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

David W Denning1,2,3

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 PCR 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, coccidiodomycosis, 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.5 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, 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 beclometasone 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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HOT off the breath

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disorders properly. The focus of GAFFI
ences, is required to address many of these
genetic and pulmonary structural differ-
interaction, taking into account human
longer period.

major contributions to lung health over a
best implementation practice, will also make
research, fundamental, translational and on
treatments for high-calibre physicians.

10-year Roadmap are the immediate pro-

exacerbations13 or sudden infant death syn-
drome,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

Chronic pulmonary aspergillosis
Post-TB, COPD, sarcoidosis, NTM disease,
post-pneumothorax, ABPA, rheumatoid arthritis etc

Invasive aspergillosis
Leukaemia, transplantation, COPD, AIDS

Pneumocystis pneumonia
AIDS

Endemic mycoses*
Non-immunocompromised

Other invasive/opportunistic lung infections†
Immunocompromised, including AIDS

*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.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Context</th>
<th>Global burden</th>
<th>Key diagnostic</th>
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<tbody>
<tr>
<td>ABPA</td>
<td>Asthma</td>
<td>4 800 000</td>
<td>Aspergillus IgE, total IgE</td>
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<td></td>
<td>Cystic fibrosis</td>
<td>6675</td>
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<tr>
<td>Severe asthma with fungal sensitisation</td>
<td>Asthma</td>
<td>&gt;6 500 000</td>
<td>Fungal IgE, skin allergy testing</td>
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<tr>
<td>Chronic pulmonary aspergillosis</td>
<td>Post-TB, COPD, sarcoidosis, NTM disease, post-pneumothorax, ABPA, rheumatoid arthritis etc</td>
<td>1 200 000 after TB, 1 800 000 other disorders</td>
<td>Antibody, CXR, CT scan, microscopy, culture</td>
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<td></td>
<td></td>
<td>&gt;300 000</td>
<td>Antigen, PCR detection, CT scan, microscopy, culture</td>
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<tr>
<td>Invasive aspergillosis</td>
<td>Leukaemia, transplantation, COPD, AIDS</td>
<td>&gt;400 000</td>
<td>PCR detection, microscopy</td>
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<td></td>
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<td>&gt;10 000</td>
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<td>Pneumocystis pneumonia</td>
<td>AIDS Immunocompromised</td>
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<td>Endemic mycoses*</td>
<td>Non-immunocompromised</td>
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<td>Antibody, culture, biopsy</td>
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REFERENCES


2. GAFFI recognises world AIDS day, by applying for itraconazole to be included on Essential Medicines List. http://www.gaffi.org/gaffi-recognises-world-aids-day-by-applying-foritraconazole-to-be-included-on-essential-medicines-list/


