

# Report

Lima Peru 3-5 September 2019



## GLOBAL FUNGAL INFECTION FORUM 4

DEVELOPING A COALITION ROADMAP FOR INTEGRATION  
OF FUNGAL DISEASE PATHWAYS AND ANTIMICROBIAL RESISTANCE  
(AMR) SOLUTIONS INTO HEALTH SYSTEMS IN LATIN AMERICA

95/95  
BY 2025





**Attendees in Lima Peru came from the following countries**

Argentina, Brazil, Canada, Chile, China, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Switzerland, UK, Uruguay, USA, Venezuela.

**Participants' roles**

Clinical and Laboratory Directors and fungal diseases experts / Radiologists / AMR specialists /  
Ministry of Health divisional heads for HIV/AIDS, Tuberculosis and lung diseases and AMR.

# Contents

## 4. Executive summary

## 5. GAFFI's mission and country participation

## 6. Introduction

## 6. Meeting objectives and scope

## 7. Burden of fungal diseases in Latin America

Health expenditure by country

Health access and quality

## 10. Health systems and fungal diseases

Country examples of health system approaches

Importance of high quality imaging interpretation

Histopathology

Research and modeling needs

Importance of fungal diagnostics

Recommendations re innovations

Recommendations re access to diagnostics

## 16. Promising practice examples

## 18. Serious fungal diseases in Latin America

HIV/AIDS

TB-like fungal diseases

Serious hospital-acquired fungal infection-

Invasive candidiasis and invasive aspergillosis

Neglected skin fungal tropical infections

## 24. Availability and price of medicines

Training and implementation of antimicrobial stewardship teams

PAHO Strategic Fund

Recommendations re access to antifungal treatment

## 30. Antifungal resistance

Challenges in antifungal drug resistance surveillance

GLASS Fungal antimicrobial resistance (AMR) Program

Preparedness for identification and susceptibility testing of *Candida* spp.

Susceptibility testing

Recommendations re laboratories and epidemiologic surveillance

## 37. Educational resources

Recommendations re continuing education

## 40. Promoting integration of fungal disease into health systems

## 42. Abbreviations

## 43. Global Fungal Infection Forum meetings

## 45. References

## Appendix 1

Detailed country and disease specific estimates of fungal disease incidence and prevalence in Latin America

## Appendix 2

Neglected Fungal Skin Tropical Diseases in Latin America

The meeting program and speaker biographies can be viewed here:

<https://www.gaffi.org/global-fungal-infection-forum-4-in-lima/>



## Executive summary

Serious fungal diseases probably affect more than 2 million people in Latin America and the Caribbean, of which >350,000 are life-threatening. The Americas have many endemic fungal infections affecting otherwise healthy people. Among those with HIV, TB, cancers and other conditions, fungal diseases can be lethal; up to 50% of AIDS-associated deaths are due to fungal infections. Under-diagnosis and missed diagnoses are likely common, partly due to the limited historic availability of both diagnostic tests and treatments.

Over the past decade, there has been a remarkable revolution in fungal diagnostics moving from conventional culture and microscopy to antigen and antibody detection, commercial and standardized PCR and recently mass spectrometry (MALDI-TOF) identification. These diagnostic tools have transformed the speed and sensitivity of diagnosis. Digital radiology permits remote interpretation of images, allowing expertise to reach small and remote communities, if they are linked up. Artificial intelligence reading of radiology images, skin lesions, pathology and direct microscopy slides is becoming a reality. But currently in most hospitals and clinics, very few patients are benefitting from these modern technologies.

In Lima, Peru on September 3 to 5 2019, 60 delegates from 18 Latin American countries met and discussed how fungal disease diagnosis and antifungal therapy could be better integrated into healthcare systems across the continent. Detailed discussions on antifungal resistance (AMR), especially in *Candida* spp. were also held.

1. All WHO recommended Essential Diagnostics for fungal diseases should be implemented for routine use in public hospitals (provincial-state equivalent and above) and AIDS focused clinics. This will strengthen diagnostic capability throughout the Region. These developments should be accompanied by engagement with external proficiency quality assurance programs. Development of National Diagnostic Mycology laboratories and networks would support critical mass in this discipline.
2. WHO-endorsed Essential Medicines should be made routinely available in public hospitals and AIDS-focused clinics, especially flucytosine for cryptococcal meningitis and liposomal amphotericin B for disseminated histoplasmosis. This will require accelerated registration processes in some countries, and use of the PAHO Strategic fund.
3. Applications should be made to the WHO to include *Pneumocystis* PCR as an Essential Diagnostic and echinocandins as Essential Medicines.

4. Strengthening of public health for fungal diseases including a) development of specific surveillance programs to track fungal infections of public health importance, including *Candida auris*, the NTD sporotrichosis and serious endemic fungal infections and b) active epidemiology research programs, using point of care and non-culture diagnostics.
5. National antifungal resistance surveillance programs should be developed for *Candida* species and species of *Aspergillus fumigatus* complex in public hospitals (provincial-state equivalent and above), with national reporting.
6. Substantial educational efforts of healthcare professionals, notably in the use of non-culture diagnostics, antifungal usage and stewardship programs, WHO Guidelines for Advanced HIV disease, cryptococcal meningitis and other international clinical and laboratory practice guidelines.
7. Assessment and then implementation of artificial intelligence systems to counteract the shortfall in healthcare professionals, notably in radiology, histopathology, dermatology, ophthalmology and education.

