



Year 1 Review

September 2014

Summary

GAFFI was formally launched in London, New York, Sao Paulo and New Delhi in late 2013/early 2014, with the mission to reduce illness and death associated with fungal diseases worldwide.

During the first 12 months of operation, GAFFI has achieved over 90% of its year 1 objectives:

- **Public health:** For the first time, burden of fungal disease estimates have been made for just over half the global population in 33 different countries and the rate of chronic fungal lung infection following TB in Africa in HIV positive and negative patients estimated.
- **Fungal diagnostics:** Six different commercial *Aspergillus* antibody (IgG) tests have been compared and a 'gold standard' test selected, commercial sources of fungal disease tests have been identified and *Pneumocystis pneumonia* diagnosis has been simplified through faster and simpler fungal DNA extraction from sputum in preparation for launch in low income countries.
- **Antifungal treatments:** Availability and costs of amphotericin B, flucytosine, fluconazole and itraconazole for most countries and availability of drug monitoring in 34 countries have been ascertained.
- **Health professional education:** In collaboration with its partner LIFE, the health professional education website has been translated into Spanish, several educational courses have been held in the UK, India and Brazil and advocacy efforts with the WHO, Global Fund, UNAIDS, MSF and other organizations have intensified.

GAFFI Launch:

GAFFI was launched on November 6th 2013 in London and New York, in Sao Paulo on November 23rd and on January 8th 2014 in New Delhi. The meetings were all well attended and attracted press attention, especially in India, with multiple radio, television interviews and newspaper coverage.



GAFFI's Goals:

GAFFI has been in operation for 12 months from July 2013. GAFFI's achievements against its Year 1 goals are summarised in this review.

GAFFI has 4 primary long term goals:

- Goal 1 - Increase awareness of the impact of fungal disease
- Goal 2 - Universal access to diagnostics for fungal disease
- Goal 3 - Universal access to appropriate and affordable antifungal therapeutics with a focus on generic agents
- Goal 4 - Improve education of health professionals about fungal disease.

Goal 1 Outcomes - Increase awareness of the impact of fungal disease

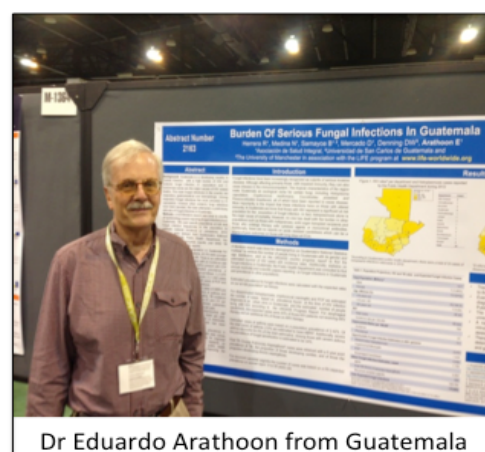
A major goal is to achieve increased awareness of fungal disease globally. There are very few public health programs in fungal disease worldwide, and clinical suspicion of fungal disease is necessary for a good clinical outcomes. GAFFI's broad approach to these deficiencies is a combination of estimating of burdens of disease, measuring the impact of fungal diseases on the

individual and their community, raising both medical and public awareness and influencing key decision-makers in individual countries and in global health agencies.

Goal 1:	Increase awareness of the impact of fungal disease
One-year Objective	
1-1 Strengthen evidence for global burden of fungal diseases by providing scientific expertise and guidance for studies in designated countries	
Key Activities	
1.	Estimate (from existing population and underlying disease data) the overall burden of fungal diseases in selected countries a. Metric: Objective owners and stakeholders identified b. Metric: Estimates of the overall burden of disease in process in at least 20 countries
2.	Initiate studies to establish global, regional or national burden of five priority serious fungal diseases a. Metric: Objective owners and stakeholders identified b. Metric: Study on global burden of <i>Pneumocystis pneumonia</i> initiated c. Metric: Studies to directly measure the regional or national burden of five priority diseases initiated

