OVER A BILLION people are affected with fungal disease across the world

IMPROVING OUTCOMES FOR PATIENTS WITH FUNGAL INFECTIONS ACROSS THE WORLD

A ROAD MAP FOR THE NEXT DECADE

95/95 BY 2025

GLOBAL ACTION FUND FOR FUNGAL INFECTIONS


95/95
BY 2025

EXECUTIVE SUMMARY With over a billion people affected by fungal disease across the world resulting in approximately 11.5 million life-threatening infections and over 1.5 million deaths every year, we face a major challenge to improve this dismal situation. Recent advances in diagnostics, robust screening programs and improved access to low cost antifungal drugs provide an unprecedented opportunity to reduce the burdens of ill health and death, especially in those with HIV/AIDS.

In this 10 year roadmap, we call upon governments, policy makers and international health agencies to:

- Support the goal of reducing AIDS deaths to under 500,000 by 2020, with a determined focus on the commonest lethal fungal infections cryptococcal meningitis, *Pneumocystis* pneumonia, disseminated histoplasmosis and chronic pulmonary aspergillosis after tuberculosis
- Ensure that 95% of people with serious fungal disease are diagnosed and 95% treated by 2025 (95-95)

To accomplish these goals, it is necessary in each country to:

- Ensure that affordable diagnostic tests for all common and uncommon fungal infections are made available, focused on rapid, non-culture testing
- Develop and maintain at least one laboratory led by an expert in fungal disease diagnostics with a comprehensive diagnostic portfolio and critical mass of healthcare professionals per country
- Develop a network of expert clinicians and 'train the trainer' programs, supported by clinical guidelines
- Ensure distribution of antifungal agents on the WHO Essential Medicine List to reach all those who need them
- Establish ongoing surveillance of fungal infections of high burden to inform clinical practice, training and research needs
- Develop local experts in public health mycology

By implementing these basic measures, GAFFI is confident that 95% of people with serious fungal disease will be diagnosed and 95% will be treated. This constitutes GAFFI's goal for the next 10 years encapsulated as '95-95 by 2025'.

Who is at risk?

About 30 fungal species cause 99% of human fungal disease. In decreasing frequency, these are cutaneous (skin hair and nails) fungal diseases, mucosal candidiasis, allergic fungal conditions usually complicating asthma, chronic skin, lung, sinus and bone infections and the acute life or sight-threatening fungal infections. The vast majority of infections are globally distributed, with a few localized to continents, tropical zones or even localized regions. This report addresses the current status of diagnostics and diagnostic skills, clinical practice and antifungal access, and follows the first Global Forum of Fungal Infections in 2015 (Appendix 1).

Fungal infections affect 6 main groups of patients

- Cancer, leukaemia, transplantation and AIDS
- Critical care - premature babies, ICU, major surgery
- Lung disease - severe asthma, TB, COPD and cystic fibrosis
- Injury - eye, burns, trauma, skin especially in tropics
- Skin, hair and nails infection in normal people
- Sexual health - thrush, often recurrent, especially in pregnancy

Professor David Denning making a point at the launch of GAFFI at the House of Commons in London in 2013

This 10 year Roadmap, an executive summary and all appendices may be downloaded from:

www.gaffi.org/roadmap

For all abbreviations see **Appendix 2**

95/95 BY 2025

‘Any efforts that are made to encourage the understanding and treatment of fungal infections, we definitely need to go as far as we can with that. What’s happened to me, I wouldn’t wish that on anybody.’

Robert Knowles, a patient with fungal keratitis.

A. THE BURDEN OF FUNGAL DISEASES

Understanding the global burden of fungal and other similar disease is critical to determine priorities. Only a small number of studies have estimated the global incidence and/or prevalence of different fungal diseases (1-9). Estimates involve major extrapolations, given the lack of high quality epidemiological data, and hence likely suffer from substantial errors (e.g. more than a 2-fold difference in burden estimate from the ‘truth’). Nonetheless, approximations of fungal disease burden and associated severity for the most common life-threatening fungal infections are possible and helpful (Appendix 3).

Major AIDS associated Fungal Infections and their impact

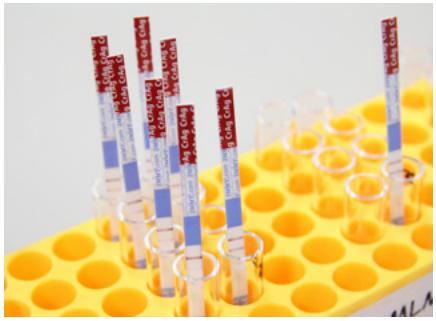
Collectively, fungal infections are by far the most common infections in AIDS (Table 1), numbering in excess of 11 million, and probably over 500,000 deaths annually. *Pneumocystis* pneumonia (PCP) occurs worldwide and is a leading initial presentation of AIDS (see Appendix 3 for details). The frequency of other fungal infections in AIDS, notably cryptococcal meningitis, disseminated histoplasmosis and rarer infections, vary by geography, and risk factors such as *Talaromyces marneffei* infection in SE Asia and invasive aspergillosis. Histoplasmosis has a high incidence in certain places in Central and South America, but is worldwide in tropical and semi-tropical countries. Oral and oesophageal candidiasis are extremely common, and worldwide. In Bangladesh, the top disease associations with death in hospital were oesophageal candidiasis (odds ratio 27.5) and PCP (OR 18.5), ahead of a CD4 cell count of <200 (OR 16.6) or cancer (OR 15.2) (10).

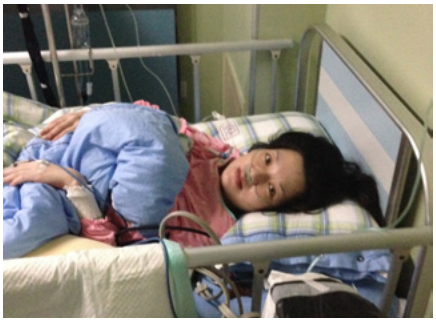
AIDS deaths remain too high because of opportunistic infections. Many people present with advanced HIV infection and very damaged immune systems and/or are not responsive to ARVs because of antiviral resistance. The incidence of PCP, cryptococccal meningitis and oesophageal candidiasis will fall as 90-90-90 (Appendix 7) rolls out, but histoplasmosis and skin and nail infections are likely to remain static. Even after starting ARVs, patients are dying of fungal disease and undiagnosed infection in the first year (Table 2). Some deaths are due to immune reconstitution, but most are probably related to continuing immune suppression, which has not yet recovered.