These actions will directly support Sustainable Development Goal 3 (SGD3), and indirectly others (SGD1, SGD4, SGD8, SGD9, SGD12, SGD16 and SGD17).



## GAFFI mission

GAFFI was set up in 2013 to persuade the WHO, international health agencies and governments that fungal diseases need to be properly addressed, notably through training of healthcare workers and access to affordable diagnostics and antifungal agents. GAFFI's successful advocacy at the global health level needs to be translated into policy and action on a country basis. The size of the fungal diseases problem and the negative impact of fungal diseases on health is now obvious for most countries. A new generation of highly sensitive diagnostic tools, many easy to use, and affordable antifungals are available. Translating all these opportunities into on-the-ground practice requires a health system approach in each country to generate graduated, sustainable solutions, reducing morbidity and saving lives.

The stimulus for the GFIF4 meeting was a paper published in Lancet Infectious Diseases by Cole et al (2017) "Improvement of fungal disease identification and management: combined health systems and public health approaches." This paper noted that a) "Fungal disease diagnosis requires a high level of clinical suspicion and specialised laboratory testing, in addition to culture, histopathology, and imaging expertise" and b) "Health systems linking diagnostic facilities with therapeutic expertise are typically fragmented, with major elements missing in thousands of secondary care and hospital settings."



**Professor David Denning** (GAFFI) addresses the meeting.



Meeting up over coffee.

## Meeting objectives and scope

The number of both healthcare and community associated fungal infections have risen dramatically over the past three decades, partially attributable to advances in immunosuppressive therapy, the HIV/AIDS pandemic, and a growing complex, multi-morbid hospitalised population. In healthcare settings, fungi have become a leading cause of bloodstream infections. Despite advances in antifungal therapy, an estimated 1.5–2 million people globally die of fungal infections each year. Many patients are never diagnosed and not treated.

As the use of antifungals has increased, so have opportunities for antifungal resistance, whether through acquired resistance or selection for inherently resistant fungi. A noteworthy example of this problem is the global emergence of *Candida auris*, a multidrug-resistant fungus, that causes severe disease and can be transmitted in healthcare facilities causing outbreaks that are difficult to control. Another is azole-resistant *Aspergillus fumigatus*, mostly related to azole fungicide use on crops leading to 'off target' emergence of multi-azole resistance and very limited options for alternative treatment.

### Objectives of the GFIF4 meeting were:

1. To gain a shared understanding of the policy landscape for health systems strengthening in Latin America for a comprehensive approach to fungal diseases.
2. To stimulate active dialogue and generate concrete steps towards the integration of fungal diagnostics into HIV/AIDS programs, TB programs, and high complexity patients (immunocompromised, neonates, transplanted, oncologic and intensive care units' patients among others).
3. To inform country policy and technical leaders about the new generation of sensitive and rapid non-culture-based diagnostics for fungal diseases.
4. To inform country policy and technical leaders about shifts in antifungal chemotherapy and generic antifungal availability and costs and to discuss strategies to improve access to quality antifungal medicines.
5. To provide a venue for individual country planning and feedback on options for improvements and donor support for those actions.



**Professor Juan Luis Rodrigues Tudela** opens the meeting.

## Burden of fungal diseases in Latin America

Like cancer, there are many different sorts of fungal infections, affecting any organ. Skin, hair and nail infections are the most common. However, we address in this report the serious fungal diseases affecting primarily patients with immune defects, lung diseases and those critically ill in the hospital. Using published country estimates for Argentina, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Guatemala, Mexico, Peru and Uruguay, GAFFI updated these and added those countries where estimates have not been published. These and the key assumptions underlying each estimate are presented in Appendix 1, and

summarized here, together with expected mortality rates with and without treatment.

Incidence refers to estimated annual incidence. The burden of skin NTDs (mycetoma and chromoblastomycosis) is not known with confidence but is several thousand cases. Overall, over 2 million people in Latin America are affected, and ~500,000 suffer a life-threatening fungal infection annually. As a general comparator, there were 198,214 pulmonary TB cases in 2018 in Latin America.