1.1.1 Burden of fungal disease

Burden of fungal disease estimates have been made in 33 countries, with another 6 country abstracts to be presented at ICAAC in Washington in September 2014, constituting just over 50% of the world's population. Partial or complete estimates of fungal disease burden have been presented as abstracts for Argentina, Austria, Australia, Belgium, Brazil, China, Czech Republic, Denmark, Dominican Republic, France, Germany, Hungary, Guatemala, India, Iran, Iraq, Ireland, Israel, Jamaica, Kenya, Mexico, Mongolia, Netherlands, New Zealand, Nigeria, Russia, Saudi Arabia, Senegal, Singapore, South Korea, Spain, Sri Lanka, Tanzania, Trinidad and Tobago, Uganda, UK, Ukraine, Uruguay, Vietnam and Zambia.



Of these country estimates, two reports have been published - Russia and Austria and those for Israel, Nigeria and Spain accepted for publication. Other country burden estimates have been submitted for publication - Ireland, India (chronic pulmonary and ABPA in asthma), Jamaica, Trinidad & Tobago and Senegal.

Global burden of aspergillosis in cystic fibrosis patients have been estimated and published in PLoS One. Global burden of recurrent vulvovaginal candidiasis has been estimated and paper submitted. Contact has been made with the Institute of Health Economics and Metrics (Christopher Murray and colleagues in Seattle), with a tentative plan to estimate allergic bronchopulmonary aspergillosis in asthma and vulvovaginal candidiasis in women.

1.1.2 Studies of burden of fungal diseases

Limited progress has been made with the global burden of *Pneumocystis pneumonia* due to the outbreak of fungal meningitis in the USA. Discussions with US Centers for Disease Control occurred in September to take this forward.



Outpatients in Gulu, Uganda

Direct measurement of chronic pulmonary aspergillosis (CPA) rate following tuberculosis in Gulu, northern Uganda is nearly complete (second survey in progress) showing an overall cavitation rate on chest Xray rate of 24% and Aspergillus antibody positivity rate of 12% requiring further analysis.

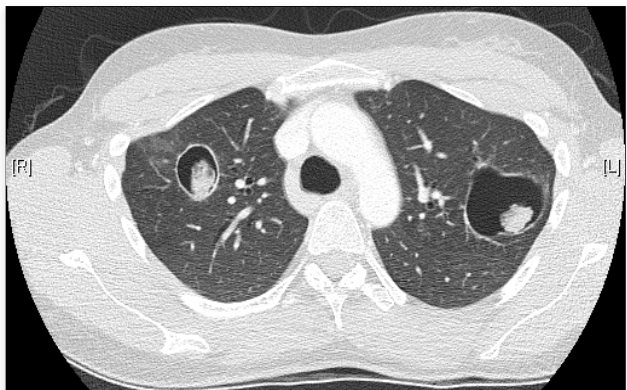
A multi-institution study of the frequency of CPA following tuberculosis in Kenya has been planned and approved by the ethical committee, but not yet funded. AIDS-related fungal

infections in Guatemala (Cryptococcal meningitis, disseminated histoplasmosis and Pneumocystis pneumonia (PCP)) have been planned and submitted for funding, but not yet funded. This project will be resubmitted for funding. A study of CPA prevalence in Lagos after tuberculosis is in progress. Other direct epidemiological studies of fungal keratitis and PCP await improved diagnostic tests.

1.1.3 Additional activities

News items on the GAFFI website have focused on major public health issues in fungal diseases. The LIFE newsletter has been delivered to over 4,600+ health professionals worldwide on a quarterly basis. GAFFI President appeared on UK breakfast television in July 2014 and talked about aspergillosis in cystic fibrosis.

Presentations at numerous scientific meetings have highlighted the burden of fungal diseases, including a recent plenary presentation at the International Union of Microbiological Societies. Link here: <http://www.gaffi.org/media/news/>. GAFFI supported a satellite meeting (December 8th, 2013) on cryptococcal meningitis in Cape Town at the International Conference of AIDS and STI's in Africa.



