

## **Report on activities for 2016**

GAFFI Roadmap 95-95 by 2025: "GAFFI estimates that there are more than 1.6 million deaths from fungal disease every year, similar to deaths caused by tuberculosis and three times those caused by malaria. In AIDS patients, the burden of fungal infections is estimated as over 11 million affected with >535,000 deaths annually. In immunocompromised and/or hospitalized patients without HIV infection more than 1.1 million cases occur every year with over 425,000 deaths. Outside of hospital, more than 14 milion fungal lung diseases attributable to fungal infection and allergy with more than 700,000 related deaths."



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#### **Summary**

GAFFI continues to make progress in its mission to reduce illness and death associated with fungal diseases worldwide. Its achievements in 2016, its third year of operation, include:

- Unavailability and price of antifungals: GAFFI has published its findings on the global availability of generic antifungals in the Journal of Antimicrobial Chemotherapy. Amphotericin B is not available in 42 of 155 (27.1%) countries representing an unserved population of 481 million. Fluconazole was licensed in all 141 (88.6%) countries for which data were available although two countries appear wholly dependent on the Diflucan Partnership Program, which is restricted to HIV/ AIDS patients. Itraconazole is unavailable in at least 5 of 125 (4.0%) : the daily price of itraconazole varies from \$1 to \$102. Flucytosine is unavailable in 95 of 125 (76.0%) countries, respectively, representing an unserved population of 2,898 million. The daily price of flucytosine varies from \$4.60 to \$1,409.
- **Essential Medicines List applications:** GAFFI has applied to the World Health Organisation to add itraconazole, voriconazole and topical natamycin 5% (for fungal keratitis) to the Essential Medicines List.
- Reducing AIDS deaths: GAFFI has published a model on how many AIDS deaths could be averted with provision of fungal diagnostics and antifungals in the Journal of the Royal Society Philosophical Transactions B. About 360 000 (24%) of AIDS deaths are attributed to tuberculosis. Fungal infection deaths in AIDS were estimated at more than 700 000 deaths (47%) annually. Rapid diagnostic tools and antifungal agents are available for these diseases and would likely have a major impact in reducing deaths. If factored in with the 90–90–90 antiretroviral campaign rollout and its effect, AIDS deaths could fall to 426,000 annually by 2020 from 1,300,000, with further reductions possible with increased coverage.
- Defining chronic pulmonary aspergillosis (CPA) for low resource settings: GAFFI convened a workshop in Liverpool, UK to develop a definition of CPA for centres without fungal diagnostic capability. Colleagues (n=33) from four WHO regions (South-East Asia, African, European, Americas) with an interest in CPA and tuberculosis to consider workable disease definitions for both public health research and clinical care. The workshop output is currently being written up for publication in 2017.
- Chromoblastomycosis as a Neglected Tropical Disease: With support from the Ministries of Health in Brazil and Madagascar, GAFFI has proposed to the WHO that chromoblastomycosis be accepted as a Neglected Tropical Disease.
- Burden of Fungal Diseases: GAFFI's program of mapping the burden of fungal disease was
  extended to include published papers for Dominican Republic, Greece, Kenya, the UK and
  France. Abstracts were submitted to ECCMID for Indonesia, Cameroon, Belarus and Italy.
  Papers were accepted for publication in a themed issue covering 832 million people in 14
  countries: Pakistan, Bangladesh, South Korea, the Philippines, Thailand and Uzbekistan
  from Asia; Ecuador, Canada, Peru, Guatemala, Chile from the Americas; Portugal from
  Europe; and Algeria and Egypt from North Africa.
- **GAFFI UK**: To expand its fund raising reach, operational capacity and country advocacy, GAFFI has developed a sister foundation In the UK.
- Health professional education: LIFE-Worldwide has developed an online microscopy and histology course, launched in late 2016. Multiple congresses have been addressed across the world, and news items and email newsletters mailed to >12,000 health professionals.

#### **GAFFI's Goals:**

GAFFI's achievements against its Year 3 goals are summarised in this review.