**Dr Matilde Roman**, Nicaragua, collects her simultaneous translation earphones.

**Table 1. Burden of fungal diseases in Latin America**

Serious and life-threatening	Incidence HIV/AIDS	Prevalence Non-HIV	Incidence Non-HIV	Total burden <sup>1</sup>	Untreated mortality (%)	Treated mortality (%)	Comment
Disseminated histoplasmosis	9,773	?	?	>10,000	100	50	
<i>Pneumocystis</i> pneumonia	26,400	39,650	39,650	66,050	100	20	
Cryptococcal meningitis	8,766	2,981	2,981	11,747	100	30	
Invasive aspergillosis	>1,364	>66,900	>66,900	>68,200	100	50	
Chronic pulmonary aspergillosis	?	33,600	33,600	33,600	75	45	Morbidity high
Invasive candidiasis	?	180,800	180,800	180,800	95	45	
Oesophageal candidiasis	89,624	?	?	>89,624	<10	<1	Morbidity high
Coccidioidomycosis	?	>20,000	>20,000	>20,000	~50	<10	Morbidity high
Paracoccidioidomycosis	?	>7,800	>7,800	>7,800	30	7	Morbidity high
Sporotrichosis	?	>10,000	>10,000	>10,000	<2	<2	Cat-associated
Fungal asthma	?	1,578,000	1,578,000	1,578,000	<5	<5	Morbidity high
Fungal keratitis	?	19,170	19,170	19,170	100 <sup>2</sup>	~40 <sup>2</sup>	Blindness, not mortality
<b>Totals</b>	<b>&gt;135,927</b>	<b>&gt;1,958,900</b>	<b>&gt;1,958,900</b>	<b>&gt;2,094,828</b>			

1. Total burden = incidence and prevalence from HIV and non-HIV combined

2. sight threatening



## Health expenditure by country

Per-person income, total health expenditure, and health expenditure from public sources.

Country	GDP per capita US \$	% Public health expenditure
Argentina	11452	60.6
Bolivia	2576	70.8
Brazil	11340	45.7
Chile	15356	47.0
Colombia	7752	74.8
Costa Rica	9396	70.1
Cuba	NA	94.7
Dominican Republic	5736	49.3
Ecuador	5425	41.0
El Salvador	3790	63.3
Guatemala	3351	35.5
Honduras	2335	48.1
Mexico	9747	49.4
Nicaragua	1754	54.3
Panama	9534	67.5
Paraguay	3813	38.6
Peru	6568	56.1
Uruguay	14449	67.6
Venezuela	12729	73.6