DEATHS from fungal infections in AIDS are estimated at 700,000 annually, nearly half the total. Concrete steps to improve diagnosis and access to therapy, including a screen and treat program for pre-symptomatic cryptococcal, disease, could realistically reduce deaths by 457,000 per year by 2020, if 60-90% of patients are reached.

90-90-90 = 90% of HIV infected patients know their infection status, 90% of all HIV patients receiving ART and 90% viral load suppression.

For all abbreviations see **Appendix 2**





Left. The cryptococcal antigen LFA which has excellent performance in many specimen types for both diagnosis and surveillance for cryptococcal disease, in AIDS and others.

Right. Young chinese woman with cryptococcal meningitis being treated with a lumbar drain to reduce intracranial pressure.

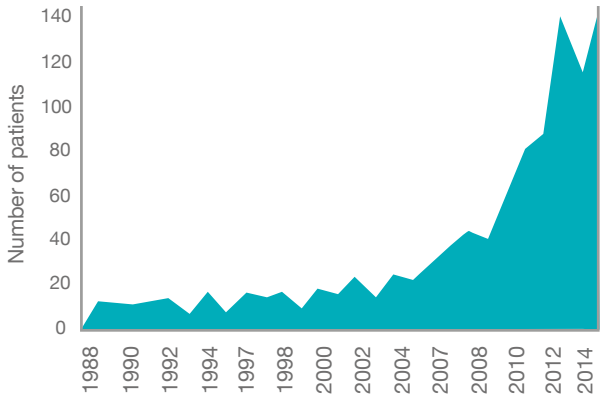
Table 1. Global estimates and related deaths of fungal infections per year among people with AIDS.

Fungal infection	Annual burden	Case fatality rate if treated	Estimated annual deaths
Cryptococcal meningitis	371,700 – 957,900	15-20% USA >50% in LMICs	125,000 – 624,700
Pneumocystis pneumonia	>400,000	15% with best treatment	>200,000
Disseminated histoplasmosis	>100,000	15-30%, if diagnosed and treated	>80,000
Chronic pulmonary aspergillosis	>185,000	15-40% mortality in HIC	>100,000
Invasive aspergillosis	>45,000	30% mortality if treated in HIC	>30,000
T. marneffei infection	>8,000	18-33%	>2,000
Mucosal and skin fungal infection	>10,120,000	<1%	<1,000
Total	**>11.22 million**		**>535,000**

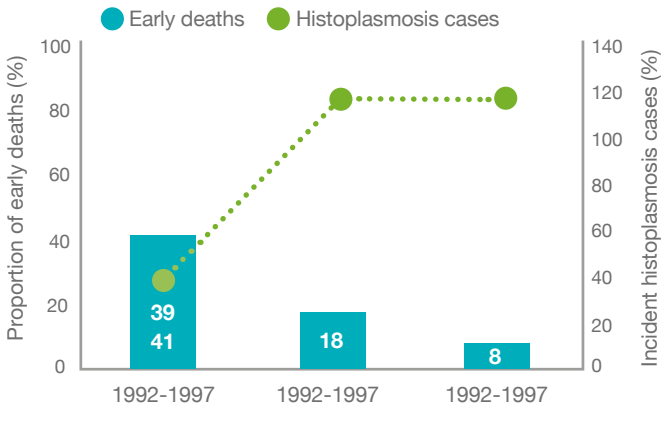
Table 2. Deaths from key infections in the first year of ART in 5 studies.

Country	Deaths in first year of ART by therapy (%)				Years
	Total	Cryptococcal meningitis	TB	Undiagnosed infections	
Senegal (11)	47/404 (12%)	5/47 (11%)	8/47 (16%)	9/47 (18%)	98-02
Morocco (12)	57/1243 (4.6%)	7/57 (12%)	20/57 (35%)	Not described	99-10
Zimbabwe and Uganda (13)	179/3316 (5.4%)	20/179 (11%)	14/179 (8%)	33/179 (18%)	03-04
Malawi (14)	190/1584 (12%)	7/190 (4%)	10/190 (5%)	35/190 (18%)	03-05
India (15)	56/759 (7%)	5/56 (9%)	27/56 (48%)	10/56 (18%)	09-10

Below. Diagnoses of histoplasmosis in Colombia, showing increase since implementation of rapid testing with antigen detection (16) and PCR (17) (Caceres et al, unpublished data).



Below. Mycology reference laboratory in Cayenne, French Guiana, transforms the outcome of disseminated histoplasmosis in AIDS with rapid PCR testing (18).



‘If the medicine is out there, I don’t understand why everyone can’t get it. It just doesn’t make sense to not get those drugs out here.’

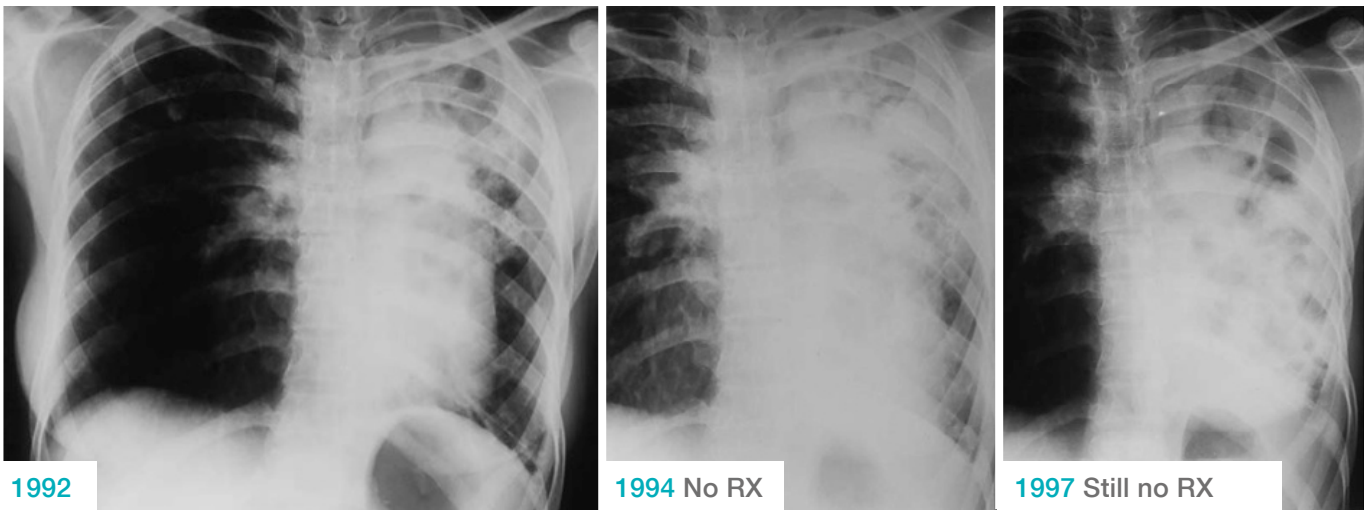
Woodrow Maitland-Brown, a patient with fungal disease.