- GAFFI has 4 primary long term goals, supported by advocacy:
  - Goal 1 Increase awareness of the impact of fungal disease
  - Goal 2 Improve access to diagnostics for fungal disease
  - Goal 3 Improve access to appropriate and affordable antifungal therapeutics with a focus on generic agents
  - Goal 4 Improve education of health professionals about fungal disease.

GAFFI 10 year Roadmap '95-95 by 2025' focused and fleshed out these objectives as follows:

- 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

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

A major goal is to achieve increased awareness of fungal disease globally, especially among global health agencies and country medical opinion leaders and decision-makers. GAFFI's broad approaches include highlighting the burden of fungal diseases, identifying diagnostic and therapeutic gaps and supporting epidemiological studies to better define fungal disease locally.

#### 1.1 Burden of fungal disease

By the end of 2015, GAFFI had supported burden of fungal disease estimates for 5 billion people (71% of the world's population) in 55 countries. In 2016, estimates for an additional 8 countries were presented including Japan, Bangladesh, Malaysia, Peru, Ecuador, Congo, Philippines, Romania and Uzbekistan. Papers documenting the burden of fungal diseases in Brazil, Greece, Kenya, France and UK were published in 2016, contributing to a total of 29 countries. Papers documenting the fungal burden in 14 other countries with a total population of 832 million were accepted for publication in the Eur J Clin Microbiol Infect Dis in 2016 for 832 million people in 14 countries: Pakistan, Bangladesh, South Korea the Philippines Thailand and Uzbekistan from Asia; Ecuador, Canada, Peru, Guatemala, Chile from the Americas; Portugal from Europe; and Algeria and Egypt from North Africa.



Collaborators have also made a number of additional contributions including a re-estimation of the burden of cryptococcal disease in AIDS by country (Radha Rajasingham et al, submitted for publication), the burden of disseminated histoplasmosis in AIDS in the Americas (Antoine Adenis et al, submitted for publication), the burden of *Pneumocystis* pneumonia in AIDS (CDC) and the country burdens of fungal disease in Italy, Cameroon, Kazakhstan, Belarus and a re-estimation in Indonesia. Epidemiological studies of chronic pulmonary aspergillosis after TB have been completed in Gulu, Uganda, Lagos, Nigeria and Blantyre, Malawi, and are underway in Kenya, Jakarta, Brazil and Portugal. Skin testing exposure surveys for *Histoplasma* are planned in Nigeria and Indonesia.

#### **1.2** Chromoblastomycosis nominated as a Neglected Tropical Disease

Chromoblastomycosis is a rare and neglected tropical disease of the skin and subcutaneous tissue. It is treatable with antifungal therapy, possibly with enhancement with immunotherapy with imiquinod and probably partly preventable. GAFFI has orchestrated the application to the WHO Strategic Technical Advisory Committee for chromoblastomycosis to be added to the internationally agreed list of Neglected Tropical Diseases (NTDs). The application was made formally by the Ministry of Health in Brazil, through PAHO, and supported by Madagascar.



## Goal 2 - 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.

#### 2.1 Demonstration project in Guatemala

GAFFI has supported a demonstration site in Guatemala in the Asociación de Salud Integral (ASI) in Guatemala City under the direction of Dr Eduardo Arathoon and Blanca Samayoa and their teams. The focus is on AIDS-related infections, especially histoplasmosis, cryptococcosis, *Pneumocystis jirovecii* pneumonia and chronic pulmonary aspergillosis after tuberculosis as well as other



AIDS opportunistic infections including other endemic mycoses. At the end of the program, Guatemala will have the first national reference laboratory specialized in mycology providing diagnostic services to HIV patients in Central America.

In Guatemala, 80% of HIV patients develop opportunistic infections as their presenting HIV illness, and disseminated histoplasmosis is the number 1 killer, cryptococcal meningitis second and TB third. The first year of activities are summarized below in relation with the program objectives.

#### 2.1.1 Training activities

Training activities were developed at two levels, national and regional. These activities started on November 24 and 25, 2015 with the 1st national workshop on fungal infections ("Actualización en el Diagnóstico de Infecciones Fúngicas"). Fifteen of 16 HIV care units attended the workshop with a total of 52 participants. Other organizations also attended, to develop partnerships such as with the Minister of Health. The goals of this workshop were: i) to introduce the project to the HIV units and Minister of Health; ii) to identify the needs of each unit and region and iii) to determine the feasibility of establishing a network with ASI as the Reference Laboratory for fungal infections in Guatemala.

