Fungal infections 8

Improvement of fungal disease identification and management: combined health systems and public health approaches

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More than 1·6 million people are estimated to die of fungal diseases each year, and about a billion people have cutaneous fungal infections. Fungal disease diagnosis requires a high level of clinical suspicion and specialised laboratory testing, in addition to culture, histopathology, and imaging expertise. Physicians with varied specialist training might see patients with fungal disease, yet it might remain unrecognised. Antifungal treatment is more complex than treatment for bacterial or most viral infections, and drug interactions are particularly problematic. Health systems linking diagnostic facilities with therapeutic expertise are typically fragmented, with major elements missing in thousands of secondary care and hospital settings globally. In this paper, the last in a Series of eight papers, we describe these limitations and share responses involving a combined health systems and public health framework illustrated through country examples from Mozambique, Kenya, India, and South Africa. We suggest a mainstreaming approach including greater integration of fungal diseases into existing HIV infection, tuberculosis infection, diabetes, chronic respiratory disease, and blindness health programmes; provision of enhanced laboratory capacity to detect fungal diseases with associated surveillance systems; procurement and distribution of low-cost, high-quality antifungal medicines; and concomitant integration of fungal disease into training of the health workforce.

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Introduction

Recent estimates of the burden of fungal diseases in low-income and middle-income countries, estimated by the Global Action Fund for Fungal Infections (GAFFI),[1] far exceed the current capacity of such countries to manage the burden. Such management would include identification of those at risk of or currently with a suspected fungal disease, accurate diagnosis of fungal diseases with use of appropriate tools in equipped laboratories, and treatment of patients with indicated and readily available antifungal agents to reduce morbidity and mortality associated with fungal diseases. Because the population at risk for fungal diseases is increasing, new fungal diseases and new at-risk groups, including those with novel genetic defects, are being discovered.

Neglected tropical diseases such as mycetoma and chromoblastomycosis are largely restricted to endemic tropical and subtropical countries and cause a progressive chronic disfiguring disease in a relatively stable population of healthy and active adults. People infected with HIV who are at an advanced stage (ie, CD4 T lymphocyte count <200 cells per µL) and who are either antiretroviral therapy (ART)-naive or ART-experienced but lost to follow-up, or with virological failure, are at highest risk of opportunistic invasive fungal infections (IFIs). These opportunistic infections include cryptococcal meningitis, pneumocystis pneumonia, histoplasmosis, *Talaromyces marneffei* infection, and emerging mycoses such as emmonsiosis and pythiosis.[2–5] Sub-Saharan Africa and southeast Asia have the highest burden of AIDS-associated opportunistic infections.[5,6] In low-income countries, the burden of chronic pulmonary aspergillosis closely tracks that of tuberculosis. Opportunistic health-care-associated infections such as candidaemia and invasive aspergillosis, by contrast, are not geographically restricted, occurring where resources exist to aggressively manage critically ill patients in

Key messages

- Estimates of the true burden of fungal diseases in low-income and middle-income countries made by the Global Action Fund for Fungal Infections exceed the current capacity of such countries to manage the burden
- Inadequate patient and clinician awareness, paucity of trained clinicians, low index of diagnostic suspicion, insufficient laboratory identification capacity (paired with poor access to diagnostic tools), and few treatment options all drive under-recognition of the true burden of fungal diseases
- Under-recognition of the burden of fungal diseases leads to decreased resource allocation for diagnosis, surveillance, outbreak response, epidemiological study, and control of fungal diseases
- Public health responses to fungal disease are rare, primarily concerned with outbreaks and, more recently, cryptococcal meningitis in patients with AIDS and mycetoma
- No recognised international authority on public health mycology is responsible for surveillance system design, coordinated outbreak response, or international guideline development
- Particular fungal diseases become a focus only in relation to already recognised diseases, such as HIV infection and tuberculosis
- There are a range of recognised resources in low-income, middle-income, and high-income countries that can support national public health capacity
- We suggest a mainstreaming approach including: greater integration of fungal diseases into existing public health initiatives and programmes for HIV infection, tuberculosis, antimicrobial resistance, diabetes, chronic respiratory disease, and blindness; provision of enhanced laboratory capacity to detect fungal diseases with associated surveillance systems; procurement and distribution of low-cost, high-quality antifungal medicines; and concomitant integration of fungal disease into training of the health workforce (including physicians, nurses, laboratory technicians and scientists, and pharmacists)

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This is the eighth in a Series of eight papers about fungal infections

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intensive care units and in those with cancer with chemotherapy and transplants. The overall incidence of these health-care-associated infections, such as candidaemia, has been reported to be higher in low-income and middle-income countries than in high-income countries, possibly due to inadequate resources for infection prevention and control and antimicrobial stewardship.[7]

Despite the overwhelming need in low-income and middle-income countries, a fundamental challenge exists. Inadequate patient and clinician awareness, paucity of trained clinicians and substantial patient loads, a low index of diagnostic suspicion, insufficient laboratory identification capacity (paired with poor access to diagnostic tools), and few treatment options all drive under-recognition of the burden of fungal diseases (figure 1; appendix pp 1–8).