Aspergillus fungal balls in cavities in both sides of the lung leading to severe bleeding and ill health. An example of chronic pulmonary aspergillosis

Key contacts with numerous health agencies including WHO, UNAIDS, UNITAID, MSF, CHAI, JICA, SIDA, Bill and Melinda Gates Foundation, CDC and others have been made and fostered. A stakeholder meeting is planned for early 2015 to draw these contacts together and develop a road map for the future.

Goal 2 Outcomes - Improve access to diagnostics for fungal disease

Both improved diagnostic tests for low and middle income countries and improved access to diagnostics are critically important GAFFI goals. Fungal disease is often clinically silent and/or mimics other infections and specific diagnostic tests are required for diagnosis. Many hospitals and countries have little or no diagnostic capability. Complex test formats, expense, inadequate laboratory infrastructure and a lack of training are all barriers to diagnostic testing. Accurate assessment of the burden of disease requires accurate diagnosis.

Goal 2:	Improve access to diagnostics for fungal disease
One-year Objective	
2-1 Establish current level of provision of conventional (microscopy, culture and serology) and commercial diagnostics worldwide	
Key Activities	
1.	Identify the manufacturers and distributors of fungal diagnostics worldwide a. Metric: Objective owners and stakeholders identified b. Metric: List of manufacturers and distributors compiled by objective owners c. Metric: Significant commercial diagnostic gaps identified and validated with stakeholders
2.	Undertake global mapping of current conventional and commercial diagnostic test provision a. Metric: Objective owners and stakeholders identified b. Metric: Map of current test provision compiled by objective owners c. Metric: Significant gaps in current provision identified and validated with stakeholders

2.1.1 Manufacturers of fungal diagnostic tests

Commercial producers of all Aspergillus IgG antibody tests, Pneumocystis real-time PCR, cryptococcal antigen, histoplasma antigen and IgE tests have all been identified. These have been linked to the relevant diagnostic section on the LIFE website at:

<http://www.life-worldwide.org/fungal-diseases/antigen-testing/>
<http://www.life-worldwide.org/fungal-diseases/antibody-testing/>
<http://www.life-worldwide.org/fungal-diseases/allergy-testing/>

2.1.2 Global mapping of current conventional and commercial diagnostic test provision

The availability of conventional mycology capability (tests and skills) has not been systematically clarified. It is apparent that large gaps exist, mostly in low income countries, but the absence of personnel working in mycology, has prevented getting a full picture of conventional testing capability. The availability of commercial tests in each country has not been fully mapped (lack of funds). The availability of therapeutic antifungal drug monitoring (TDM) has been mapped in 34 countries, and is being analysed.



Dr Subho Chakrabarti from Kolkata & David Denning who worked on TDM availability

2.1.3 Additional Activities

A. Demonstration Sites:

A major grant was submitted to the Japanese International Cooperative Agency (JICA) for Kenya to provide CT scanners, mycology labs and histopathology labs/autopsy rooms in 9 hospitals in development with the Kenya Medical Research Institute (KEMRI) as the implementing partner. The focus of this initiative is both fungal disease and cancer, given some of the similarities in diagnostic testing. Malcolm Richardson did a week long site visit to multiple hospitals to ensure that the physical lab plans can be implemented and discuss training.

The fungal diagnostic market in China was estimated at \$1.9Bn. A National Plan was developed with key opinion leaders to develop Mycology Reference Laboratories in each province of China, set up a National Training Centre for short fungal diagnostic courses for technical staff, develop public health and clinical expertise and undertake surveillance.



B. Diagnostic Developments:

Pneumocystis pneumonia: The development of a simpler and quicker sputum fungal DNA extraction system was funded by GAFFI and undertaken by Lumora. This comprises a simple process comprising two steps: 250ul sputum is liquefied in 2 parts buffer one part sputum and processed via a heat elution column with a resin cocktail to remove PCR inhibitors. A prototype will now be produced and will be tested in a clinical laboratory.