During 2016, two regional workshops were accomplished. The first one included training for 30 participants from 6 HIV care units and the second for 18 participants from 4 HIV care units, one of them dedicated to paediatric patients.

Regional workshops comprised a preliminary visit to establish capabilities and needs of the HIV Units. The CrAg test (Cryptococcal antigen) assays, was provided during these visits. Attendees to these workshops included clinical and laboratory staff. The program of these workshops incorporated educational talks for management of fungal infections including clinical cases, current laboratory portfolio available in ASI, and safe delivery of clinical samples towards ASI.



#### 2.1.2 Transfer of technology

To strengthen the ASI laboratory capabilities for the molecular diagnosis of fungal infections, the ASI molecular biology specialist received a 2-week training (May 30th – June 10th) at the Mycology Department, Spanish National Centre for Microbiology of Instituto de Salud Carlos III, Madrid,

Spain. This training was focused on the real time multiplex PCR for detection of *Cryptococcus neoformans*, *Pneumocystis jirovecii*, and *Histoplasma capsulatum*, as well as real time PCR for the detection of *Coccidioides* spp. The techniques are in the final phase of validation in ASI Reference Laboratory.

#### 2.1.3 Building Strategic Alliances

This project has a counterpart alliance with the Ministry of Health and USAID | Capacity – PEPFAR. The Ministry of Health participated during training activities through the National HIV Program. Agreements to ensure that the units have access to antifungals continue via the national HIV Program. However, ASI has been exploring other options such as Diflucan Partnership Program by Pfizer, and Novartis. For the time being, amphotericin B deoxycholate has been purchased with the project budget to treat patients with fungal infections in the network (including some HIV unit cares attended at training activities). ASI has established an agreement with USAID | Capacity – PEPFAR to cover the costs for a quick delivery of clinical samples from distant HIV units to the ASI Reference Laboratory in Guatemala City.

#### 2.1.4 Implementing a model website

To provide the network with a communicative platform, it was decided to develop a website. This website (<u>www.fungired.gt</u>) comprises three layers: i) General information; ii) Education and Training; and iii) Laboratory IT System.

General information describes the network called FUNGIRed<sup>™</sup>, which includes the HIV care units and ASI acting as the Reference Laboratory as well as a clinical consultancy for fungal infections. This section also provides information actions, workshops, lectures and results of the project. Education and Training is key for the network to maintain awareness of the participants and provide an ongoing training platform. Therefore, an e-Learning course has been set up. The course consists of six sections, each containing interactive lectures on various subtopics. At the end of each section, participants are asked to do some homework and answer a short quiz. Additionally, a monitor will be assigned and forum discussions will be organized. Participants must have at least 80% of the course completed to develop competencies and qualify for the course certificate. Laboratory System To provide a quick and accurate diagnostic for patients with fungal infections, a laboratory system has been developed. Through this system, each HIV unit can order on line the tests required to diagnose a suspected fungal infection at the ASI Reference laboratory. The required samples are quickly sent via courier. As soon as the results are ready, they are delivered to the person in charge of the patient. The ASI Laboratory system has been developed on a web environment, which allows remote access through computer, tablet or smartphone, and prior app or software installation are not required. An encrypted username and password is provided to each HIV care unit to access the system, fully confidentially.

This system will allow a permanent communication between HIV units and ASI Reference Laboratory which means that those patients with a fungal infection will get a quicker diagnostic and treatment than that provided before the implementation of the system.

#### 2.1.5 Diagnostic guidelines

As a component of reinforcing high quality fungal infection management, Fungal Diagnostic Guidelines are being developed as protocols for HIV care units and their laboratories. The guideline provides recommendations on transport and sample processing, as well as diagnostic procedures.