These limitations in awareness, diagnosis, and management stem from deficits of the health system in education, provision, and infrastructure. Consequently, under-recognition of the burden of fungal diseases leads to reduced resource allocation for surveillance, outbreak response, epidemiological study, and control of fungal diseases. Public health responses to fungal disease are hence rare, primarily concerned with outbreaks and, more recently, cryptococcal meningitis in patients with AIDS. To address this challenge of under-recognition, joint improvements in health system and public health capacities are required.

A line of action to this challenge would build on WHO's approach to health systems strengthening (panel).[8]

However, because WHO, governments, non-governmental organisations, and funding agencies are not ready to place a priority on fungal diseases with separate programmes and financing for low-income and middle-income countries at this stage, we suggest a mainstreaming approach of greater integration of fungal diseases into existing health programmes (HIV-associated opportunistic fungal infections within care and treatment programmes for HIV infection, chronic pulmonary aspergillosis within tuberculosis control or chronic respiratory disease programmes,[9] aspergillus and candida acquired resistance within antimicrobial resistance and antimicrobial stewardship functions, fungal keratitis within blindness control programmes, and mycetoma and chromoblastomycosis within the WHO Neglected Tropical Disease Programme); complementary resource development and provision to support such integration (enhanced capacity for mycology laboratories to detect fungal diseases, enhanced systems for research and development and for procurement, and distribution of low-cost, high-quality antifungal medicines); and concomitant integration of fungal disease into training of the health workforce.

In this Series paper, we combine an assessment of the current state of identification and management of fungal diseases, provide a description of promising initiatives that are specific for fungal diseases in selected low-income and middle-income countries using a systems approach, and identify potential avenues for development to bolster health-care and public health capacities in national health systems with international support.

Figure 1: **Emergency medical ward of Postgraduate Institute of Medical Education and Research, Chandigarh, India, showing that patient load is more than its capacity**

Health system components

Diagnostic laboratory capacity

Diagnostic capacity is a cornerstone of the health-care system; however, laboratories offering front-line diagnostic assays can struggle with a burden of bacteriological specimen workflow, inadequate resources or training, and poor retention of skilled staff. Other barriers can exist to the use of such diagnostic laboratories: a perception by physicians that tests are unreliable, the high cost of laboratory tests, and the need for patients to self-fund tests. A higher standard of fungal disease diagnosis would be best achieved by combining clinical and microbiological expertise of mycology with a comprehensive laboratory testing portfolio. Unfortunately, economies of scale often drive a concentration of laboratory capacity and clinical expertise towards large and urban centres, creating service gaps in diagnostic capacity at general microbiology laboratories at district hospitals, where they are truly needed. Hence, we envisage a staged sequence of laboratories at various levels of the health system with growing mycology expertise and diagnostic test capacity (table). The first two levels are split in recognition that reliable electricity supply is more common for laboratories in middle-income countries.

In the laboratory, the greatest diagnostic gains in speed and accuracy come from direct testing of specimens. Direct microscopy with staining of potassium hydroxide preparation and point-of-care antigen, antibody, and

nucleic acid detection are usually faster than culture. There are three commercially available point-of-care tests currently for detection of cryptococcal or aspergillus antigen. A histoplasma antigen point-of-care test is in clinical development, and other point-of-care tests, particularly for pneumocystis pneumonia and candida, are needed. Galactomannan antigen testing is a useful biomarker of disseminated histoplasmosis in patients infected with HIV (sensitivity 77%),[10] and aspergillus galactomannan antigen testing is now used in hundreds of centres across the world although not available in many countries with large populations of patients with cancer, in critical care, and with complex respiratory tract problems. Partnerships with industry can facilitate access to simple accurate fungal diagnostics. For example, one pharmaceutical company recognised that missed and late diagnosis of invasive aspergillosis was the biggest limitation to adequate treatment, and so provided seed money and training opportunities to increase access to aspergillus antigen testing in selected middle-income and high-income countries. Many countries and most other technologies have not benefited from such direct support.