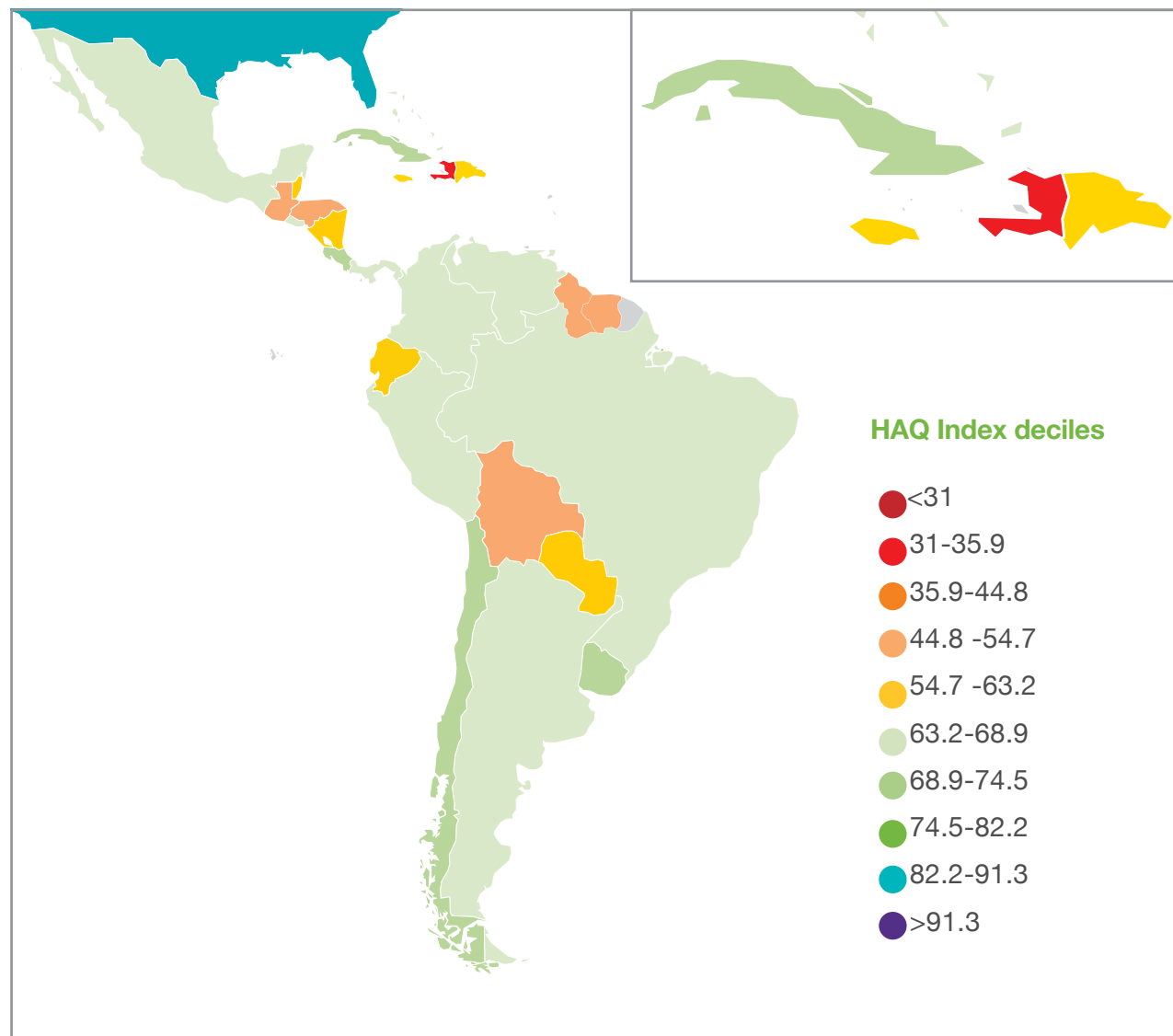
**Figure 1.**

Atun R et al. Lancet. 2015; 385: 1230-47

## Health access and quality

The Healthcare Access and Quality index (HAQ) was created from several datasets including: country burden of disease (not including fungal diseases), injuries and disease risk factors layered on the socio-demographic index for each country. The scales for each are in deciles and the HAQ Index is also presented in deciles. Principal component analysis was used to construct the HAQ Index.

In terms of global comparisons, Canada is 14th with an HAQ Index of 94, the USA is 29th with a HAQ Index of 89, and the next country in Latin America is Chile at 49th with an HAQ index of 78, Cuba at 55th with an HAQ Index of 76 and Costa Rica at 62nd and an HAQ Index of 74.



**Figure 2.**

GBD 2016 Healthcare Access and Quality  
Collaborators. Lancet. 2018; 391: 2236–2271

## Health Systems and Fungal Diseases

Health systems in Latin America have widely different histories of public and private provision of services and current approaches to governance and financing, with associated implications for efforts towards universal health coverage (Atun et al., 2015). Most face continuing challenges in striving towards health equity (Commission of the Pan American Health Organization on Equity and Health Inequalities in the Americas, 2019). By 2030, it is estimated that the healthcare worker (HCW) shortage for 2030 for the region of the Americas will be 640,000. Both overall state of development and income of a country, and the extent of social inequalities within a country (Cotlear et al., 2015) impact access to and quality of health services in each country (Wagstaff et al., 2015; GBD 2016 Healthcare Access and Quality Collaborators, 2018). Hence integration of fungal diagnostics, surveillance and treatments into health systems (Cole et al., 2017) currently varies considerably across countries (Falci & Pasqualotto, 2019).

HCW shortage is one of the major factors affecting health systems. In 2013, 70% of countries in the Americas had enough HCWs to meet basic health needs and in some cases address them thoroughly, but the challenges are distribution, training and migration. (Tercer foro mundial sobre recursos humanos para la salud, Recife-Brasil, 2013). Current health workforce per 10,000 population (2017-2018) is for all the Americas 89.3, distributed as North America 170.8 and Latin America and the Caribbean 42.6 (Indicadores básicos 2019: Tendencias de la salud en las Américas. OPS).

The relative salaries compared with other workers, contract durations and incentives vary substantially by country, without apparent sharing of best practice to ensure a balanced and stable workforce (Carpio & Santiago Bench, 2015).

Several presenters at GAFFI Forum 4 noted the *different contexts* in which diagnostics could be applied to identify fungal diseases cases. One major issue is the particular *geographic area* and endemic mycoses. More common was reference to fungal diseases which occur among those with *other primary diseases* – HIV-AIDS being the most important one, but also those with tuberculosis, asthma, cancer etc. – hence the place of integrating fungal diagnostics and treatment into specialized clinics and some hospital services. Fungal infections are much more prevalent among those cared for by *certain health services*, the prime examples being dermatology and respiratory medicine in outpatients and intensive care and leukaemia units in the hospital. Particular *occupations* of workers, such as those in agriculture or forestry, are linked to certain fungal diseases. Each of geographic area, occupation, primary disease and specific health service provides a way of initially focusing often limited public fungal diagnostic and treatment resources at the most important points in health systems in different countries to engage in case-finding, surveillance, treatment and follow-up.



**Dr Guillermo Garcia Efron**, Argentina, summarised fungal diagnostics - the easy, the standard and the complex.



### Country examples of health system approaches

Examples of *health systems responses* presented at GAFFI Forum 4 ranged from the rudimentary to the sophisticated. We learned that the Dominican Republic had no public provision for fungal diagnosis and treatment, though diagnostics and treatments were available through private payment. In Honduras, some diagnostics and trained personnel were available at hospitals in the capital city, primarily through international collaboration from the US CDC, and several medications were approved for use. Nicaragua described greater advances, particularly around diagnosis, treatment, and surveillance of cryptococcosis and histoplasmosis among those with HIV through specialized clinics. Costa Rica has developed an integrated system across public health and social security services for fungal disease diagnosis and management at primary, secondary and tertiary levels of health services, along with an integrated One Health surveillance system. Diagnostic services and a range of antifungal therapies are available, many through public health systems. Cuba has a public system with trained personnel and diagnostics for case finding and inexpensive treatment of fungal infections for all, though more advanced (non-culture) diagnostics and surveillance remain challenges. Guatemala has developed an integrated set of specialized clinics for those with HIV-AIDS, training of clinicians, links with a centralized laboratory and information system with rapid turnaround of a limited set of fungal disease diagnostic results and specific treatment. Sustainability of this advanced system was an ongoing concern.