#### 2.2 Guidelines for chronic pulmonary aspergillosis

In 2016, guidelines on the diagnosis and management of chronic pulmonary aspergillosis were published by European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society and separately by the Infectious Disease Society of America. These are the

world's first substantive guidelines about this disease entity. Discussions with the WHO indicated that a straightforward definition of disease was required for low and middle income countries.

GAFFI convened the second Global Fungal Infection Forum in Liverpool on October 26<sup>th</sup> to develop

such a definition. Thirty-three experts from institutions with some CPA diagnostic capacity, or in the process of developing it, as well as some senior doctors from several Sub-Saharan African lower income countries with TB and respiratory disease experience. After a day of debate and follow up discussions by email, a draft manuscript is in preparation for submission in 2017 entitled "Operational definitions of chronic pulmonary aspergillosis in



low resource settings". The proposed definition includes symptoms of persistent cough, weight loss, and haemoptysis combined with progressive cavitary infiltration on imaging, with or without a fungal ball, and-or pleural thickening, all present for at least 3 months, together with a positive *Aspergillus* IgG antibody test.

#### 2.3 Engage with the manufacturers and distributors of fungal diagnostics worldwide

Numerous interactions with companies providing cryptococcal antigen assays and *Aspergillus* antibody tests are ongoing.

Chronic pulmonary aspergillosis: commercial *Aspergillus* antibody testing comparisons of 6 test systems are complete and published (Page, 2016). Two 'gold standard' tests have been identified. A separate report (Dummolard, 2016) compared 3 different ELISA tests and introduced a new assay, with high performing characteristics, that may also be a gold standard assay, when replicated by others. Alternative cut-offs have been derived, which need evaluation in a wide spectrum of people. Proposals for European cut-offs have been validated and submitted for publication.

#### 2.4 Kenya – the FIP-Kenya program

GAFFI has been working with several leaders in Kenya and JICA to provide much greater capacity for fungal disease and cancer diagnosis in Kenya. The FIP-Kenya development program aims to provide all 10 of the major urban centers with excellent radiology, histopathology and fungal disease diagnostics and support leading clinical personnel through training, in combination with networking, quality assurance and surveillance programs. Unfortunately the program has stalled after a major scandal hit the Ministry of Health in Nairobi.

## <u>Goal 3 - Improve access to appropriate and affordable antifungal</u> therapeutics with a focus on generic agents

Access to affordable antifungal agents remains a critical goal for GAFFI, with considerable progress made in 2016.

#### 3.1 Global survey of generic systemic antifungals

GAFFI published a landmark paper in 2016, mapping registration, availability and price of itraconazole, fluconazole, conventional amphotericin and flucytosine across the world, although data are incomplete. All but itraconazole are on the WHO Essential Medicines List. This is

<u>1</u>							
Disease/status	Intravenous only	Intravenous and oral					
	Amphotericin B	Fluconazole	Itraconazole	Flucytosine			
Countries where				89/123			
not licensed	22/155 (14.2%)	0/151	3/123 (2.4%)	(72.4%)			
Countries where	42/155 (27.1%)	0/143 *	5/125 (4.0%)	94/120 (78.3%)			
not available							
Population	480,963,000	None	77,960,000	2,898,245,000			
antifungals	(6.62% World)		(1.07% World)	(39.9% World)			

summarized in the table below and visible on dynamic maps for each antifungal online here: <a href="http://www.gaffi.org/why/burden-of-disease-maps/">www.gaffi.org/why/burden-of-disease-maps/</a>:

**Amphotericin B**, broad spectrum and intravenous, is not licensed in 22 of 155 (14.2%) and not available in 42 of 155 (43.1%) countries, representing an unserved population of 480 million. For amphotericin B, as an example, 50mg (usually single day's dose) varied from substantially. Low prices were seen in Netherlands (\$0.13), Russia (\$0.52), Chile (\$0.77) and Tunisia (\$1.05). High prices were seen in Canada (\$171.47), Finland (\$85.44), Germany (\$81.66), Hungary (\$28.73), Bulgaria (\$25.38), Libya (\$20.57), Egypt (\$18.14), Iraq (\$15.17), Israel (\$15.83), Malawi (\$14.08), Vietnam (\$13.76), Brazil (\$13.50), Costa Rica (\$12.20) and South Korea (\$11.54).