Culturing of specimens is an important technique for diagnosis of skin, mucosal, and some systemic fungal diseases, because it allows definitive identification of the infecting fungus and susceptibility testing. However, this technique requires careful sample handling, laborious preparation, and identification training to avoid inadequate sensitivity—eg, up to 60% of cases of candidaemia might be missed on blood culture. Matrix assisted laser desorption and ionisation–time of flight with a good database is an alternative rapid diagnostic technique for identifying yeasts and some filamentous fungi. Histopathology expertise allows definition of the tissue response to a fungal infection and might be able to identify the causative pathogen to some accuracy, supported by molecular identification of unusual fungi directly from tissue.[10] Laboratories that can do Xpert MTB/RIF (Cepheid, Sunnyvale, USA) tests for tuberculosis are likely to have the expertise to work with other commercial PCR tests, including the systems currently available for pneumocystis, aspergillus, and candida detection, although further standardisation work is needed.

A mycology reference laboratory, as an integral part of the clinical laboratory network, should ideally be present for every 5–10 million people. Within the few that exist in low-income and middle-income countries, the mycology reference laboratory in Chandigarh in northern India is a WHO collaborating centre, and another in Sudan is a clinical centre focused on diagnosis and treatment of the subcutaneous fungal disease mycetoma. Such reference laboratories (figure 2) should be accredited to the internationally recognised standard ISO 15189: 2012 for medical laboratories, participating in external quality assessment.[11] Their key functions (table) include offering specialised diagnostic assays for other laboratories, holding a fungal culture collection, confirming identification and antifungal susceptibility results of unusual fungal isolates, providing technical assistance with proficiency testing schemes, offering training (as per Mozambique's efforts), and evaluating existing and novel diagnostic assays. The South African National Institute for Communicable Diseases (NICD), which does all the reference laboratory functions listed above, also runs a microbiology proficiency testing scheme, which includes fungal isolates and simulated cerebrospinal fluid or blood samples for cryptococcal antigen testing, for the WHO African Region for several years.[11]

***Panel:* Example interventions for dealing with fungal diseases in national health systems**

Medical products and technologies
- Selectively deploy feasible fungal disease diagnostics
- Develop monitoring capacity for antifungal resistance

Human resources
- Incorporate instructions for fungal diseases into existing programmes and training of clinicians (eg, physicians, nurses, microbiologists, and pharmacists)
- Develop laboratory personnel expertise in diagnostics
- Incorporate fungal disease burden, outbreaks, and screening programme issues (ie, cryptococcal meningitis and antifungal resistance); and laboratory strengthening (antimicrobial resistance control and reducing deaths) into public health education

Service delivery
- Adapt clinical guidelines to national circumstances, engaging clinicians at different levels of the health system
- Strengthen secondary care—ie, fungal reference diagnostic laboratory and teaching hospital linkages
- Implement auditing of processes and outcomes

Financing
- Provide coverage of fungal disease diagnostics
- Access support for antifungals on the WHO Model Lists of Essential Medicines
- Mobilise funding for mycetoma and chromoblastomycosis treatment as neglected tropical diseases

Information
- Establish regional reference centres for referral, diagnosis, resistance monitoring, and reporting
- Mount fungal disease surveillance within existing priority programmes—eg, chronic pulmonary aspergillosis within a tuberculosis control programme
- Establish outbreak response capacity

Governance
- Organise an advocacy group for citizens affected by fungal diseases and concerned professionals
- Develop regional or continental quality assurance programmes for mycology
- Accredit national mycology reference laboratories

This panel was adapted from information in De Sevigny and Adam (2009).[8]

Clinical expertise

Medical personnel

Strong relationships with clinicians greatly strengthen the laboratory's effectiveness and the quality of patient care; however, clinical expertise in fungal infection and

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See Online for appendix

	Level 1 microbiology laboratory (eg, district, state, and provincial hospital)	Level 2 microbiology laboratory (eg, centres handling specialised patients or national services)	Level 3 reference mycology laboratory
Low-income country	Point of care in high-burden areas (eg, CrAg LFA); and microscopy, including India ink staining if CrAg LFA is unavailable	Culture and identification of common fungal pathogens (yeasts and moulds); antifungal susceptibility testing for yeasts; aspergillus serology for CPA; serological tests for antigens and antibodies of common endemic mycoses in endemic areas (eg, histoplasmosis); and IgE serology for fungal asthma	Identification of unusual fungi to species level by molecular techniques (eg, MALDI* and sequencing); all specialised tests (serological and molecular) requiring expert capacities, including PCR; laboratory diagnosis of low prevalence mycoses (eg, endemic mycoses in non-endemic areas or imported cases); molecular typing techniques for outbreak investigation; antifungal susceptibility testing of moulds; confirmation of AST of yeast showing unusual patterns of antifungal resistance; molecular resistance detection; culture collection; national standards and quality control programme, along with participation in international programmes; surveillance programmes in conjunction with epidemiologists; and training programme
Middle-income country	Aspergillus serology for CPA; culture of skin (dermatophytes) and mucosal (oral and vaginal) samples; and culture of yeasts and ability to differentiate *Candida albicans* from other *Candida* spp	Therapeutic drug monitoring; fluorescent microscopy with optical brightener (eg, tuberculosis laboratory) and other specialised fungal stains; β-1,3-D-glucan for suspected invasive candidiasis in high-volume laboratory; and galactomannan tests for aspergillus infection	Linked diagnostic capabilities for level 3 reference mycology laboratories are the same for middle-income and low-income countries