Hospital-associated infection, including cancer-associated fungal infection

For the hospitalized patient, the most common life-threatening infections are invasive candidiasis (including *Candida* bloodstream infection) and invasive aspergillosis. Less commonly PCP, mucormycosis and a large number of rarer fungi may cause infection, usually acquired in the community prior to hospitalization (Appendix 3.2). Mortality from fungal infections in hospital is unknown in LMICs but approaching 100% because many countries do not have diagnostic tools and antifungals for these diseases.

Table 3. Global estimates of fungal infections and related deaths per year in immunocompromised and/or hospitalized patients without HIV infection.

Fungal infection	Annual burden	Case fatality rate if treated	Estimated deaths
Invasive candidiasis	>750,000	~45% mortality in HIC	>350,000
Invasive aspergillosis	>250,000	~50% mortality in HIC	>125,000
Pneumocystis pneumonia	>100,000	~50% non-AIDS, in HIC	>50,000
Total	>1.1 million		**>425,000**



Above. Progression of chronic pulmonary aspergillosis without treatment over 5 years after TB in a woman from Gujarat leading to complete destruction of the left lung.

With 1.5 million deaths from AIDS-related causes, there is a major need to improve management of opportunistic fungal infections in HIV/AIDS care settings.

Lenias Hwenda Medicines for Africa.

Population (non-hospital) fungal infections of the lung and severe asthma

From 10 to 20% of patients treated for pulmonary tuberculosis (TB) will develop *Aspergillus* antibodies indicating infection and a large proportion of these patients develop chronic pulmonary aspergillosis (CPA). CPA is a slowly progressive lung fungal infection, which progresses to death over several years, unless arrested with treatment. The key diagnostic test, *Aspergillus* antibody detection, is not available in Africa and many other centres, so CPA is not diagnosed or treated. After TB, modeling suggests that about 375,000 will go on to develop CPA each year, and with an annual 15% mortality (2). Therefore about 1.2 million people probably have CPA.

A topic of real uncertainty currently is 'smear negative TB', which in many instances is not TB at all. In an unpublished study of 39 HIV positive, smear negative patients in Kampala, 26% had detectable *Aspergillus* antibodies and 40% of these patients died within 2 months. Based on their compatible radiology, symptoms and positive serology, it is highly likely these patients suffered from CPA, or invasive aspergillosis. Other consistent data from Iran and Brazil will be published. Patients with smear negative TB who fail to respond to therapy may be diagnosed with multi-drug resistant TB (MDR) and treated with second line agents. In 2012, the WHO estimated that there are ~4 million MDR TB cases with 1M deaths (19); some of these patients probably have CPA, or another fungal infection.

About 300 million people have asthma with adults comprising 197 million (4). Atopic individuals may develop fungal allergy of the lungs or sinuses. The air is full of fungal spores and hyphae. *Aspergillus* produces more fungal allergens than any other known organism. Fungi exacerbate asthma, and lead to additional complications such as bronchiectasis. Severe asthma with fungal sensitization (allergy) (SAFS) probably contributes to up to half of the ~489,000 deaths from asthma each year (20), yet it is treatable with antifungal drugs. About 25% of adults seen in secondary care have *Aspergillus* (and other fungal) sensitization (8). Although, no global or national SAFS prevalence estimates have been made, it is thought that about 6.5 million adults have SAFS (sensitivity analysis 3.5-15 million) (8). In terms of resource utilization for asthma, 70% of cost is spent on the 10% of adult asthmatics with severe disease. (Appendix 3.3)

Table 4. Prevalence estimates of lung diseases and related estimated deaths per year in non-hospitalized populations attributable to fungal infection and allergy.

Fungal infection	Annual burden	Annual case fatality rate	Estimated deaths
Chronic pulmonary aspergillosis	>3,000,000	~15% mortality in developed world	>450,000
SAFS	>6,500,000	<1% but no good figures	350,000 - 489,000 asthma deaths - ~50% SAFS related
ABPA (asthma)	>4,837,000	<1%	<10,000
ABPA & *Aspergillus* bronchitis (cystic firbosis)	>19,000	<1%	<100
Total	**>14 million**		**>700,000**

Ending the fungal infections crisis means that patients with debilitating and life-threatening fungal infections will be diagnosed and treated in a timely manner, so that they can resume a normal life, maintain their family structure and contribute to society.

David Perlin Public Health Research Institute, New Jersey Medical School, USA.

‘It just doesn’t make sense not to get those drugs out there. If they can control it quickly you can get away with it.’

Lesley Hill, survivor from *Pneumocystis* pneumonia.

Severe fungal infections of the eye, skin and vagina, some injury related

Infectious keratitis is common, and in temperate climates is usually caused by bacteria (or viruses) (>90%) but in tropical and semi-tropical areas is ~50% fungal. Fungal infection of the eye is thought to affect over 1 million adults and children globally (Appendix 3.4). Early antifungal therapy saves sight, but late diagnosis or inadequate therapy results in loss of vision and sometimes the eye. The most affected by fungal keratitis are young male agricultural workers (21), and the impact on their lives is considerable. In Uganda a remarkable 22% of cases of visual impairment in children was attributable to corneal ulceration, probably fungal (22) and among these children, 80% were blind.

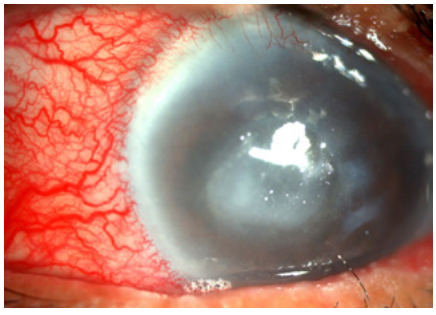
Localized injury to the skin in agricultural workers in tropical environments may lead to chromoblastomycosis or mycetoma. The latter is designated a neglected tropic disease. There are no global estimates of either condition. In Madagascar, the incidence of chromoblastomycosis was 14/100,000 (23) and in Brazil was 3/100,000 (24).