**Flucytosine**, required for cryptococcal meningitis in AIDS, is not licensed in 89 of 123 (72.4%) and is unavailable in 94 of 120 (78.3%) countries, representing an unserved population of 2,900 million, including not a single country in Africa. Few countries have flucytosine, but there is a massive variation in daily treatment cost, from \$1,409 (USA), \$626 (United Arab Emirates) to \$8.12 (Greece). In contrast to the UAE, the price in Kuwait is \$10.97 and \$17.00 in Qatar. The price in South Korea has fallen precipitously since we first accessed pricing info, from \$1300 to \$12.74, with a new supplier.

**Itraconazole**, broad spectrum oral with activity for histoplasmosis and aspergillosis, is not licensed in 3 of 123 (2.4%), and 5 of 125 (4.0%) countries, representing an unserved population of at least 78 million. Oral itraconazole at 400mg daily varied from as low as 1 cent in Zambia (\$0.01), to \$98.15 in Sweden. Countries with costs less than \$1 a day for itraconazole therapy include Sri Lanka, India, Vietnam, Lebanon, Bangladesh, Turkey, New Zealand, Uganda and Turkey. Other low priced countries include Taiwan (\$1.01), Slovakia (\$1.14) and Greece (\$1.67). High daily prices are found in Sweden (\$98.15), Norway (\$18.59), South Africa (\$11.56), Iraq (\$10.57), Libya (\$10.70), Belgium (\$10.35) and Denmark (\$10.09).

**Fluconazole**, used for *Candida* infections and cryptococcal meningitis, is available in all 143 countries, but in Africa, 3 are wholly dependent and 13 partially dependent on the Diflucan Partnership Program, which is restricted to HIV/AIDS patients. Comparing prices for the most commonly recommended induction dose of fluconazole for cryptococcal meningitis at 750-800mg daily, the range in price was from \$0.13 in Ethiopia to \$30.52 in Australia. Other countries with very low costs include Zambia (\$0.01), Peru (\$0.20), India (\$0.21), Lebanon (\$0.25), Costa Rica (\$0.26), Vietnam (\$0.34), Iran (\$0.48), Namibia (\$0.51), United Kingdom (\$0.61), Sri Lanka (\$0.64), Malawi (\$0.72), Guatemala (\$0.76), Bangladesh (\$0.97), Slovakia (\$1.09), New Zealand (\$1.47), Kyrgyzstan and Bolivia (\$1.50), Uganda (\$1.56), Tanzania (\$1.85), Bahrain (\$1.89), Moldova (\$2.10) and Kenya (\$2.20).

#### 3.2 Engagement with generic manufacturers of antifungals.

GAFFI has identified a number of generic manufacturers interested in working to expand access to antifungals. Work is ongoing to develop these partnerships – meetings have been held with 7 generic manufacturers to date. GAFFI is aiming for WHO PQ and/or stringent regulatory approval (SRA) approved products in all locations and addresses this in all discussion with potential partners.

# **3.3** Application to the WHO for itraconazole, voriconazole and natamycin 5% ophthalmic solution to be added to the Essential medicines List.

GAFFI has applied for itraconazole (capsules and oral suspension), voriconazole (capsules and intravenous solution) and natamycin 5% ophthalmic solution to be placed on the World Health Organization (WHO) Essential Medicine List (EML), in collaboration with colleagues from the Instituto de Salud Carlos III, International Foundation for Dermatology, London School of Hygiene of Tropical Medicine and The University of Manchester.

The proposed indications for itraconazole capsules are chronic cavitary pulmonary aspergillosis, invasive aspergillosis, histoplasmosis (therapy, primary and secondary prophylaxis), sporotrichosis, paracoccidioidomycosis, infections



caused by *Talaromyces marneffei* (formerly penicilliosis) (therapy, primary and secondary prophylaxis) and chromoblastomycosis. These are all conditions in which fluconazole is ineffective. Itraconazole oral solution is preferred in late stage AIDS patients, leukaemia patients and children. The proposed indications for voriconazole are invasive and chronic pulmonary aspergillosis, with intravenous therapy preferred initially in invasive disease. The only indication for topical natamycin 5% in the eye is fungal (mycotic) keratitis and 3 randomised studies have shown it to be more efficacious than other topical medicines, given alone. There is currently no Essential Medicines listing for any preparation active against fungal keratitis.