*MALDI-TOF for species-level identification of filamentous and yeast-like fungi based on analysis of the protein signature of an organism. CrAg LFA=cryptococcal antigen lateral flow assay. CPA=chronic pulmonary aspergillosis. MALDI=matrix-assisted laser desorption and ionisation. TOF=time of flight. AST=antimicrobial susceptibility testing.

Table: **Linked laboratory diagnostic capabilities, by level of health system, and by country income level**

Figure 2: **Partial view of a mycology laboratory at the Microbiology Department, Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique**

allergy is often rare with many doctors knowing little about the diagnosis and management of fungal diseases, reflecting inadequate medical undergraduate education, scarcity of fungal disease topics in postgraduate courses or continuing professional education activities, and use of traditional versus more active pedagogical approaches fostering practical skills. The spectrum of fungal diseases is broad and depending on their area of practice, doctors require different levels of knowledge. Front-line doctors working in secondary care or hospital emergency rooms need to know enough to order key tests and, if available, refer patients at risk of serious fungal infections for further specialist care. In larger outpatient and hospital settings, several medical specialties might be involved, requiring intensified and sustained efforts to educate a range of doctors about suspicion of fungal infection within differential diagnoses in parallel with provision of necessary diagnostic assays, adequate support from radiologists with expertise in examination of the chest, brain, and sinuses, and treatment options.

IFIs are not usually empirically treated outside haematology and critical care units, and they will usually require laboratory confirmation. Patients infected with HIV and pneumocystis pneumonia are often treated empirically without recourse to laboratory testing, partly because of the challenge of assessing colonisation versus disease and partly because of inadequate availability of accurate confirmatory assays, such as PCR and immunofluorescent microscopy. The implication of a positive or negative test in steering clinicians to start or stop antifungal therapy is profound, as long as the result is provided in a timely fashion. The toxicity of some antifungal agents, drug–drug interactions, and prohibitive costs are all inhibitory to empirical therapy in many settings, leaving some patients undertreated for so long that they deteriorate or die, or both.

There is also a case to be made for integrating fungal diagnostics into global antimicrobial resistance reduction efforts. Patients, in whom a positive diagnosis of fungal disease can be made, can often stop antibacterial therapy. A good example of this scenario, needing research validation, is sputum smear-negative pulmonary tuberculosis, for which patients are often treated unnecessarily with antituberculous therapy while pneumocystis pneumonia, chronic pulmonary aspergillosis, cryptococcosis, blastomycosis, histoplasmosis, or coccidioidomycosis might go undiagnosed. Another example is invasive candidaemia in critically ill patients, which if positively diagnosed allows only antifungal therapy to be given and, if excluded, with use of newer diagnostic assays with an excellent negative

predictive value, can allow antifungal therapy to be stopped.[12] Informed risk assessment by clinicians, early suspicion of fungal disease, and accurate and fast diagnosis are key to improving outcomes and reducing unnecessary therapy.

Nursing personnel

Many experienced nurses with excellent clinical skills contribute substantially to the management of fungal infections in the context of complex underlying problems. For example, in South Africa, the diagnosis and management of cryptococcal disease will shift from hospital to primary health-care level with screening for cryptococcal antigenaemia in patients with advanced HIV infection. In this setting, nurses who are trained to initiate ART will also be required to act on a positive test result for cryptococcal antigenaemia, and will need to be trained to know when to up-refer patients for specialist care. Furthermore, many infection prevention and control practitioners are nurses and have a crucial role in monitoring, identifying, and controlling outbreaks of fungal infections in high-risk settings, such as intensive care, renal dialysis, and central venous catheter care for reducing bloodstream candida infections.[13] A third group is nurses in respiratory medicine for asthma and tuberculosis. Recognition that patients are struggling despite adequate therapy will prompt consideration of fungal complications and appropriate testing.