Cases of mucormycosis follow environmental catastrophes such as tsunamis and tornadoes, as a result of flying or floating debris (25,26).

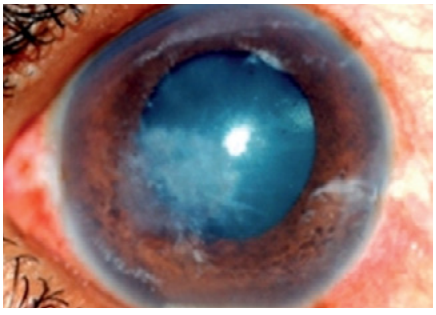
Skin fungal infections affect a billion people worldwide (7). Most are transmissible from person to person. The commonest infections are tinea capitis (hair infection), onychomycosis (nail infection) and ringworm. While most of these are unsightly and impinge on quality of life, some lead to significant consequences. Severe and distinctive onychomycosis is an early feature of HIV infection. Athlete’s foot (tinea pedis) can lead to lower limb cellulitis and hospital admission.

Tinea capitis can be inflamed (kerion) leading to pain, discharge, secondary bacterial infection and scarring with permanent hair loss. Of the estimated 200 million children with tinea capitis, most in our poorest communities, up to 10% get kerion (27), are excluded from school and suffer for months or years. See Appendix 3.5 for more information on children with fungal disease.

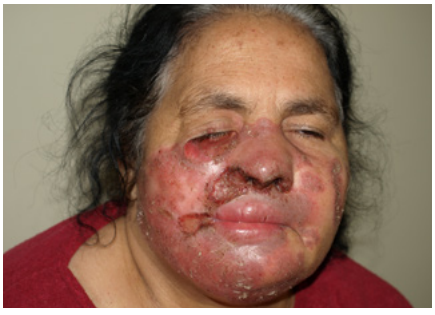
The majority of women (70%) have at least one episode of vulvovaginal candidiasis (VVC), often in pregnancy, during their lifetime. Recurrent VVC occurs in some women for no apparent reason. Based on internet surveys and supported by clinical experience, rVVC probably affects ~138 million women annually (range 103 to 172 million) and ~492 million over their lifetime (9). The toll of rVVC on women’s health and quality of life is substantial including long-lasting soreness and discomfort, limitations in physical activity, impact on concentration, and interference with sexual activity and intimate relationships. Recurrent VVC can occur at any point during a woman’s reproductive life, and after the menopause in diabetic women and those taking hormone replacement therapy. In high-income countries VVC costs more than $2.2 billion annually in lost productivity. Treatment and care costs exceed $1.8 billion in the US alone.



Severe fungal keratitis poorly responsive to topical therapy.



Severe *Aspergillus* keratitis.



Brazilian with severe chromoblastomycosis of over 4 years duration, unresponsive to treatment. Thanks to Dr Flavio Queiros-Telles.

B. FUNGAL DISEASE DIAGNOSIS

Rapid and conventional diagnostics

Once fungal disease is suspected in a patient, the diagnosis requires one or more of the following procedures: clinical examination (especially skin, hair, nails and mouth), indirect assays such as imaging with X-rays, CT, MRI or ultrasound scanning, skin testing (fungal allergy and exposure to endemic fungi) and/or direct detection laboratory procedures. The different approaches necessary are described on the LIFE website here: http://life-worldwide.org/fungal-diseases/diagnostics

Sicker patients, especially those with compromised immunity, require a fast diagnosis to minimize mortality. For example, every hour that elapses in a patient with a *Candida* bloodstream infection increases mortality by 2.5%. As fungi take 1-20 days to grow on agar, waiting for culture often introduces a fatal delay, and culture is quite often negative. For this reason, the last 20 years have seen the development and marketing of rapid testing systems including antigen and nucleic acid-based molecular diagnostics, which increase sensitivity, specificity and speed of detection (Table 5). Properly implemented, these tests reduce mortality, and reduce hospital costs by minimizing inappropriate therapies and reducing length of stay, especially in high intensity and costly hospital units.

Table 5. Rapid tests for serious fungal diseases. (See Appendix 4 for more details).

Infection	Test	Diagnostic sensitivity	Turnaround time*	Approvals		
				FDA	EU	WHO
All invasive, skin, hair and nails	Direct microscopy	30-90%	2 hours	N/A	N/A	N/A
Cryptococcal meningitis	Antigen LFD on serum, plasma, CSF and urine	99%	15 mins	Y	Y	N
Cryptococcal meningitis	Antigen on serum and CSF	98%	2 hours	Y	Y	N
Disseminated histoplasmosis	Antigen (ELISA) on urine and serum	90%	1 day	N	N	N
Pneumocystis pneumonia	PCR on respiratory samples	98%	1 day	N	Y	N
Invasive aspergillosis	Antigen (ELISA) on serum	80%	1 day	Y	Y	N
Invasive aspergillosis	Antigen LFD on serum and respiratory samples	75%	4 hours	N	N	N
Invasive aspergillosis in leukaemia	PCR on serum and respiratory samples	45-90%	1 day	N	Y	N
Most fungal infections except cryptococcal disease and histoplasmosis	Glucan detection on serum	65-77%	1 day	Y	Y	N
Invasive candidiasis and candidaemia	PCR on blood	>90%	1 day	Y	N	N

N/A = not applicable as old technology

LFD = lateral flow device, point of care test **CSF** = cerebrospinal fluid **PCR** = polymerase chain reaction **ELISA** = enzyme-linked immunosorbent assay

***TURNAROUND TIME** includes transport to laboratory, test time (daily batching), reporting and assumes a normal working day

