, occupying the third-last position in the ranking, with a low score for both R&D needs and perceived public health importance. This ranking does not fulfil the expectations of scientists who had advocated for the recognition of talaromycosis as a neglected tropical disease,^{56,57} especially when compared with that for *Scedosporium* spp, which, as observed in the case of *L. prolificans*, is mainly driven by a disproportionately high rank for R&D needs and low rank for public health perception. Among the various unmet needs of talaromycosis, the microbiological culture-based diagnosis (mainly blood culture) takes up to 14 days

for identification of the fungus, and still misses up to 50% of infections.⁵² Therefore, there is an urgent need for rapid, accurate, and affordable point-of-care tests to facilitate early initiation of treatment.⁵⁸ Though talaromycosis has not received the recognition it deserves in the WHO FPPL ranking, its inclusion in the list itself will hopefully call attention to the impact of this fungal disease in southeast Asia and drive research efforts to fill knowledge gaps.

Cryptococcus spp

The two main species of the cryptococcal complex (*Cryptococcus neoformans* and *Cryptococcus gattii*) have been assigned completely different priority levels (table 1). The cryptococcal disease caused by *C. neoformans* is one of the most common opportunistic infections in people living with HIV at an advanced stage of infection, resulting in marked morbidity (152 000 cases of cryptococcal meningitis) and mortality (112 000 cryptococcus-related deaths) in 2020.⁵⁹ Moreover, approximately 48 000 cases of cryptococcal meningitis are estimated to occur annually among either individuals with immunodeficiency unrelated to HIV (26 693) or people with no underlying diseases (21 280).¹⁶ *C. gattii* was traditionally considered endemic only to Australia and Papua New Guinea and tropical areas of Africa and South America.⁶⁰ However, this assumption was dismissed when an outbreak of cryptococcal meningitis that started in the early 2000s on Vancouver Island subsequently spread to mainland BC and the Pacific northwest region of the USA.^{60,61} The identification of the presence of the six distinct lineages (VGI–VGVI) within the *C. gattii* complex on nearly all continents, including Asia and Europe, although with different degrees of pathogenicity, highlights the need for enhanced knowledge about this largely neglected fungal complex.⁶² Although the mortality rate attributed to *C. gattii* (10–43%) is lower than that of *C. neoformans* (20–61% in people living with HIV and 8–50% in non-HIV), neurological sequelae and immune reconstitution inflammatory syndrome are more frequently observed with *C. gattii*.⁶¹ For all the reasons mentioned above, we believe that *C. gattii* should be listed at least as a high-priority pathogen.

Pneumocystis jirovecii

P. jirovecii was ranked as a medium-priority pathogen in the WHO FPPL, just before *Paracoccidioides* spp, considering that the drugs for the prophylaxis and treatment of *P. jirovecii* have been available for more than 40 years. Although people living with HIV were disproportionately affected in the past, *P. jirovecii* pneumonia has in the past few years emerged as an important opportunistic infection among different populations of immunocompromised hosts (especially kidney transplant recipients and those affected by vasculitis).^{63–65} According to estimates, *P. jirovecii* pneumonia accounts for over 500 000 cases annually (400 000 in people living with HIV and 105 000 in other non-HIV-infected immunocompromised individuals), with an attributable 126 000 deaths

in people living with HIV and 49 000 deaths in immuno-compromised individuals.¹⁶ Besides this high morbidity and mortality burden, important gaps have been noticed in terms of treatment, prophylaxis, and diagnosis of *P jirovecii* pneumonia, with the gaps in treatment including the optimal therapeutic strategy for severe disease; best second-line agent in case of failure or toxicity of trimethoprim–sulfamethoxazole; role of adjunctive echinocandins; and the role of steroids (dexamethasone and hydrocortisone) other than prednisone.^{66–71} In our opinion, the factors described above advocate an upgradation in the prioritisation of this fungus.