Pharmaceutical use

Diagnostic capacity without the means of treatment is problematic. Although several antifungal agents are on the WHO Model Lists of Essential Medicines, financing, procurement, and distribution remain a challenge in many low-income and middle-income countries (as seen in the maps of antifungal drug availability and local price).[1,14] Effective agents might be particularly scarce at the level of secondary care compared with tertiary care. Existing antifungal compounds also have disadvantages: fungistatic rather than fungicidal activity (eg, fluconazole, although itraconazole is fungicidal for histoplasma and some isolates of aspergillus), need for intravenous administration (amphotericin B and echinocandins), very high costs (lipid formulations of amphotericin B), drug–drug interactions (azoles), toxic effects (conventional amphotericin B and voriconazole), and a low threshold for antifungal resistance (flucytosine). Only a modest number of antifungal compounds are in the research and development pipeline,[15] and only one for cryptococcal disease.

Pharmacist expertise

Drug–drug interactions can be a particular problem for antifungal agents. Pharmacists can guide clinicians in mitigating toxic effects and increasing effectiveness via well informed usage of antifungals. Therapeutic monitoring is useful for itraconazole, voriconazole, fluconazole, and flucytosine to reduce liver and kidney dysfunction, but it is not widely available, especially in low-income and middle-income countries. An international proficiency testing programme is available.[16] Electronic resources for pharmacists and health-care professionals can allow antifungal and HIV drug interactions to be checked online or as a smartphone application at the point of prescription or dispensing.[17] The introduction of an expert training curriculum in the UK for specialised antimicrobial pharmacists, which includes antifungal expertise, will support these professionals in delivering antimicrobial stewardship and assist in reducing antimicrobial resistance.[18] Fungal disease training with adequate laboratory capacity could be done along such antimicrobial stewardship initiatives.[19]

For more on **the electronic resource of aspergillus** see http://www.aspergillus.org.uk/content/antifungal-drug-interactions

Addressing antifungal resistance

Mitigation of antifungal resistance with stewardship is a growing need.[20] Examples of fungi intrinsically resistant to certain antifungals include *Aspergillus terreus* to amphotericin B, *Candida krusei* to fluconazole, and *Cryptococcus* spp to the echinocandins. Investigators of an Indian study[21] found that 12% of *Candida* spp (among them *Candida tropicalis* [41·6%], followed by *Candida albicans* [20·9%] and *Candida parapsilosis* [10·9%]) were resistant to fluconazole, similar to China,[22] whereas investigators in South Africa[23] found dominance of azole-resistant *C parapsilosis* causing candidaemia, an unusual epidemiological finding. In clinical or environmental samples, multi-azole resistance in aspergillus has been detected in multiple countries in all continents.[21]

Fluconazole and echinocandin resistance in *Candida* spp and triazole resistance in *Aspergillus fumigatus* are very important to track internationally. However, WHO is not yet planning to collect any fungal resistance data as part of its country-by-country surveillance returns through the Global Antimicrobial Resistance Surveillance System.[24] Provided adequate laboratory capacity is secured, integration of antifungal resistance into broader stewardship for antimicrobial resistance is an opportunity, with possible different stewardship models for high-income countries compared with low-income countries.[20]

For more details on **antifungal drug availability and prices** see http://www.gaffi.org/antifungal-drug-maps/

Surveillance

Surveillance of disease is a cornerstone of public health. A variety of surveillance options exist for fungal diseases. In a hospital setting, a syndromic approach might be used for surveillance of health-care-associated infections—for example, urinary tract infections, complicated intra-abdominal infections, and ventilator-associated pneumonia—with linked laboratory data providing evidence for a fungal cause. Laboratory-based approaches work best for fungal diseases with accurate diagnostic assays that are available to clinicians, routinely used,[25] and aggregated with use of computerised systems.[26] Community-based surveys can assess burden

in targeted locations or populations—for example, fungal sinusitis in a rural region of India,[27] chromoblastomycosis in Madagascar,[28] or in specific occupations such as lymphocutaneous sporotrichosis in mineworkers.[29] More complex fungal diseases, such as fungal sinusitis or invasive aspergillosis, require more complex, costly, and hence usually one-off diagnostic and epidemiological studies to accurately estimate burden.

Outbreaks can be an important indication of gaps in adequate health care—eg, a large cluster of fungaemia in a tertiary care centre in India.[30] Candidaemia in neonatal intensive care units can be linked to undetected or hidden clusters of cases, which are propagated from person to person in overcrowded nurseries with staff shortages.[30–32] Construction activities in hospitals can also cause outbreaks of invasive aspergillosis, as can poor maintenance of relief material after natural disasters.[33–35] Tracking down sources of fungal disease outbreaks might require a hint of something odd: an unusual species, a new resistance pattern, or a distinctive process of infection.[36]

Ideally, outbreaks would be detected close to real time, with adequate communication infrastructure. Genotyping tools could be invoked when products or new subspecies are suspected that require specific identification. South Africa's GERMS-SA network of approximately 200 microbiology laboratories (figure 3; appendix pp 5,6) primarily does laboratory-based surveillance of selected IFIs but also has the capacity for detection of outbreaks.[25,37]