#### 3.4 Global mapping of current availability of voriconazole and topical natamycin

GAFFI has started its process to map country availability and price of intravenous and oral voriconazole, and ophthalmic antifungal preparations (especially natamycin 5%). This work is ongoing, and should report in 2017.

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

Health professionals need to have fungal disease at the front of their mind when dealing with patients with complex health problems. 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. In addition to its 'Fact sheets': <a href="http://www.gaffi.org/media/fact-sheets/">http://www.gaffi.org/media/fact-sheets/</a> GAFFI also has a twitter account with >1,000 followers.

#### 4.1 Launch by its partner LIFE of an online microscopy and histology training program

Experts at The University of Manchester and the Mycology Reference Centre, Manchester have developed the course. It will teach not only how to rapidly and accurately diagnose life-threatening fungal infections, but also how to set up direct microscopy in a diagnostic laboratory. It is available at <u>www.microfungi.net</u>. The course comprises 4 modules:



- 1. Basic microscope handling, sample preparation, safety and preparation of stains
- 2. Identification of different fungi by direct microscopy
- 3. Histology of the top 10 most common fungal infections
- 4. Fungal histology of unusual fungi.

The course includes knowledge assessments, tests, quizzes and practice assessments. Participants who pass the final assessment are awarded a certificate of completion accredited by The University of Manchester. The course is currently being translated into Spanish, French and Portuguese.

### 4.2 Educational presentations of GAFFI's work for health professionals

Presentations at numerous scientific meetings have highlighted fungal diseases, in multiple countries, usually at national or internal congresses including UK (Advances Against Aspergillosis meeting), Netherlands (Royal Netherlands Academy of Arts and Sciences), UAE (Gulf Congress of Clinical Microbiology and Infectious Diseases), Russia (Scientific Conference on Medical Microbiology and Clinical Mycology (XIX Kashkin readings), South Africa (EMBO Workshop on AIDS-related Mycoses), India



(Society for Human and Animal Mycology of India), Indonesia (Asia Pacific Society of Medical Mycology congress), Iran (1<sup>st</sup> IFRC International Conference on Clinical Mycology, Aspergillus and Aspergillosis), Pakistan (Symposium - Reducing the Burden of Fungal Infections: Early Diagnosis and Treatment and Course - Utility of Galactomannan and Beta-D-Glucan for the diagnosis of invasive fungal infections), Uzbekistan (Training in *Aspergillus* galactomannan detection), Chile (II Training in medical mycology, at Public Health Institute of Chile, XXXVIII Chilean Congress of Microbiology, XIV INFOCUS Latin America and XIX International Immunocompromised Host Society), Brazil (National Academy of Medicine), Hungary (Educational talk at the 20TH Training Course on Haemopoietic Stem Cell Transplantation) as well as multiple smaller, local meetings. Local training was also delivered in Guatemala as part of that project.

In Mexico, a closed Facebook group called "the Mycologist" set up in 2012 has attracted >200 members, and provides an information source on fungal meetings, diagnostic images and hot topics in spanish. Since 2016, live transmissions have been shown on many key topics, including antifungal therapy.

### 4.3 News items and newsletter distributed by GAFFI's educational partner LIFE

LIFE-Worldwide focuses on health professional education and provides summaries of pivotal literature which has the potential to change clinical practice and focused on public health on a weekly basis, together with major strategic developments in the area. These posts are posted every 7-10 days. The quarterly LIFE newsletter is emailed to over 12,000 health professionals around the world. Usage of the LIFE website is ~12,000 unique users monthly.

## Advocacy supporting the above 4 goals

Advocacy is a key continuing mission for GAFFI.