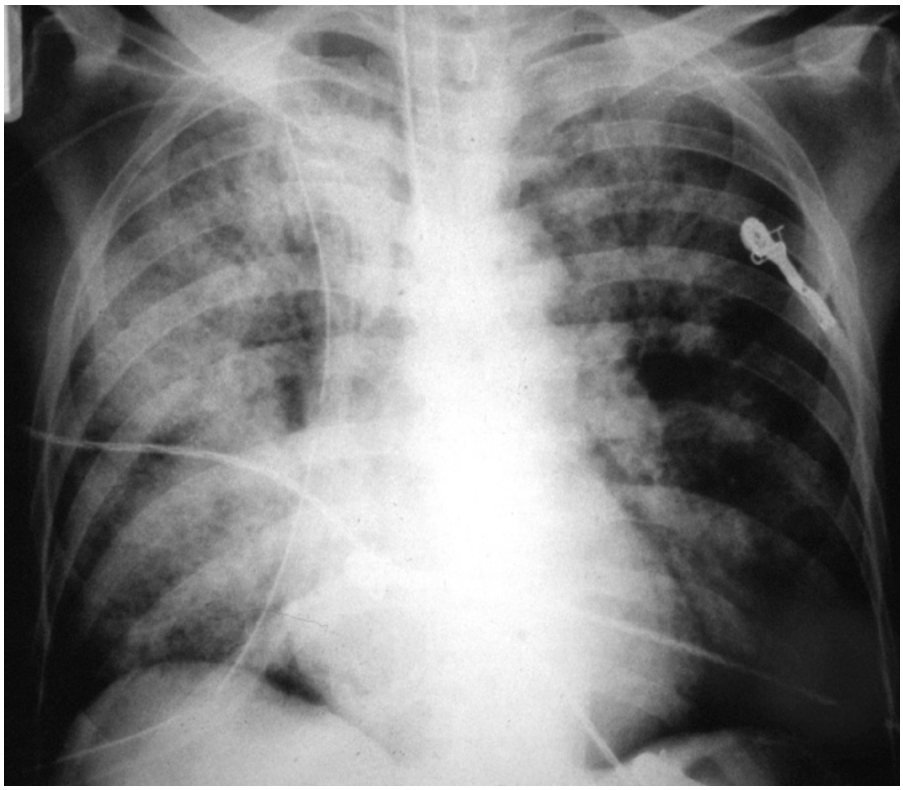
‘In lots of ways I have been very lucky. The infection I had, you actually have to be quite lucky to still have your eye at the end of it.’
Jason David Cooper, cured from fungal keratitis.

Rapid and conventional diagnostics ctd.

External quality assurance
Internationally many laboratories subscribe to microbiology quality assurance schemes. They include NEQAS (correct identification of fungi) (28), Scandinavia (mock samples containing fungi) (29), Australia (30), the American College of Pathologists and others. In addition, an international proficiency testing program for azole antifungals is run from Nijmegen, Netherlands (31). There is a need for more regional schemes, and distribution of samples for antigen, antibody or molecular identification. EQA schemes based on identification on culture places the wrong emphasis on skills in the laboratory.

Major gaps in diagnostic capabilities
There are several important gaps in our diagnostic capabilities. This is a partial listing.

- Point of care test for *Histoplasma* antigen
- Point of care test for *Aspergillus* antibody
- Point of care test for fungal keratitis
- Low cost molecular assay for *Pneumocystis*
- Direct assay to detect azole resistance in *Aspergillus* without a positive culture
- Rapid test for invasive candidiasis which determines infecting species
- Rapid test for mucormycosis
- Improved serological assays to distinguish allergic and chronic pulmonary aspergillosis in asthma and cystic fibrosis
- Rapid test for azole and echinocandin drug resistance
- Prognostic tests to identify patients likely to fail therapy who need maximal or additional therapy
- Risk stratification tests to determine who requires antifungal prophylaxis or increased in middle or low risk groups (such as cystic fibrosis, chronic leukaemia, systemic lupus erythematosus)
- Tests for latent infections, especially histoplasmosis and coccidioidomycosis



Pneumocystis pneumonia in a man with lymphoma.

Unless we treat opportunistic infections in AIDS we can’t reach the Three Zeros targets, particularly Zero Deaths.

Dr Peter Godfrey-Faussett
From his talk, Making three Zeros a reality: Treating Opportunistic infection.

C. ANTIFUNGAL THERAPY

Antifungal drugs – old and new

There are several antifungal agents available but very few classes of compound, and new antifungals are urgently needed (32). The patents protecting fluconazole, itraconazole, terbinafine and amphotericin B expired years ago; voriconazole and caspofungin generics are just appearing. While fluconazole is available in almost all countries, itraconazole and amphotericin are not, and so large swathes of the global population do not have access to these life-saving drugs. In tandem with new drug development, ensuring access to the older and still useful antifungals is important. Until 2013, only the antifungals griseofulvin and fluconazole were on the World Health Organisation's Essential Medicine List, and fluconazole remains the only systemic azole on that list. Very large numbers of topical azoles are available clinically for thrush (only clotrimazole included in WHO EML); not all these are covered here. Cotrimoxazole for PCP is also included on the WHO EML. The table below explains the common formulations of the most important preparations in clinical use. Appendix 5 details availability by country.

Table 6. Status and activity of current and approved oral and intravenous antifungals.

Disease/status	Intravenous only		Intravenous and oral (azoles and flucytosine)						Oral only	
	AmB	Candins*	Flu	Itra	Vori	Posa	Isavu	5FC@	Terbinafine	Griseofulvin
On the WHO EML?	Y	N	Y	N	N	N	N	Y	N	Y
Generics available?	Y	N	Y	Y	Y	N	N	Y	Y	Y
Cryptococcosis	+++		++	++	++	++	?	+++		
Candidiasis	+++	+++	++	++	++	++	++	++		
Aspergillosis	+	+		+	++	++	++	?		
Histoplasmosis	+++		+	+++	++	+++	?			
Pneumocystis										
Mucormycosis	++					++	++			
T. marneffei infection	+++		+	+++	++	?	?			
Skin, hair nails			++	++	?	?	?		+++	++
Mycetoma										
Chromoblastomycosis				+	?	++	?			

Y yes **N** no **?** not studied **+** some activity **++** good activity but not maximally effective **+++** highly efficacious
***** micafungin, caspofungin, anidulafungin azoles and flucytosine **@** = flucytosine
Note: AmB = amphotericin B; azoles = fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole.

Chronic pulmonary aspergillosis is a serious public health issue in countries with high prevalence of tuberculosis or AIDS. This problem is almost entirely neglected at present, with neither diagnosis nor testing available in most resource poor settings.