Figure 3: **A patient with cryptococcal meningitis providing written informed consent for participation in a decade-old national surveillance project (GERMS-SA), Johannesburg, South Africa**

Public health infrastructure

The presence of one or more surveillance programmes is both a tool to raise the profile of fungal diseases and an indication of its perceived importance among public health leaders. South Africa has done national population-based surveillance for cryptococcal meningitis since 2005, national surveys for candidaemia since 2009, and passive laboratory surveillance for rarer mycoses and outbreak investigations (sporotrichosis, candidiasis, and histoplasmosis) under the leadership of the NICD. NICD is an example of a national public health agency that is linked down to provincial, regional, and district teams, and linked outwards to international partners. Such agencies, centres, or institutes can not only do outbreak response and surveillance but also evaluate public health programmes.[38,39] To do so, they need staffing by public health personnel skilled in mycology or mycologists with training in public health. Unfortunately, most schools of public health only touch on fungal disease in their curricula, despite the breadth of important texts in the field.[40,41] Additionally, there are no current fellowships or available public health mycology programmes to collaborate with these schools. The US Centers for Disease Control and Prevention (CDC) has an internal epidemic intelligence service training programme, but relatively few graduates are offered an opportunity to work in the field of mycology. CDC's training programme for international field epidemiology is currently supported in 33 countries but few residents get exposure to fungal disease surveillance or outbreak activities.

No recognised international authority on public health mycology is responsible for surveillance system design, coordinated outbreak response, and international guideline development. Particular fungal diseases become a focus only in relation to already recognised diseases, such as HIV infection and tuberculosis. Nevertheless, there are a range of recognised resources in low-income, middle-income, and high-income countries (appendix pp 9,10), which can support national public health capacity. Some agencies arguably have an international role in public health mycology—eg, US CDC through its extensive support to national laboratories.[42]

Future directions

We have argued from a health systems and public health perspective that the four major foci of the GAFFI 95–95 by 2025 roadmap[43]—diagnostics, professional education, antifungal agents, and burden of disease data—are

Search strategy and selection criteria

We searched PubMed and Google Scholar in English from Jan 1, 2000, to Oct 1, 2016. Because of the broad scope of this Series paper, we used the search terms "fungal", "public health", and "developing countries". On the basis of the title and abstract, and subsequently full text, a minority of articles, chapters, and books returned were relevant for the main body of our review. These sources were supplemented by earlier review work by members of the Global Action Fund for Fungal Infections available in existing reports and well known texts in the mycology field. Country case studies drew upon the intimate knowledge of clinical and public health systems and literature for each country, including existing peer-reviewed papers and recent peer-reviewed abstracts.

intimately related as part of a combined health system. To move them forward requires attention to two additional building blocks, governance and financing, each of which requires involvement of multiple stakeholders (as per the South African example with cryptococcal meningitis; appendix pp 5,6). We can imagine application of the proposed Ten Steps guidance for interventions[8] to the design of options for integration of fungal disease diagnostics and management for different national health-care systems.

The guidance starts with national public health agencies or ministries of health convening system stakeholders, including providers and users of the health system. Ministries of health could potentially be represented by non-governmental organisations engaged in advocacy for access to diagnostics and antifungals, and financing. It would also include relevant clinical or professional and scientific societies who could be involved in guidelines for diagnosis, management, surveillance, and antimicrobial resistant stewardship; and involve representatives of the research community (academics in public health mycology, clinical microbiology, and implementation research). Together, these stakeholders could collectively brainstorm system options, with the aim of minimising negative effects and optimising synergies in system components. A key aspect of our proposed approach would be to systematically evaluate initiatives undertaken, with adequate implementation research designs.[44]

Contributors

DCC and DWD conceived the paper and drafted the initial outline. All authors contributed to the references, revised the structure of the paper, and wrote the paper. NPG, AC, JS, and DWD contributed to the country examples. DCC constructed the table. NPG and DWD adapted the table. NPG, AC, and JS provided the figures. All authors revised the manuscript and approved the final version.

Declaration of interests

NPG has, in the past 5 years, received speaker honoraria from Pfizer, Astellas, and Merck Sharp & Dohme; has received travel grants from Merck Sharp & Dohme; has provided educational materials for TerraNova; and has acted as temporary consultant for Fujifilm Pharmaceuticals, all outside of this submitted work. DWD has Founder shares in F2G, a University of Manchester spin-out antifungal discovery company; and has current grant support from the National Institute of Health Research, Medical Research Council, Global Action Fund for Fungal Infections, and the Fungal Infection Trust. DWD acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Syncexis, Pulmocide, Pulmatrix, Zambon, and Biosergen. In the past 3 years, DWD has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck Sharp & Dohme, and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups. DCC, AC, and JS declare no competing interests.