A follow on grant to evaluate the diagnostic potential of this extraction system and a PCP molecular diagnostic in adults and children with HIV infection was submitted to UNITAID, but not funded.

Fungal keratitis: Pilot work on a point of care diagnostic test for fungal keratitis has been completed and a diagnostic grant submitted but not funded. The groundwork for this diagnostic test is completed.

Chronic pulmonary aspergillosis: *Aspergillus* antibody testing comparison (7 commercial assays) is in progress, using UK and Ugandan sera. A 'gold standard' test has been identified.

C. Advocacy:

Launch meetings in November - January pivotal. Continuing efforts in India to implement plan of a fungal reference lab in each state in India is being worked on (election halted matters).

Productive meetings were held with UNAIDS and separately the Global Fund in June 2014, after many prior meetings. A costing/funding model for UNAIDS to support fungal infections in AIDS, will be developed in partnership with others. GAFFI will initiate this, linking into the 'Spectrum model' on HIV (Futures Institute) and the One Health tool the WHO uses. See news item on the GAFFI website: <http://www.gaffi.org/media/news/>

A meeting was held with Manica Balasegram (Director of MSF Access program) in June to discuss collaboration/common cause with MSF, notably with their access campaign and supporting their TB program with *Aspergillus* antibody testing and training in the management of CPA.



D. GAFFI Fund raising:

Fund raising efforts were initiated. Approaches to other experienced fundraisers to develop fund raising infrastructure are ongoing.

Kirschel Foundation in London have agreed to hold an auction for GAFFI in London for 60 select guests. Details are still to be thrashed out. Fund raising meetings have been held with Rotary (Geneva local), Rotary international (in India), UBS Foundation, Wise in Geneva, Total in France (stalled pending Pasteur deliberations on their overseas branches). Contacts have also been made with ~25 other foundations including Louis Dreyfus Foundation, Rothschild, Herrod, Bertarelli (no feedback), Soros, and others.

Goal 3 Outcomes - Improve access to appropriate and affordable antifungal therapeutics with a focus on generic agents

The majority of work in this topic has related to mapping access to itraconazole, fluconazole, conventional amphotericin and flucytosine across the world, and understanding documenting local prices. While amphotericin B and flucytosine have been available for over 50 years and are the key drugs for cryptococcal meningitis and other fungal infections, they are unavailable in many countries. Itraconazole and terbinafine are the leading drugs for skin fungal infections but are not on the WHO essential medicines list. GAFFI aims to make all these agents universally available.