### The critical importance of high quality imaging interpretation

Imaging of all modalities plays an important part in the initial recognition of many serious fungal diseases, as well as excluding some. Chest radiographs are critical to the recognition of TB-like fungal diseases. In the lungs and sinuses, CT scanning is essential, and can be life-saving for leukaemia patients, if done promptly. Ultrasound diagnoses heart valve, kidney, liver and intra - abdominal abscesses. MR scanning is especially useful for fungal brain infections and also for bone infections, including assessing mycetoma. As fungal disease is relatively uncommon, radiological interpretation is best done by specialists, often those with neuroradiology or thoracic expertise. Best practice recommendations for radiology and fungal disease have been promulgated in the UK (Schlenz, 2015).

In most high income countries all radiology is now digital and this allows transfer of images to specialist centres for remote reading. (See figure 3 on page 14) In the future, artificial intelligence (AI) reading of radiographs and scans will facilitate high throughput locally with complex images being flagged for expert reading. The GAFFI Forum 4 heard from one expert in this area, focused on TB in chest radiographs and the results of ongoing trials are very promising. Integration of AI into digital systems in smaller hospitals and clinics, combined with remote access to expert radiologists was a future model supported by the meeting. A significant concern of capacity for fast remote reporting was raised, which needs addressing.



Discussion group on radiology and artificial intelligence.



Mayda Perurena outlining how Cuba provides fungal diagnostics and antifungal therapy to its citizens.

### Research and modeling needs

A number of *health system research and modeling needs* emerged both in GAFFI Forum 4 presentations and in the discussions which flowed. Some initial work on the costs associated with fungal infections among those with HIV in Colombia and Mexico (Corzo-León et al. 2018) were relevant to persuading policy makers as to economic burden. One presentation modeled the potential for savings or efficiencies associated with earlier case-finding and better management of fungal diseases in hospitalized patients, primarily through reducing nosocomial spread of infections and duration of hospitalizations (Corzo-León's presentation to GAFFI Forum 4). Cost-effectiveness analysis of different approaches to case-finding and treatment at different points in health systems could adopt various perspectives: that of the patient-family around ability to continue working and quality of life, that of health services society on both the costs and benefits associated with fungal diagnosis and treatment, and that of society incorporating both. Such research will be important to better include fungal diseases in health system planning exercises based on cost-effectiveness ratios for example, see: <https://www.who.int/heli/economics/costeffanalysis/en/> or other metrics of potential impact of mainstreaming the diagnosis and treatment of fungal disease.

### Histopathology - a core service for fungal disease diagnosis

Given that many fungal infections mimic cancer and that fungal culture is often not requested or is negative, there is a continuing core role for histopathologists in the diagnosis of all forms of fungal disease. Best practice reporting has been recommended, as well as an emphasis on speed of processing in immunocompromised and burn patients (Schlenz, 2015). The faster the diagnosis, the more the chance of survival. A free online course in multiple languages is available to augment current training and expertise [www.microfungi.net](http://www.microfungi.net) In the future, AI could transform the reading of histopathology slides.

### WHO endorsed Essential *in vitro* Diagnostic Tests for fungal diseases

Direct microscopy

Histopathology

Blood culture

Fungal culture

Cryptococcal antigen

*Histoplasma* antigen

### Applications submitted in 2019

*Aspergillus* antigen

*Aspergillus* IgG antibody

*Pneumocystis* PCR



Discussion on AMR, laboratory management systems and the role of diagnostics in controlling excess antibiotic and antifungal use.