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References

1 GAFFI. Burden of disease maps. Global Action Fund for Fungal Infections. 2016. http://www.gaffi.org/why/burden-of-disease-maps (accessed April 15, 2016).
2 Govender NP, Chiller T, Poonsamy B, Frean JA. Neglected fungal diseases in sub-Saharan Africa: a call to action. *Curr Fungal Infect Rep* 2011; **5:** 224–32.
3 Kenyon C, Bonorchis K, Corcoran C, et al. A dimorphic fungus causing disseminated infection in South Africa. *N Engl J Med* 2013; **369:** 1416–24.
4 Slavin MA, Chakrabarti A. Opportunistic fungal infections in the Asia-Pacific region. *Med Mycol* 2012; **50:** 18–25.
5 Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* 2017; published May 5. https://doi.org/10.1016/S1473-3099(17)30243-8.
6 Denning DW. Minimizing fungal disease deaths will allow the UNAIDS target of reducing annual AIDS deaths below 500 000 by 2020 to be realized. *Philos Trans R Soc* 2016; **371:** 20150468.
7 Colombo AL, Nucci M, Park BJ, et al. Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. *J Clin Microbiol* 2006; **44:** 2816–23.
8 WHO. Systems thinking for health systems strengthening. Geneva: World Health Organization. 2009. http://whqlibdoc.who.int/publications/2009/9789241563895_eng.pdf (accessed April 10, 2016).
9 Bousquet J, Ndiaye M, Aït-Khaled N, Annesi-Maesano I, Vignola A-M. Management of chronic respiratory and allergic diseases in developing countries. Focus on sub-Saharan Africa. *Allergy* 2003; **58:** 265–83.
10 Iriart X, Blanchet D, Menard S, et al. A complementary tool for management of disseminated *Histoplasma capsulatum* var *capsulatum* infections in AIDS patients. *Int J Med Microbiol* 2014; **304:** 1062–65.
11 Frean J, Perovic O, Fensham V, et al. External quality assessment of national public health laboratories in Africa, 2002–2009. *Bull World Health Organ* 2012; **90:** 191–99A.
12 Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev* 2011; **24:** 247–80.
13 Kabbani S, Jacob JT, Gaynes RP, Rimland D. Decrease in candida bloodstream infections in veterans in Atlanta. *Am J Infect Control* 2016; **44:** 488–90.
14 Kneale M, Bartholomew JS, Davies E, Denning DW. Global access to antifungal therapy and its variable cost. *J Antimicrob Chemother* 2016; **71:** 3599–606.
15 Denning DW, Bromley MJ. How to bolster a sparse antifungal pipeline. *Science* 2015; **347:** 1414–16.
16 Brüggemann RJ, Touw DJ, Aarnoutse RE, Verweij PE, Burger DM. International inter-laboratory proficiency testing program for measurement of azole antifungal plasma concentrations. *Antimicrob Agents Chemother* 2009; **53:** 303–05.
17 Bartholomew JS, Banfield S, Atherton GT, Denning DW. Comment on: antifungal therapy: drug-drug interactions at your fingertips. *J Antimicrob Chemother* 2016; **71:** 2062.
18 Sneddon J, Gilchrist M, Wickens H. Development of an expert professional curriculum for antimicrobial pharmacists in the UK. *J Antimicrob Chemother* 2015; **70:** 1277–80.

19 Denning DW, Perlin DS, Muldoon EG, et al. Delivering on antimicrobial resistance agenda not possible without improving fungal diagnostic capabilities. *Emerg Infect Dis* 2017; **23:** 177–83.

20 Muñoz P, Bouza E. The current treatment landscape: the need for antifungal stewardship programmes. *J Antimicrob Chemother* 2016; **71** (suppl 2): 5–12.

21 Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole resistance in *Aspergillus fumigatus*: can we retain the clinical use of mold-active antifungal azoles? *Clin Infect Dis* 2016; **62:** 362–68.

22 Liao X, Qiu H, Li R, et al. Risk factors for fluconazole-resistant invasive candidiasis in intensive care unit patients: an analysis from the China survey of candidiasis study. *J Crit Care* 2015; **30:** e1–5.

23 Govender NP, Patel J, Magobo RE, et al. Emergence of azole-resistant *Candida parapsilosis* causing bloodstream infection: results from laboratory-based sentinel surveillance in South Africa. *J Antimicrob Chemother* 2016; **71:** 1994–2004.

24 WHO Regional Office for Europe. Global antimicrobial resistance surveillance system. Geneva: World Health Organization. 2015. http://www.who.int/drugresistance/surveillance/GLASSmeeting/en/ (accessed April 29, 2016).