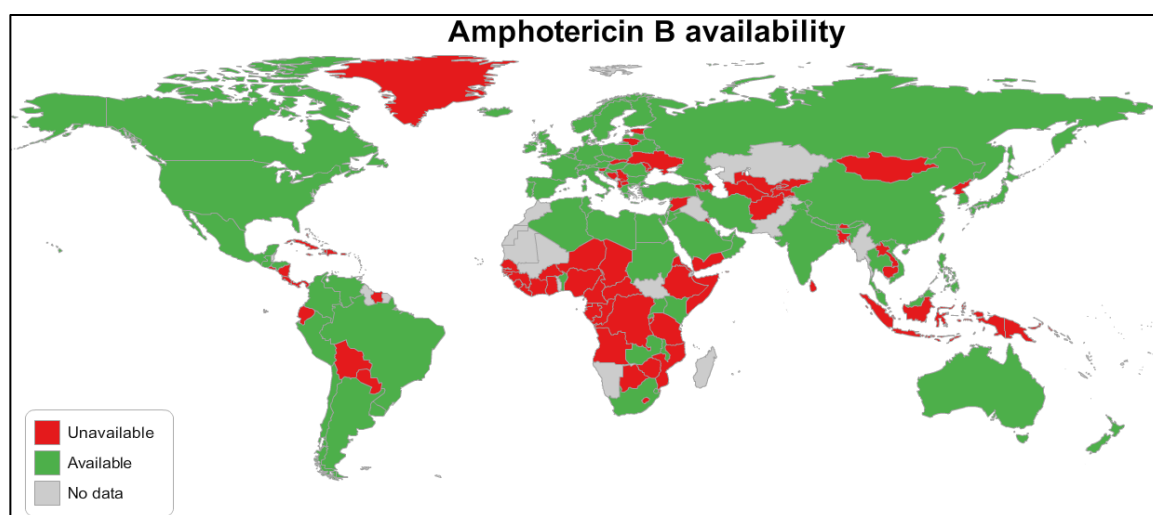
Goal 3:	Improve access to appropriate and affordable antifungal therapeutics with a focus on generic agents
One-year Objective	
3-1 Conduct evaluation of current provision of systemic antifungal agents worldwide	
Key Activities	
1.	Identify the manufacturers and distributors of antifungal agents worldwide a. Metric: Objective owners and stakeholders identified and project work commenced b. Metric: List of manufacturers of generic antifungal compounds prepared
2.	Initiate global mapping of current availability and costs of amphotericin B, flucytosine and itraconazole a. Metric: Objective owners and stakeholders identified and project work commenced b. Metric: List of in-country distributors for each compound prepared c. Metric: Estimated costs of provision of these compounds (at current prices) determined
3.	Initiate global mapping of current availability of ophthalmic antifungal preparations (especially natamycin) a. Metric: Objective owners and stakeholders identified and project work commenced b. Metric: List of in-country distributors for each compound prepared

3.1.1 Identify the manufacturers and distributors of antifungal agents worldwide

Limited progress has been made on this other than identifying the manufacturers of flucytosine.

3.1.2 Initiate global mapping of current availability and costs of amphotericin B, flucytosine and itraconazole

This work is partially completed, with maps posted on the GAFFI website and an abstract and poster presented at ECCMID in Barcelona in May 2013. Additionally fluconazole availability and price was mapped.



3.1.3 Initiate global mapping of current availability of ophthalmic antifungal preparations (especially natamycin)

The manufacturers of ophthalmic preparations of natamycin have been identified, but their distribution and global coverage not yet documented.

Goal 4 Outcomes - Improve education of health professionals about fungal disease

There have been numerous initiatives in this domain, mostly small scale. Health professionals need to have fungal disease at the front of their mind when dealing with patients with complex problems, notably cancer, AIDS, critical care and respiratory disease. Laboratory training is critical for building diagnostic capability. Antifungal prescribing can be complex and pharmacists need to be aware of drug interactions and dose adjustments. GAFFI, in concert with many others, is committed to improving health professional competence related to fungal diseases.

Goal 4:	Improve education of health professionals about fungal disease
One-year Objective	
4-1 Provide on-line educational resources and facilitate learning opportunities for health professionals	
Key Activities	
1. Working with its partner LIFE complete development of its educational website and translate content into French and Spanish a. Metric: Objective owners identified b. Metric: Project work initiated and completed	
2. Develop self-directed learning modules for selected fungal diseases, with its partner LIFE a. Metric: Objective owners identified b. Metric: On-line content compiled, reviewed and made available to health professionals in English c. Metric: Initiate application for CME approval	

3. Initiate contact with non-governmental organizations and other potential partners to provide training courses appropriate to selected clinical disciplines
 - a. Metric: Objective owners and stakeholders identified
 - b. Metric: Assess training needs and develop plans for at least three different clinical disciplines
 - c. Metric: Initiate design and development of on-line instruction modules for clinicians in English, Spanish and one other language
 - d. Metric: Initiate design and development of local training courses

4.1.1 Working with its partner LIFE complete development of its educational website and translate content into French and Spanish



Dr Juan Luis Rodriguez-Tudela
speaking with Dr Michel
Glauser about GAFFI

LIFE (Leading International Fungal Education) is an initiative of the UK's charity Fungal Infection Trust that has supported The Aspergillus Website since 1998. The LIFE website (www.LIFE-worldwide.org) was translated into Spanish by Juan Luis Rodriguez Tudela. A proposal to place the whole website into a electronic tagging system, allowing automated translation into multiple languages and updating was prepared by an external agency. Two pharmaceutical companies were approached for support but have so far declined this invitation. This approach would also allow development of ebooks, for the whole website, or just sections for particular medical groups.