## Digital radiology connectivity

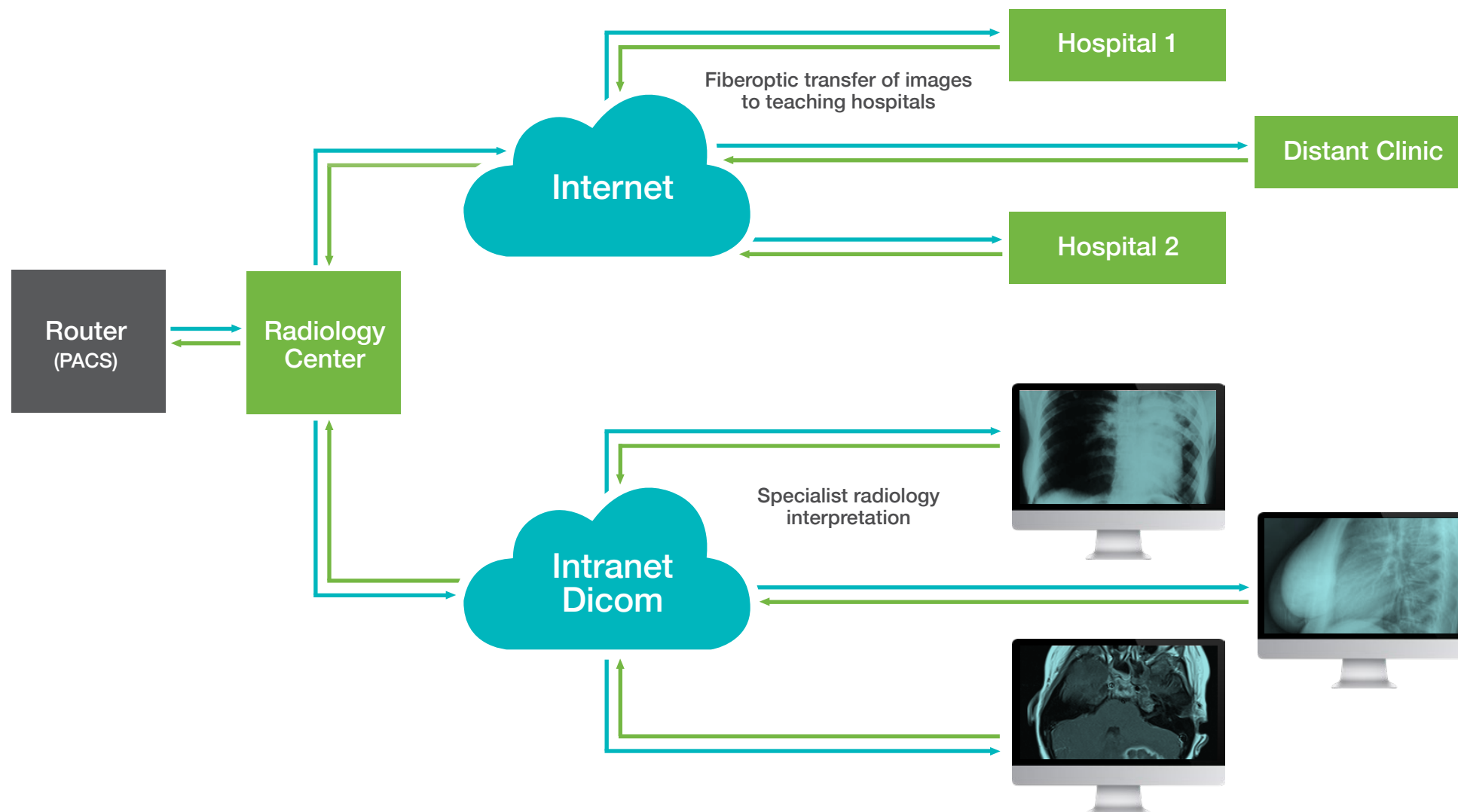


Figure 3

[https://www.who.int/medical\\_devices/publications/Standalone\\_document\\_v8.pdf?ua=1](https://www.who.int/medical_devices/publications/Standalone_document_v8.pdf?ua=1)



### Importance of fungal diagnostics for optimal antifungal prescribing

The lack of routine and timely fungal disease diagnostic testing contributes to excess use of antibacterial drugs, when the clinical problem is fungal. Likewise, if a fungal disease is diagnosed, anti-bacterial therapy can be stopped or if fungal infection can be ruled out, empirical antifungal therapy can be stopped. Among the many examples, are the following:

- In patients with coccidioidomycosis in southern California, 70% received antibiotics before the diagnosis of coccidioidomycosis was made serologically (Chi et al, 2019).
- *Candida* BSI is commonly suspected in Intensive Care. Testing for fungal disease with the  $\beta$ -1,3-D-glucan allows discontinuation of antifungal therapy in >60% of patients, easily covering the cost of the testing (Rautemaa-Richardson, 2018). Broad-spectrum antibacterial therapy can be stopped or reduced in those with invasive candidiasis.
- Patients with GeneXpert or smear-negative pulmonary 'tuberculosis' may have chronic pulmonary aspergillosis, histoplasmosis or paracoccidioidomycosis. Antibody testing for these conditions will result in the correct diagnosis and discontinuation of anti-tuberculous therapy.
- COPD patients admitted to hospital are often given antibiotics, especially if they have pulmonary infiltrates. Life-threatening invasive aspergillosis is found in 1.3-3.9% of all COPD admissions (Guinea, 2011; Xu, 2012) and diagnosis is dependent on fungal culture, *Aspergillus* antigen and antibody testing.

Non-culture fungal diagnostics have the potential to have substantial benefits for clinical outcome, antimicrobial stewardship and AMR control.

### Recommendations re key innovations

1. Promote research on point of care and simple to use diagnostics.
2. Introduction of telemedicine, teleradiography in Latin America.
3. Analysis of the feasibility and importance of artificial intelligence systems for the region.

Table 2. Key diagnostic tests

Serious and life-threatening	Key diagnostic
Disseminated histoplasmosis	Antigen or PCR
<i>Pneumocystis pneumonia</i>	PCR or microscopy
Cryptococcal meningitis	Antigen or culture
Invasive aspergillosis	Antigen and radiology
Chronic pulmonary aspergillosis	Antibody and radiology
Invasive candidiasis	Culture or glucan or PCR
Oesophageal candidiasis	Endoscopy
Coccidioidomycosis	Culture, antibody, microscopy
Paracoccidioidomycosis	Culture, antibody, microscopy
Sporotrichosis	Skin biopsy and culture
Fungal asthma	IgE antibody or skin prick test
Fungal keratitis	Microscopy and culture



Panel discussion on fungal diagnostics.