#### 5.1 Open Letter on Disseminated histoplasmosis and AIDS

An Open Letter on disseminated histoplasmosis and AIDS from multiple individuals was addressed and delivered to key stakeholders tackling the AIDS epidemic in February 2016. It was addressed to the WHO, UNAIDS, PAHO, MSF, the Gates Foundation, DNDi, UNICEF as well as national public health agencies and governments. It requested these organisations to realize the following measures:

1. To enable direct, rapid access to reliable and practical diagnostic tests in all areas where histoplasmosis occurs or is suspected;

2. To define the real extent of morbidity and mortality of histoplasmosis so as to define all histoplasmosis endemic areas in the world;

3. To bring therapy for histoplasmosis within the reach of all who need it, especially in endemic areas

4. To stimulate scientific investigation on histoplasmosis epidemiology, diagnosis and treatment

5. To organize regular conferences and educational sessions concerning histoplasmosis with support for those living in endemic areas to participate and enable disease awareness amongst treating physicians.

## **5.2** Mobilise the international global health funding community to support fungal complications of AIDS and TB

Three talks were delivered at the WHO in Geneva, one to the TB group entitled 'Differential diagnosis of smear negative TB – opportunities for better patient outcomes" one to the TB, AIDS, NTD cluster entitled "Global Action Fund for Fungal Infections (GAFFI) - Why, Who, Where and How? What can and should WHO do?" and a third to the AMR GLASS meeting (with representatives from all WHO regional offices present) on "Emerging AMR in fungi causing invasive infections in humans". Individual discussions were held with the TB, AIDS and NTD groups at WHO, as well as the Antimicrobial Resistance and Essential Medicines groups, also at WHO. Additional meetings were held with the Global Fund for AIDS, TB and Malaria, UNITAID, DNDi, Red Cross, Amref and South African Medical Research Council, as well as numerous individual interactions.



At the Royal Society in London, on March 7-8<sup>th</sup>, a symposium "Tackling emerging fungal threats to animal health, food security and ecosystem resilience" was held and GAFFI President David Denning presented a model for AIDS showing how action to improve fungal diagnosis and antifungal therapy could reduce deaths by over a million within 5 years. This work was then

published December in 2016. The potential for reducing deaths is substantial, as shown in this graphic and assumes that 60% patients with AIDS have access to the above diagnostic and tests antifungal therapy on а gradually increasing rate. From 100,000 lives saved in year 1, to over 300,000 lives saved per year by year 5, major strides could be made in reducing deaths. It is also is assumed that improved access to anti-HIV therapy (90-90-90) is also important.



The actions required to achieve this are shown in the table from the publication:

disease entity	diagnostic test	diagnostic action	treatment	proposed action to be taken
cryptococcal antigenaemia pre- meningitis	antigen test on serum, plasma and whole blood	screening <200 (<100) CD4 counts	fluconazole therapy	promote rapid adoption of WHO guidelines ensure access to rapid antigen tests
cryptococcal meningitis	antigen test on blood or CSF, lumbar punctures	rapid antigen testing (LFA) lumbar punctures	amphotericin B + flucytosine, followed by fluconazole	promote rapid adoption of WHO guidelines ensure access to rapid antigen tests improve access to drugs in high burden countries
Pneumocystis pneumonia	microscopy or PCR on sputum, induced sputum or BAL, NPA PCR in children	enable rapid testing on respiratory samples on AFB smear-negative samples	empirical therapy usually given, so discontinuation of unnecessary empirical therapy in those negative oral therapy of mild cases avoiding hospitalization	promote implementation of rapid molecular diagnostic develop treatment guidelines for LMICs
disseminated histoplasmosis	antigen test on serum or urine PCR on blood	antigen (or PCR) testing on hospitalized HIV patients in relevant countries	immediate treatment with amphotericin B, followed by itraconazole. Itraconazole alone for mild cases, avoiding hospitalization	ensure access to antigen and/or PCR diagnosis and drugs in high burden countries develop WHO/PAHO treatment guidelines. Place itraconazole on the WHO EML and national EMLs
chronic pulmonary aspergillosis in 'smear-negative TB'	serum <i>Aspergillus</i> IgG antibody test	testing all AFB smear- negative cases, and any relapse cases	itraconazole or amphotericin B	ensure access to <i>Aspergillus</i> antibody diagnosis and drugs in high burden countries place itraconazole on the WHO EML and national EMLs

## **Moving forward - Year 4**

GAFFI has set up a sister foundation (Charitable Incorporated Organisation) in the UK to support both fund raising and operational delivery of some of its programs. GAFFI UK has identical objectives to GAFFI and some common Board members.