Proposal for the improvement of the WHO FPPL

The WHO FPPL marks an inaugural global initiative for the systematic prioritisation of fungal pathogens, with an aim to guide research efforts. Though designed to be globally applicable, the list does not take into consideration the diverse nature of fungal infections and non-uniform distribution of pathogenic fungi. In recognition of the fact that prioritisation can vary by geographical region, our proposal is to customise priorities to the region of interest, possibly using WHO regions as a proxy to upgrade or downgrade the ranking of the pathogens, while considering FPPL as a starting point (table 2).

Global prioritisation

In our proposal, four major pathogens deserve crucial prioritisation in all WHO regions. The first, cryptococci, have a clear rationale for prioritisation, in view of the substantial attributable mortality, effect on immunocompromised hosts (not restricted to people living with HIV and individuals with AIDS), and treatment-related challenges (availability and cost of liposomal amphotericin, toxicity, and treatment duration). The second, *Aspergillus* spp, deserves the highest prioritisation level, considering that, apart from its widespread distribution and the growing concern of azole resistance, recent estimates of the burden of invasive fungal infections highlight invasive aspergillosis as the leading fungal infection in terms of mortality, followed by chronic pulmonary aspergillosis.¹⁶ We also advocate prioritising the third pathogen *Candida* spp as a whole, regardless of the species, given the substantial burden of invasive candidiasis (ranked as the third leading cause of deaths from fungal diseases) and the emergence of antifungal resistance in some species, particularly *C auris* and *C parapsilosis*.¹⁶ We firmly believe that the fourth pathogen, *P jirovecii*, merits a substantially higher level of prioritisation on a global scale, based not only on the disease burden but also the evolving epidemiology (which is causing a progressive increase in the population at risk) and treatment-related challenges discussed earlier (table 2).

High-priority group stratified by WHO regions

Five fungal pathogens should be placed in the high-priority group, with notable distinctions to be emphasised based on the different WHO regions.

	Regional prioritisation
Critical-priority group	
<i>Aspergillus fumigatus</i>	Global
<i>Candida</i> spp	Global
<i>Pneumocystis jirovecii</i>	Global
<i>Cryptococcus neoformans</i>	Global
High-priority group	
<i>Histoplasma</i> spp	Americas, Africa
Mucorales	South-East Asia
<i>Coccidioides</i> spp	Americas
<i>Paracoccidioides</i> spp	Americas
<i>Talaromyces marneffei</i>	South-East Asia, Western Pacific
<i>Cryptococcus gattii</i>	Americas, Africa, Western Pacific, South-East Asia
Medium-priority group	
<i>Scedosporium</i> spp	Global
<i>Eumycetozoa</i> causative agents	Global
<i>Fusarium</i> spp	Global
<i>Lomentospora prolificans</i>	Global
The fungal pathogens are grouped into three priority groups (critical, high, and medium) and, for each fungal entity, a revised prioritisation has been reported according to geographical region. Pathogens within the same priority levels are presented in no specific order.	
Table 2: Revised fungal priority pathogen list	

Coccidioidomycosis and paracoccidioidomycosis might be viewed as minor concerns on a global scale. However, the placement of *Coccidioides* and *Paracoccidioides* spp in the medium-priority group and at a lower ranking than that of *L. prolificans* and *Scedosporium* spp should be reviewed, particularly when accounting for the region of the Americas, where *Coccidioides* and *Paracoccidioides* spp should be regarded at least as high-priority pathogens.

Mucorales present a substantial threat in the South-East Asia and Eastern Mediterranean regions, warranting their consideration as critical-priority pathogens. In other regions, however, especially Europe, the prioritisation level for Mucorales should be relatively lower, particularly when compared with that for specific *Candida* species (*N. glabratus*, *C. tropicalis*, and *C. parapsilosis*), which are classified in the same high-priority group in the FPPL.

Although the disease burden of histoplasmosis remains unclear, the region of the Americas and Africa act as substantial reservoirs for this disease. Consequently, at least in these regions, the priority level of *Histoplasma* spp should be higher, as compared with that for Mucorales and other pathogens in the high-priority group (excluding *Candida* spp, as stated earlier).