4.1.2 Develop self-directed learning modules for selected fungal diseases, with its partner LIFE

A grant from the Fungal Infection Trust has allowed the development of the world's first online microscopy and histopathology course in fungal disease. This is being developed at the University of Manchester in 4 modules, and is intended to be a self-taught course for those with different levels of prior training and laboratory roles.

4.1.3 Initiate contact with non-governmental organizations and other potential partners to provide training courses appropriate to selected clinical disciplines

The University of Manchester has set up a 1 year taught Masters in Medical Mycology (course director Riina Richardson), with a particular focus on developing mycology lab directors. Several sections of the course have been independently accredited for postgraduate medical training (CPD/CME). To build capacity and allow teaching in other languages, this course has been offered to teaching institutions in other countries, notably in Spain, France and Uganda, with discussions ongoing. Scholarships were provided by Gilead and Astellas.



Deaf and blind patient from
cryptococcal meningitis being
comforted

4.1.4 Additional Activities

In Brazil:

Two 3 day preceptorships (May and August-2014) were held on the Clinical Management of Invasive Infections, each with the participation of 30 medical leaders from different regions in Brazil. These were supported by by Pfizer and United Medical.

Preparations were laid for a meeting of a medical leaders in Latin America during the INFOCUS meeting in Curitiba to prepare guidelines for the clinical management of the main endemic mycoses. This effort is support by the PanAmerican Association of Infectology.

In India:

The Center of Advanced Research in Medical Mycology and WHO Collaborating Center for Reference & Research of Fungi of Medical Importance In Chandigarh has added the GAFFI and LIFE materials to its regular training program. The center has trained 109 faculty and 78 technicians diagnostic mycology in 17 training courses over 8 years. Short term training in mycology for people from India, Sri Lanka, Nepal, Myanmar and Thailand. This has resulted in the development of a national diagnostic mycology network in India, involving 27 centres, who participate in epidemiological study.

Moving forward - Year 2

GAFFI has delivered over 90% of its year objectives as well as important additional steps forward in other areas. Year 2 will be focused on continuing to document and estimate the burden of fungal diseases and continuing health professional education. If the funding applications for the Demonstration Sites in Kenya and Guatemala are funded, these will be major activities of work. Real progress towards development of re-engineering the *Pneumocystis* pneumonia diagnostic test and the first point of care test for fungal keratitis is expected. Publication of the findings on chronic pulmonary aspergillosis after TB in Uganda are anticipated in a high profile journals, with subsequent extensive dialogue about rolling out *Aspergillus* antibody testing widely. Closing the loop with UNAIDS, PEPFAR and the Global Fund on provision of diagnostic testing and treatment of cryptococcal meningitis is a major objective, allowing funding for testing and antifungal drugs to flow to needy countries. A stakeholder meeting for key country and international decision-makers is planned for February 2015 and funding is being sought. An additional focus of activity related to the neglected skin disease chromoblastomycosis will be scoped out.

Glossary of organisations:

Bill and Melinda Gates Foundation,
CDC – US Centers for Disease Control
CHAI – Clinton Health Access Initiative
Global Fund – Global Fund to fight AIDS, Tuberculosis and Malaria
ICAAC - American Society for Microbiology Interscience Conference on Antimicrobial Agents and Chemotherapy
JICA – Japan International Cooperative Agency
LIFE – Leading International Fungal Education
MSF – Medicines Sans Frontieres
PEPFAR – President’s Emergency Program For AIDS Relief
SIDA – Swedish International Development Agency
UNAIDS – WHO-affiliated and co-located organization focused on AIDS
UNITAID – Agency hosted by WHO in Geneva.
WHO – World Health Organisation