GAFFI's objectives are gradually being met, partly by co-operative actions by the GAFFI ambassadors, partly by the GAFFI advisers and the recognition by multiple NGO and governmental agencies of the major deficits in this area. The major focus for 2017 is to establish routes for improved access to antifungal drugs. This major task will be assisted by the appointment of Henk den Besten as a GAFFI senior advisor.

#### **Glossary of organisations:**

Gates Foundation – Bill and Melinda Gates Foundation, CDC – US Centers for Disease Control DNDi – Drugs for Neglected Diseases initiative Global Fund – Global Fund to fight AIDS, Tuberculosis and Malaria LIFE – Leading International Fungal Education MSF – Medicines Sans Frontieres PEPFAR – President's Emergency Program For AIDS Relief PAHO – Pan-American Health Organization <u>http://www.paho.org/</u> UNAIDS – WHO-affiliated and co-located organization focused on AIDS UNICEF - United Nations Children's Fund UNITAID - Agency hosted by WHO in Geneva. WHO – World Health Organisation

#### Publications

- 1. Giacomazzi J, Baethgen L, Carneiro LC, Millington MA, Denning DW, Colombo AL, Pasqualotto AC. The burden of serious human fungal infections in Brazil. **Mycoses** 2016;59:145-50.
- 2. Page ID, Richardson MD, Denning DW. Comparative diagnostic performance of six Aspergillus-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis. J Infect 2016;72:240-9.
- 3. Al-shair K, Muldoon EG, Morris J, Atherton GT, Kosmidis C, Denning DW. Characterisation of fatigue and its substantial impact on health status in a large cohort of patients with chronic pulmonary aspergillosis (CPA). **Resp Med** 2016;114:117-22.
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#### Press releases and GAFFI news items:

**Disseminated histoplasmosis in the Americas – a lethal blind spot of health organisations** Posted January 7, 2016.

How to stop crypto- a deadly disease so neglected it is missing on the neglected list Posted January 11, 2016.

## GAFFI delivers its 2015 annual report

Posted February 15, 2016.

<u>Open Letter on Disseminated histoplasmosis and AIDS – to key stakeholders tackling the AIDS</u> <u>epidemic</u>

Posted February 16, 2016.

India State Minister announces free antifungal agents for the poor Posted March 22, 2016.

Burden of fungal diseases in Japan, Bangladesh, Malaysia, Peru and Congo presented at AAA7 and ECCMID Posted April 11, 2016.

Save the Children campaign: Every last child Posted April 26, 2016.

Henk den Besten to join GAFFI as Senior Advisor Posted May 16, 2016.

**O'Neill final report on AMR has specific recommendations about antifungal resistance** Posted May 19, 2016.

Essential medicines in the USA – acquisition of generic marketing licenses causing exponential price rise Posted June 6, 2016.

Importance of access to fungal disease diagnostics in AIDS highlighted in Russia by GAFFI's
President
Posted June 15, 2016.

<u>Cryptococcal meningitis persists despite 90-90-90 – Botswana experience</u> Posted July 18, 2016.

Millions deprived of life- saving antifungal medicines Posted August 11, 2016.

Online fungal microscopy course will teach rapid diagnosis of fungal infection for everyone worldwide Posted September 6, 2016.

Over a million AIDS deaths preventable by 2020 Posted October 24, 2016.

**Promoting Innovation and Access to Health Technology** Posted October 31, 2016.

HealthWell Foundation Opens New Fund for the Prevention and Treatment of Fungal Infections Posted November 1, 2016.

**550 AIDS patients can be saved every day by detecting and treating fungal infections** Posted December 1, 2016.

Itraconazole, voriconazole and natamycin 5% ophthalmic preparation proposed as WHO <u>'essential antifungal medicines'</u>

Posted December 19, 2016.