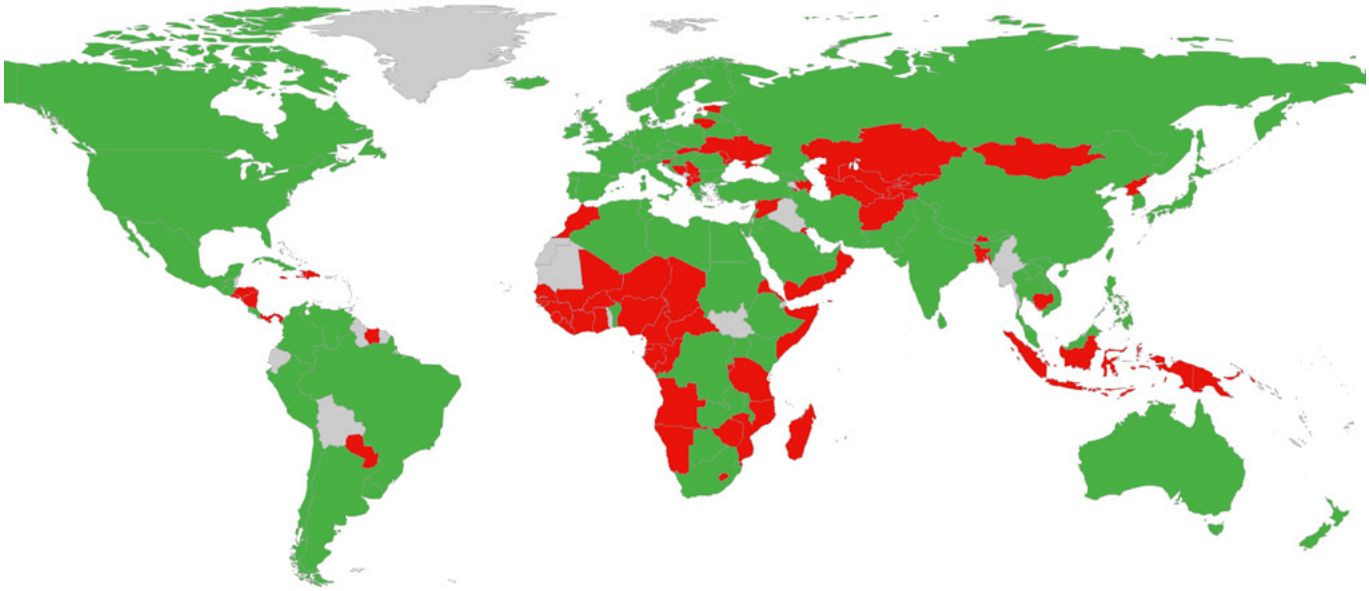
Dr Iain Page The University of Manchester.

RECENT ADVANCES in fungal diagnostics and screening provide an unparalleled opportunity to reduce the burdens of ill health.

Major gaps and key deficiencies

Aside from late diagnosis, which undoubtedly contributes in a major way to poor outcomes, there are some fungal diseases, which respond poorly to antifungal therapy. These include:

- Continuing mortality of ~50% in *Candida* bloodstream infections
- Emergence of multidrug resistant strains of normally susceptible *Candida* species
- Continuing mortality of invasive aspergillosis of 30-90% depending on patient group and speed of diagnosis
- Emergence of azole resistant strains of *Aspergillus* species
- Limited data and efficacy for 'fungal asthma' with current medication
- Modest response rates in chronic pulmonary aspergillosis, breakthrough and relapse common
- Often ineffective therapy for mucormycosis, with radical disfiguring surgery required, and a mortality of 30-50%
- Often ineffective therapy for many other fungal species as *Fusarium, Scedosporium*, black fungi, etc. causing invasive diseases
- No effective medical therapy for mycetoma
- Poor visual outcomes for fungal keratitis, unless diagnosed extremely early
- No effective medical therapy for rVVC
- No effective medical therapy for vaginitis caused by *C. glabrata*
- Very few treatment options for patients with significant liver disease
- Very few clinical trial data on fungal diseases in children



Amphotericin B availability

In 72 countries, the workhorse antifungal amphotericin B is unavailable, yet is critical for cryptococcal meningitis and disseminated histoplasmosis.

Key

Available
Not available
No data

THE KEY ANTIFUNGAL amphotericin B was first used in the late 1950's and is still unavailable in 72 countries. It is critically important for fungal meningitis cure.

D. SYSTEMS FOR FUNGAL DISEASE DIAGNOSIS & TREATMENT

D1 / Fungal diagnostic capacity

Empiricism versus definitive diagnosis

In contrast to bacterial infection which are often successfully treated with empiric choices of antibiotics, with bacteriological data of limited value in changing therapy, fungal diseases are not usually empirically treated outside haematology and critical care units. 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 antifungals, drug interactions and cost are all inhibitory to empirical therapy in many settings, leaving some patients undertreated for so long that they deteriorate and/or die. Informed risk assessment by clinicians, early suspicion of fungal disease and accurate fast diagnosis are the keys to improving outcomes as well as reducing unnecessary therapy.

Laboratory diagnostic capabilities

The greatest diagnostic gains will come from direct testing on specimens, without depending on culture. Direct microscopy, antigen (including glucan), antibody and PCR detection are usually faster than culture. There are only two point of care tests currently, for cryptococcal or *Aspergillus* antigen, but others are welcome. Culture is an important technology for some diseases, although insensitive, because it allows definitive identification of the infecting fungus and susceptibility testing. Growth of *Aspergillus* galactomannan antigen testing in hundreds of centres across the world in HIV and some middle income countries has been directly supported by Pfizer with seed money and training opportunities. Most other technologies have not benefitted from this direct support.

Large populations of patients, whether congregated in large referral hospitals, or with a large community population, or both, require a high standard of fungal disease diagnosis. This is best done in most centres, by combining mycological expertise, with a comprehensive testing portfolio in a mycology reference laboratory (see Appendix 4), within existing university hospitals or other reference centres. Many of the simpler tests will be done by smaller laboratories in regional hospitals, which if quality assured, is critical to saving lives as it is likely to be faster. Economies of scale will drive some concentration of testing and expertise. One mycology reference laboratory should be present for every 5-10 million people, depending on the configuration of health services.

Monitoring of treatment and detection of resistance are also critically important laboratory functions, by means of therapeutic drug monitoring and susceptibility testing.

GAFFI seeks to improve existing health capacity and calls for at least one expert in fungal disease diagnostics in each country to provide the combination of critical mass, scale for economy and quality, surveillance data and a training focus. Strong clinical links are very important for hospital integration and education.

Research has shown that majority of the deaths from HIV/AIDS are as a result of co-infections and opportunistic infections that could otherwise be easily avoided. Of particular importance in this respect are AIDS-related fungal infections of the respiratory system, they can present with symptoms similar to the flu or TB, and particularly in HIV where patients are prone to TB co-infection, aspergillosis and *Pneumocystis* are often missed, resulting in significant morbidity and mortality. Awareness is low.