**Recommendations re access to diagnostics:**

1. Availability of all diagnostic techniques included in the WHO List for Essential Diagnostics plus diagnosis of Pneumocystosis.
  - a Registration of all diagnostic techniques on a country by country basis.
  - b Improvement of diagnostic procurement at competitive prices (e.g. PAHO Strategic Fund).
  - c Ongoing training for fungal diagnostics.
  - d External Quality Control of all techniques put in place.
  - e Analysis of fungal disease burden post-introduction of diagnostic techniques.
2. Routine consideration and diagnosis of TB-like fungal diseases including:
  - a Histoplasmosis.
  - b Chronic pulmonary aspergillosis.
  - c Paracoccidioidomycosis.
  - d Coccidioidomycosis.
3. Improvement of the diagnosis of fungal complications of common respiratory diseases like, COPD, asthma and influenza.
4. A plan for fungal nosocomial infections control with special emphasis in outbreaks caused by fungi such as *Candida auris*.
5. A plan for in situ diagnosis of fungal skin infections, probably including artificial intelligence when fully developed.

6. Cost effectiveness studies of the implementation of diagnostic techniques.

The meeting also agreed that the WHO should be requested to accept PCR for *Pneumocystis* as an Essential Diagnostic.

**Key priority 1**

All WHO recommended Essential Diagnostics for fungal diseases should be implemented for routine use in public hospitals (provincial-state equivalent and above) and AIDS focused clinics. This will strengthen diagnostic capability throughout the Region.

**Key priority 2**

These developments should be accompanied by engagement with external proficiency quality assurance programs. Development of National Diagnostic Mycology laboratories and networks would support critical mass in this discipline.

**Key priority 3**

Applications should be made to the WHO to include *Pneumocystis* PCR as an Essential Diagnostic.



Sample receipt and initial processing at the mycology Diagnostic Laboratory Hub in Guatemala City. (see page 18).

## Promising practice examples

### National Reference Laboratory in Argentina

In 1996, the National Reference Laboratory in Clinical Mycology, the Mycology Department (MD) of the National Institute of Infectious Diseases “Instituto Carlos G. Malbrán”, created a laboratory network in order to support diagnosis by transfer of samples from low complexity laboratories to high complexity laboratories. This network is currently comprised of approximately 150 laboratories representing all 24 jurisdictions in the country. In the same year, a National External Program of Quality Control in Mycology was introduced which offered quality assessment to the members of the network and other mycology laboratories. Moreover, the national reference laboratory has a full quality management system and national accreditation for the determination of susceptibility of clinical yeasts against antifungal drugs. The lab also produces in-house controlled reagents for serological diagnosis.

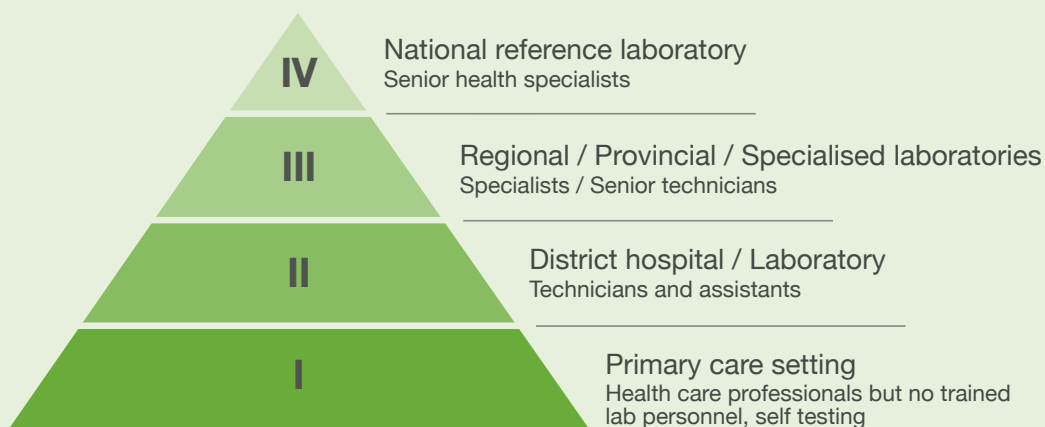
Through this network, national passive surveillance of mycosis is achieved by reference lab diagnosis (including conventional and molecular diagnosis of mycosis; identification of yeasts, molds and endemic dimorphic fungi; and susceptibility tests). Fungal infection notifications are not mandatory in Argentina, with the exception of the province of Catamarca where coccidioidomycosis is a notifiable disease. Active surveillance is carried out by epidemiological surveys and by performing multicenter studies of the most important mycoses to determine trends in aetiology, frequency, and antifungal resistance patterns. In 2019, a fourth national multicenter study of fungemia by yeasts was initiated.