25 du Plessis D, Poonsamy B, Msimang V, et al. Laboratory-based surveillance of *Pneumocystis jirovecii* pneumonia in South Africa, 2006–2010. *S Afr J Infect Dis* 2016; **1:** 1–6.

26 Meiring ST, Quan VC, Cohen C, et al. A comparison of cases of paediatric-onset and adult-onset cryptococcosis detected through population-based surveillance, 2005–2007. *AIDS* 2012; **26:** 2307–14.

27 Chakrabarti A, Rudramurthy SM, Panda N, Das A, Singh A. Epidemiology of chronic fungal rhinosinusitis in rural India. *Mycoses* 2015; **58:** 294–302.

28 Esterre P, Andriantsimahavandy A, Ramarcel ER, Pecarrere JL. Forty years of chromoblastomycosis in Madagascar: a review. *Am J Trop Med Hyg* 1996; **55:** 45–47.

29 Govender NP, Maphanga TG, Zulu TG, et al. An outbreak of lymphocutaneous sporotrichosis among mine-workers in South Africa. *PLoS Negl Trop Dis* 2015; **9:** e0004096.

30 Chakrabarti A, Shivaprakash MR, Pratibha K, et al. Epidemiological study of a large cluster of fungemia cases due to *Kodamaea ohmeri* in an Indian tertiary care center. *Clin Microbiol Infect* 2014; **20:** 83–89.

31 Britz E, Iyaloo S, Naicker S, et al. Large outbreak of *Candida krusei* bloodstream infection in a neonatal intensive care unit—Pretoria, South Africa, 2014. 7th Congress on Trends in Medical Mycology; Lisbon; Oct 9–12, 2015. S20.4.

32 Chakrabarti A, Singh K, Narang A, et al. Outbreak of *Pichia anomala* in the pediatric service of a tertiary care center in northern India. *J Clin Microbiol* 2001; **39:** 1702–06.

33 Gunaratne PS, Wijeyaratne CN, Seneviratne HR. Aspergillus meningitis in Sri Lanka—a post-tsunami effect? *N Engl J Med* 2007; **356:** 754–56.

34 Torres R, Gonzalez M, Sanhueza M, et al. Outbreak of *Paecilomyces variotii* peritonitis in peritoneal dialysis patients after the 2010 Chilean earthquake. *Perit Dial Int* 2014; **34:** 322–25.

35 Benedict K, Park BJ. Invasive fungal infections after natural disasters. *Emerg Infect Dis* 2014; **20:** 349–55.

36 Benedict K, Richardson M, Vallabhaneni S, Jackson BR, Chiller T. Emerging issues, challenges, and changing epidemiology of fungal disease outbreaks. *Lancet Infect Dis* 2017; published on XX. https://doi.org/10.1016/http://dx.doi.org/10.1016/S1473-3099(17)30443-7.

37 Magobo RE, Corcoran C, Seetharam S, Govender NP. *Candida auris*—associated candidemia, South Africa. *Emerg Infect Dis* 2014; **20:** 1250–52.

38 Govender NP, Roy M, Mendes JF, Zulu TG, Chiller TM, Karstaedt AS. Evaluation of screening and treatment of cryptococcal antigenaemia among HIV-infected persons in Soweto, South Africa. *HIV Med* 2015; **16:** 468–76.

39 Vallabhaneni S, Longley N, Smith M, et al. Evaluation of a public-sector, provider-initiated cryptococcal antigen screening and treatment program, Western Cape, South Africa. *J Acquir Immune Defic Syndr* 2016; **72:** e37–42.

40 Park BJ, Chiller TM, Brandt ME, Warnock DW. Epidemiology of systemic fungal diseases: an overview. In: Kauffman CA, Pappas PG, Sobel JD, Dismukes WE, eds. Essentials of clinical mycology. New York, NY: Springer-Verlag, 2011: 27–37.

41 Viegas C, Pinheiro A, Sabino R, Viegas S, Brand J, Ver Ssimo C. Environmental mycology in public health: fungi and mycotoxins risk assessment and management. London: Academic Press, 2016.

42 CDC. CDC at work: mycotic diseases branch. US Centers for Disease Control and Prevention. http://www.cdc.gov/fungal/cdc-and-fungal.html (accessed April 24, 2016).

43 GAFFI. 95/95 by 2025. Global Action Fund for Fungal Infections. 2015. http://www.gaffi.org/roadmap (accessed April 10, 2016).

44 WHO. Implementation research toolkit. Geneva: World Health Organization. 2014. http://www.who.int/tdr/publications/topics/ir-toolkit/en/ (accessed April 10, 2016).