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OF THE 2 BILLION euro IMI (EU) budget and the R&D funded by the BARDA Broad Spectrum Antimicrobials program, not a single project has been funded to support the development of novel antifungals

D2 / Clinical expertise

Medical personnel

Unfortunately, many doctors know little about fungal diseases. This reflects limited education in medical school and postgraduate courses and the hidden nature of many of the diseases. Knowledge is diffused among different specialties, notably dermatology, infectious diseases and microbiology, haematology, radiology, respiratory medicine, allergy and immunology and critical care. In part this is appropriate, but in part not. Rectifying this problem requires education in parallel with provision of necessary diagnostics. Education without the means of achieving a diagnosis is problematic, and exacerbated if treatments are not available.

Pharmacist expertise

Pharmacists can and do play a critical role in guiding doctors and patients in the appropriate use of antifungal medication. Drug interactions are a particular problem for antifungal drugs, and toxicities can be avoided or minimised with well-informed usage. Some antifungals require monitoring of blood levels or for abnormal kidney or liver function.

The recent introduction of a new expert training curriculum in the UK for specialised antimicrobial pharmacists -which includes antifungal expertise, will support antimicrobial stewardship and assist in the battle against antimicrobial resistance. Electronic resources for pharmacists and healthcare professionals can check antifungal and HIV drug interactions online or as a smartphone App. This initiative needs to be replicated in other countries.

Adverse drug reactions account for as many as 1 in 6 hospital admissions, and 1 in 7 serious adverse reactions. As one example, drug reactions cost the UK NHS ~$722m a year in 2004. In addition, common antifungal drugs have over 2,000 drug:drug interactions. Similar issues face prescribers of HIV medications.

Nursing expertise

Nurses make important contributions to good care for patients with. Many experienced nurses develop excellent clinical skills, which contribute to diagnosis of complex problems, including fungal diseases. This is particularly true in nursing staff working in HIV/AIDS, haematology, allergy and respiratory medicine because the fungal infection and/or allergy rates are relatively high.

A new generation of clinical experts in fungal diseases

With an increasing number of chronic fungal diseases requiring treatment, there is an opportunity to train a new generation of clinicians with fungal expertise. With appropriate diagnostic support, major improvements in diagnostic success and improved patient outcomes are assured.

D3 / Clinical guidelines – who, where and about what

The WHO has issued clinical guidelines on the screening, diagnosis and management of cryptococcal meningitis in AIDS (33). The WHO has also issued guidelines on oral and cutaneous fungal infections and other conditions in AIDS (34). Within the last decade, the IDSA, ESCMID, BSMM, BAD and others have published guidelines on aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, onychomycosis, sporotrichosis, as well as HIV and other management guidelines for specific risk groups. Many countries and national societies have published guidelines on the prophylaxis, empiric therapy and treatment of fungal infections in profoundly immuncompromised and critical care patients, with a focus on aspergillosis and candidiasis. A few paediatric guidelines have been published.

There are no published guidelines on the diagnosis and management of *Pneumocystis* pneumonia, fungal keratitis, *T. marneffei* infection, fungal asthma, recurrent vulvovaginal candidiasis, tinea capitis, allergic fungal rhinosinusitis, paracoccidioidomycosis, mycetoma or chromoblastomycosis. There are essentially no public health strategies for the prevention or large scale management of fungal infections, with the exception of guidelines on the prevention of aspergillosis related to hospital building work and composting facilities.

D4 / The lack of public health mycology

Surveillance of disease is a cornerstone of public health and therefore the presence of one of more surveillance programs an indication of the perceived importance of a given topic amongst public health leaders. The UK has a voluntary reporting scheme for *Candida* bloodstream infection and neonatal infections and reports its antifungal susceptibility patterns for one reference laboratory. France collects national data on rarer fungal infections and numerous sophisticated national epidemiology studies have been undertaken.

The US CDC has run post-transplant and *Candida* bloodstream epidemiology studies, as well as outbreak investigations (fungal meningitis, coccidioidomycosis, fungal keratitis, sporotrichosis and others). Academics, usually supported by industry, have run prospective epidemiology studies in invasive fungal infections in many countries, notably in *Candida* bloodstream infections, antifungal susceptibility and latterly in invasive aspergillosis. So only the UK and France have ongoing fungal disease surveillance and this is limited in scope. (See Appendix 6 for more details).

PUBLIC HEALTH MYCOLOGY is a non-existent discipline, which needs fostering by Schools of Public Health, scholarship programs, development of surveillance networks and incorporation into mainstream global health institutions.

E. GLOBAL HEALTH ARCHITECTURE FOR FUNGAL INFECTIONS

The first global estimation of the burden of fungal disease was published in 2009 (cryptococcal meningitis in AIDS) (1). There is no recognized national or international authority on public health mycology. There is no WHO program on mycology. Schools of public health and tropical medicine barely cover fungal disease in their curricula. A small number of Mycology Reference Laboratories exist, most disconnected from public health agencies, with a focus on providing expert and unusual diagnostic tests for clinical care (Table 9). One, in Chandigarh, is a WHO collaborating center, and another in Sudan is a clinical center focused on the subcutaneous fungal disease mycetoma.

Few international health agencies or funders have a fungal diseases program. WHO in Geneva has enabled, with external grant support, the formulation of HIV focused cryptococcal management guidelines (HIV Division) and supported the development of skin and oral health in HIV guidelines, through the maternal and child health division. Mycetoma has been accepted as a Neglected Tropical Disease, without any financial support. None of the regional WHO offices, including PAHO, have any fungal disease program. Medecins Sans Frontiere run an access program endeavouring to enable access to amphotericin B and flucytosine for cryptococcal meningitis. PEPFAR provides fluconazole to many countries. The Pfizer donation program has also provided fluconazole to millions of patients worldwide.

F. RESEARCH SUPPORT FOR FUNGAL INFECTIONS

Research grant funding is provided by numerous national agencies and by the European Commission. The vast majority of government funding is spent on pre-clinical, pathogenesis type work. An analysis of UK funding between 1997-2010 found 171 studies (2.8%) related to mycology (total investment £48.4 million, 1.9% of all infection research, with mean annual funding £3.5M) (35). Studies related to global health represented 5.1% of this funding (£2.4M) and preclinical work received 87% of grants. A similar situation exists in the USA with NIH funding (3). The vast majority of epidemiology studies and most clinical training has been funded by the pharmaceutical industry.