The main geographical areas of distribution reported for *T. marneffei* include the South-East Asia and Western Pacific regions. The seventeenth position of *T. marneffei* in the ranking (medium priority) does not reflect the true burden of talaromycosis in these regions and the availability of accurate diagnostics. We advocate a higher prioritisation for *T. marneffei* than for other pathogens in the group (except pneumocystosis and *Candida* spp) and at least some

pathogens in the high-priority group (such as *Fusarium* spp and eumycetoma causative agents; table 2).

Medium-priority group

The four fungal pathogens, namely, *Scedosporium* spp, *L. prolificans*, eumycetoma causative agents, and *Fusarium* spp, which have a substantially lower disease burden than the other fungal pathogens on the list, should be moved to the medium-priority group. Although global R&D efforts should still aim to address the considerable gaps in knowledge about the associated fungal diseases, a lower prioritisation would be adequate.

Conclusions

According to the review authored by Denning, in 2024,¹⁶ the updated estimates for invasive fungal infections stand at 6.5 million cases and 2.5 million attributable deaths annually. Despite this estimate, the global burden of fungal infections is still not well defined, and many crucial gaps persist in the data, which can be mainly attributed to the scarce surveillance systems in specific regions and for particular fungal diseases. Even with the numerous gaps in diagnosis and treatment, fungal infections continue to receive insufficient attention, highlighting the need for more focused research initiatives to fill these gaps.

The FPPL, a global collaborative effort, aims to raise awareness about the current and future impact of specific fungal diseases to drive global research. This list globally ranks the fungal pathogens according to priority, without considering the need to customise this prioritisation based on geographical regions. Though the list reflects the real burden of some fungal entities (cryptococci or *Aspergillus fumigatus*), it probably overlooks the actual threat of other pathogens in some regions (Mucorales in southeast Asia and *Coccidioides* or *Histoplasma* spp in the region of Americas). Importantly, the conventional geographical boundaries of endemic mycoses are evolving. At least 10% of these infections are now diagnosed beyond their customary geographical regions, and intensified efforts could further elevate the diagnosis rate. Notably, travel or migration also contribute to fungal pathogens transcending conventional geographical boundaries.^{33,72}

The intrinsic limitations of the multiple criteria decision analysis methodology might have influenced the final rankings, specifically the low capacity to consider the substantial variability of fungal diseases in terms of epidemiology, diagnostics, and treatment. This shortfall possibly underestimated some aspects, such as the burden of *T. marneffei* and expanding epidemiology of histoplasmosis or coccidioidomycosis, while simultaneously overestimating other factors, such as the global burden of *L. prolificans*. Moreover, the ranking of the pathogens might have been biased by the geographical background of the survey participants, particularly in terms of public health perceptions. Despite this potential bias, the authors state that they have made efforts to ensure geographical representativeness among the respondents. Lastly, in the discrete

choice experiment surveys conducted for R&D, antifungal resistance as a criterion received the highest importance. Although the growing antifungal resistance presents a substantial threat to public health, its effect on the treatment of fungal infections is not currently comparable to the adverse effects of antibiotic resistance on the treatment of bacterial infections. An estimated 4.95 million deaths associated with bacterial infections occurred in 2019, of which 1.27 million could be attributed to antibiotic resistance, whereas close to 4 million people die each year because of fungal infections; however, the exact contribution of antifungal resistance to this death rate remains unknown.^{15,73}

The worldwide emphasis on antimicrobial resistance might have considerably influenced the panel experts of the FPPL to designate antifungal resistance as the highest prioritised criterion, surpassing mortality, incidence, access to diagnostics, and other criteria listed in the FPPL document. Consequently, the ultimate ranking of some fungi that show high levels of resistance (ie, *L. prolificans*, *Fusarium* spp, and *Scedosporium* spp) was notably skewed due to their high R&D ranking, potentially overlooking their public health significance and disease burden. This observation might also clarify why fungi that generally show low levels of resistance (such as *T. marneffei*, *Paracoccidioides* spp, and *Coccidioides* spp) received a lower R&D ranking, despite the need for enhanced research efforts to control and prevent the associated fungal infections.

Contributors

SA conceptualised the Personal View. GC wrote the original draft. SA and GC did the literature research. SA and AG critically reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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