

The ambitious '95–95 by 2025' roadmap for the diagnosis and management of fungal diseases

David W Denning^{1,2,3}

Fungal lung disease affects tens of millions worldwide and leads to over a million deaths annually. After skin disease (1 billion affected) and mucosal candidiasis (most women at some time and oral and oesophageal candidiasis), pulmonary fungal disease is the third most common fungal disease group, and the most serious.

On 5 May 2015, the Global Action Fund for Fungal Infections (GAFFI) launched a 10-year ambitious target to enable 95% of the world's population to have access to fungal diagnostics and 95% to have access to antifungal therapy by 2025.¹ The key pulmonary fungal diseases and the necessary diagnostics are shown in table 1.

The current deficiencies in diagnostic provision across the world are stark. No *Aspergillus* IgG or precipitins testing for chronic pulmonary aspergillosis and aspergilloma in Africa, and many other countries. No low cost PCR for *Pneumocystis pneumonia* (PCP) diagnosis anywhere, and currently PCP is diagnosable before death in children in only the most sophisticated hospitals. Skin prick testing and/or fungal-specific IgE testing for allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation is barely used in the assessment of severe asthma outside a few centres with a special interest. The diagnosis of invasive aspergillosis is difficult everywhere, but impossible in any timely fashion without CT scanning and *Aspergillus* antigen detection. Differentiation between TB, chronic pulmonary aspergillosis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis in non-immunocompromised patients in endemic areas is difficult without access to antibody and antigen serology and specialised fungal culture; many centres in the Americas where these endemic mycoses regularly occur do not have this capability.

Antifungal therapy is also not widely available, with the exception of fluconazole. Unfortunately fluconazole has no activity against *Aspergillus*, and is inferior to itraconazole and other extended azoles for histoplasmosis, blastomycosis and paracoccidioidomycosis. Itraconazole is not yet on the WHO Essential Medicines List, and unfortunately GAFFI's application in December 2014² was not successful; the reviewers confused the role and spectrum of fluconazole and itraconazole. Amphotericin B use was first reported in 1959 to treat a woman in Detroit with chronic pulmonary aspergillosis³ and chronic histoplasmosis,⁴ but is still unavailable in 72 countries across the world.¹ As generic voriconazole becomes more widely available, greater access will be necessary to improve outcomes in aspergillosis.

GAFFI is calling for six actions to address these major problems:

- ▶ 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 per country, led by an expert in fungal disease diagnostics with a comprehensive diagnostic portfolio and critical mass of healthcare professionals, and more than one such laboratory in populous countries (each serving a population of 5–10 million).
- ▶ Develop a network of expert clinicians and 'train the trainer' programmes, 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 experts in public health mycology, currently a non-existent discipline probably because most fungal infections are non-transmissible.

The respiratory medicine community can make a massive difference to reducing mortality and morbidity across the world in several ways. The first is to consider chronic pulmonary aspergillosis (and other endemic mycoses) as a possible diagnosis in patients

with suspected TB but negative microbiological investigations. With a similar clinical presentation and radiology to TB (but usually without pyrexia), and cultures for *Aspergillus* being routinely negative, *Aspergillus* IgG testing is critically important. There are an estimated 450 000 deaths due to chronic pulmonary aspergillosis annually, often ascribed to TB,⁵ yet this condition is antifungal responsive.

The second area relates to asthma. Poorly controlled and severe asthma is often linked to fungal sensitisation and some adults have ABPA. *Aspergillus fumigatus* is probably the major driver in bronchiectasis and fixed airflow obstruction. While the data are not conclusive, many patients improve with antifungal therapy. The most recent global burden of disease estimates indicate that as many as 489 000 are dying of asthma each year.⁶ While some of these deaths reflect a lack of access to simple medicines such as beclomethasone and salbutamol, others reflect poorly controlled asthma that could be reversible with antifungal therapy. *Aspergillus* infection and allergy in cystic fibrosis is also problematic, although affecting many fewer people.⁷ Much more work needed to address these major problems, and diagnostic capability with fungal skin prick testing or IgE assays is required as a starting point.

Optimising the management of *Pneumocystis pneumonia* in AIDS to reduce the gap in mortality of ~10–15% in high income countries to 30% in middle and low income countries is necessary. Having a reliable diagnostic to identify milder cases before they deteriorate is one key development need, and being able to stop empiric, and often toxic, therapy by ruling out the diagnosis is another.⁸

Invasive aspergillosis is also problematic. Untreated, almost 100% of patients die. Late diagnosis is associated with worse outcomes. The largest group of patients suffering from invasive aspergillosis is probably those with COPD, simply because there are so many such patients. Once admitted to hospital, 1.3–3.9% of patients with COPD develop culture-positive invasive aspergillosis, not always as a result of receiving oral corticosteroids.^{9 10} Cultures are insensitive, and so the real incidence is probably higher than this. Current mortality rates are shockingly high.

While the above pulmonary disorders are well recognised and diagnosable, there are others that are poorly understood, for example the fungal contribution to bronchiectasis progression and symptoms, fungus-associated chronic cough,¹¹ *Aspergillus* bronchitis,¹² the role of *Pneumocystis* and/or *Aspergillus* in driving COPD

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Table 1 Common fungal lung diseases, their estimated burden and required diagnostic tests

Disorder	Context	Global burden	Key diagnostic
ABPA	Asthma Cystic fibrosis	4 800 000 6675	<i>Aspergillus</i> IgE, total IgE
Severe asthma with fungal sensitisation	Asthma	>6 500 000	Fungal IgE, skin allergy testing
Chronic pulmonary aspergillosis	Post-TB, COPD, sarcoidosis, NTM disease, post-pneumothorax, ABPA, rheumatoid arthritis etc	1 200 000 after TB, 1 800 000 other disorders	Antibody, CXR, CT scan, microscopy, culture
Invasive aspergillosis	Leukaemia, transplantation, COPD, AIDS	>300 000	Antigen, PCR detection, CT scan, microscopy, culture
<i>Pneumocystis</i> pneumonia	AIDS Immunocompromised	>400 000 >100 000	PCR detection, microscopy
Endemic mycoses*	Non-immunocompromised	??	Antibody, culture, biopsy
Other invasive/opportunistic lung infections†	Immunocompromised, including AIDS		Microscopy antigen, culture, biopsy

*Endemic mycoses = coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis in non-immunocompromised patients.

†Mucormycosis, cryptococcal pneumonia, histoplasmosis, coccidioidomycosis.

ABPA, Allergic bronchopulmonary aspergillosis; CXR, chest radiograph; NTM, non-tuberculous mycobacterial infection; TB, pulmonary tuberculosis.

exacerbations¹³ or sudden infant death syndrome,¹⁴ fungal-associated extrinsic allergic alveolitis and adverse effects of mould exposure at home and at work. A much better understanding on the fungus–lung interaction, taking into account human genetic and pulmonary structural differences, is required to address many of these disorders properly. The focus of GAFFI's 10-year Roadmap are the immediate problems of ensuring access to diagnostics and treatments for high-calibre physicians. Research, fundamental, translational and on best implementation practice, will also make major contributions to lung health over a longer period.

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Correction notice This article has been corrected since it was published Online First. The provenance and peer review statement has been corrected.

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