DEATHS from fungal infections in AIDS are estimated at 700,000 annually, nearly half the total. Concrete steps to improve diagnosis and access to therapy, including a screen and treat program for pre-symptomatic cryptococcal disease, could realistically reduce deaths by 457,000 by 2020, if over 60% of patients are reached.

G. ROADMAP FOR THE NEXT 10 YEARS

GAFFI sees a huge opportunity to reduce unnecessary deaths from fungal diseases over the coming decade (See appendix 7). GAFFI's specific proposals for improving outcomes in patients with fungal disease are summarized here:

Short term (1-3 years)

- Roll out point of care, or simple molecular/antigen assays for *Pneumocystis* pneumonia and disseminated histoplasmosis
- Roll out *Aspergillus* antibody testing post-TB/smear-negative TB and access to itraconazole/voriconazole in high burden TB countries
- Consolidate and deliver GF and PEPFAR funding (diagnostics and drugs) for cryptococcal meningitis, *Pneumocystis* pneumonia and disseminated histoplasmosis in AIDS in LMICs
- Develop a network of expert clinicians, supported by laboratory diagnostics, with clinical guidelines and 'train the trainer' programs
- Enable access to fluconazole, itraconazole, amphotericin B in all countries and flucytosine in those countries with a large cryptococcal burden (Appendix 5)
- Undertake implementation science research to understand the optimal means of bringing in combined diagnostics and treatments on different community and hospital settings
- Develop low cost infection control procedures to reduce hospital-acquired infections in countries with high rates
- Greatly increase the capacity for training in diagnostics and public health mycology
- Facilitate mycology telemedicine for diagnosis through data and image sharing

Medium term (3-5 years)

- Roll out point of care diagnostic for fungal keratitis
- Expand the portfolio of standard diagnostic testing to include hospital-acquired infections and ongoing surveillance to inform national governments
- Develop mycology reference laboratories in each country to provide a critical mass, focus for real clinical expertise, epidemiological data and local training (Appendix 4)
- Roll out preventative programs for injury-related fungal diseases in farmers and other occupational risk groups, based on solid epidemiological evidence
- Support public health mycology with high quality epidemiology studies
- Share experience of sustainable successful programs with other countries to enable widespread sustainability of both diagnostics and treatments
- Develop local and national clinical guidelines for locally prevalent fungal diseases
- Develop more regional or continental external quality schemes for mycology, with a focus on assessing antigen, antibody and molecular assays

Table 7 Modelling of the potential for reduction in deaths in HIV infection and after TB in those without HIV infection if improved diagnosis, cryptococcal antigen screening and treatment are implemented (Appendix 7). An estimate of the cost of the program for cryptococcal disease and pneumocystis pneumonia, indicates that implementing the program in AIDS would cost ~$30 per HIV patient, about $2300 per life saved, with additional huge benefits for others with less severe fungal disease.

Table 7. Estimated numbers of lives saved by implementing at least 60% coverage of diagnostics and treatment for HIV and TB patients by 2020.

Implementation plan	Deaths if recommendations implemented to >60% by 2020 (1000's)						Annual reduction in deaths by 2020
Year	2015	2016	2017	2018	2019	2020	
Current ARV track	1,340	1,260	1,180	1,100	1,020	940	560,000
90-90-90		1,220	1,100	980	860	740	760,000
CM	304	263	228	178	142	93	211,470
PCP	266	238	213	177	143	113	152,185
DH	80	72	60	48	32	16	64,000
CPA in HIV	50	45	40	33	28	20	30,000
CPA in non-HIV	158	142	126	102	87	63	94,680
Total fungal deaths	858	760	667	538	432	305	

CM = cryptococcal meningitis **PCP** = *Pneumocystis* pneumonia **DM** = disseminated histoplasmosis
CPA = chronic pulmonary aspergillosis

Long term (6-10 years)

- Expand the number of mycology reference laboratories with allied clinical expertise to most countries and additional cities in large countries
- Adopt the best antifungals and immunotherapies as guided by high quality clinical studies, across the world
- Compare time trends in incidence and outcomes of fungal infections to allow best practice to be identified and then adopted regionally and internationally
- Refine strategies for screening for and/or prophylaxis against fungal infections in different prevalence situations
- Utilize advances in genetic risk profiling to identify high risk patients, prior to infection or allergy, and study/adopt optimal strategies for monitoring and early therapy

If the recommendations in this report are implemented diligently in all countries, except those wracked by war, GAFFI is confident that **95**% of people with serious fungal disease will have access to the best diagnostics and the vast majority of these will be diagnosed. Assuming access to antifungal therapy becomes universal, at least for the generic agents, **95**% will be treated. This constitutes GAFFI's goal for the next 10 years encapsulated as **95-95 by 2025.**

Supporters of the Global Fungal Infection Forum

No supporter has had input into the content of the materials and presentations used in the Global Fungal Infection Forum (Appendix 1).

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Technical Abbreviations

ABPA-Allergic Bronchopulmonary Aspergillosis **AIDS**-Acquired Immunodeficiency Syndrome **ART**-Anti-Retroviral Therapy **ARV**-Anti-Retroviral
CM-Cryptococcal Meningitis **COPD**-Chronic Obstructive Pulmonary Disease **CPA**-Chronic Pulmonary Aspergillosis **CSF**-Cerebrospinal Fluid
CT-Computed Tomography **DH**-Disseminated Histoplasmosis **ELISA**-Enzyme-Linked Immunosorbent Assay **HIV**-Human Immunodeficiency Virus
LFA-Lateral Flow Assay **LFD**-Lateral Flow Device **MDR-TB**-Multidrug-Resistant Tuberculosis **MRI**-Magnetic Resonance Imaging **PCP**-*Pneumocystis* Pneumonia
PCR-Polymerase Chain Reaction **RVVC**-Recurrent Vulvovaginal Candidiasis **SAFS**-Severe Asthma with Fungal Sensitization **TB**-Tuberculosis


95/95
BY 2025

LEAVE NO ONE BEHIND. Too many people have no access to life-saving fungal diagnostics and antifungal medicine. This has to change

GAFFI is a registered International Foundation based in Geneva, focussed on 4 major tasks related to serious fungal infections. These are:

- Universal access to diagnostics for serious fungal disease
- Universal access to antifungal agents
- Accurate data on the number and severity of fungal infections
- Health professional education related to better recognition and care for patients with serious fungal disease

95/95 BY 2025