Other activities are coordinated to ensure accurate, reliable and timely laboratory results and support continuous improvement of laboratory performance. Basic and advanced courses in diagnosis and identification of fungi, training of professionals in the national reference laboratory were held. The National Laboratory provides controlled reagents, reference strains and standard protocols as well as continuous professional assistance by request. Professionals also participate in the national network of MALDI-TOF and other activities to determine the diagnostic performance of new techniques and procedures in clinical laboratories.



**Cristina Canteros**, Argentina, making her point about data collection for antifungal resistance surveillance.

**Figure 4. WHO classification of laboratory services**



**Reference** [https://www.who.int/medical\\_devices/publications/Standalone\\_document\\_v8.pdf?ua=1](https://www.who.int/medical_devices/publications/Standalone_document_v8.pdf?ua=1)



### GAFFI Demonstration site in Guatemala

Since 2016, GAFFI in collaboration with the 'Asociación de Salud Integral (ASI)' has developed a project to provide access to diagnosis and treatment of fungal opportunistic infections (OIs) to people with HIV in Guatemala (Samayoa 2020). A network of 13 HIV units and a Diagnostic Laboratory Hub, localized at the headquarters of ASI, was set up.

This new Health System has uncovered a more accurate estimate of the burden of tuberculosis, histoplasmosis and cryptococcosis in people with HIV in Guatemala; histoplasmosis is the most common AIDS-defining opportunistic infection. Almost 10% of those patients with a life threatening infection have 2 or more infections, so active case finding is mandatory and should not rely alone on clinical judgement.

In addition, the network has shown that more than 50% of the patients diagnosed with HIV already have advanced disease, and 1 in 3 of these patients had one or more life-threatening infections. These infections are the main risk for a premature death independent of the patients immunological status, so early diagnosis and treatment can save many lives. Despite providing access to early diagnosis, the mortality caused by these OIs is high, and so better treatments have to be deployed in Guatemala. A number of interventions are required which have been identified through the analysis of the network, which will be reported and discussed with Health Ministry officials.

However, taking into account the global shortage of HCWs, novel approaches have to be put in place in LMICs. Although a successful training investment policy is deployed in LMICs, the retention of health professionals will be jeopardized because of the global demand, so health coverage will have to be delivered with a limited health workforce. Our vision is to develop an ambitious program to deploy robotics and artificial intelligence developments in LMICs in order to automatise laboratories, help in the diagnosis and treatment process of patients and maintain a continuous education of the limited health workforce. This approach would allow quality provision of essential health services in LMICs.



**Dr Eduardo Arathoon** (ASI Guatemala) describes the national diagnostic project in Guatemala for HIV-infected patients.

## Serious fungal diseases in Latin America

### HIV/AIDS

Nearly 50% of deaths in AIDS patients are due to fungal diseases. In 2018, UNAIDS estimate that 35,000 people died of AIDS in Latin America and another 6,700 in the Caribbean, out of a total number of HIV-infected people of ~2 million. The commonest potentially lethal fungal infections are disseminated histoplasmosis, cryptococcal meningitis, *Pneumocystis* pneumonia, and infrequently invasive aspergillosis, coccidioidomycosis and paracoccidioidomycosis. Early diagnosis is critical to survival, concurrent infection with TB is common, and ruling out infection allowing ART to be started immediately can be life-saving. In many countries in Latin America, many patients present with advanced HIV disease and so mortality is high, especially if accurate diagnosis is delayed.

Progressive disseminated histoplasmosis is an increasingly commonly recognized cause of infection in patients with advanced HIV disease from areas endemic for histoplasmosis. The Guiana Shield and Guatemala are hyper-endemic areas (Medina, 2017). Only Chile, Uruguay and Paraguay are low endemicity areas. Disseminated histoplasmosis often resembles and can be misdiagnosed as TB in AIDS and is a major cause of death among HIV patients. Skin lesions are uncommon but helpful if present, as they can be biopsied. Gastrointestinal symptoms are often prominent in disseminated histoplasmosis, unlike in tuberculosis. Pancytopenia is more profound than in other patients with advanced HIV disease. *Histoplasma* antigen can be detected in the urine of 95-100% and

in the serum of 80% of patients with disseminated histoplasmosis (Nacher, 2018) – alternative means of establishing the diagnosis include bone marrow or skin biopsy, blood film (40% sensitivity) and PCR. Culture is insensitive and too slow.

Cryptococcal infection is acquired through inhalation and occasional cases of cryptococcal pneumonia or lung nodule are diagnosed. Much more commonly it leads to meningitis. Cryptococcal antigen (CrAg) is detectable in serum and CSF in almost all patients with cryptococcosis (and is probably the best test in microbiology given its sensitivity, specificity, simplicity and low cost). India ink microscopy is less sensitive. Culture is usually positive but takes time. Optimal therapy with amphotericin B and flucytosine yields survival in >80% of patients; ART must be delayed or mortality increases because of the immune reconstitution syndrome.



**Dr Fernando Riera**, Argentina, summarising AIDS-related fungal infections in Latin America.

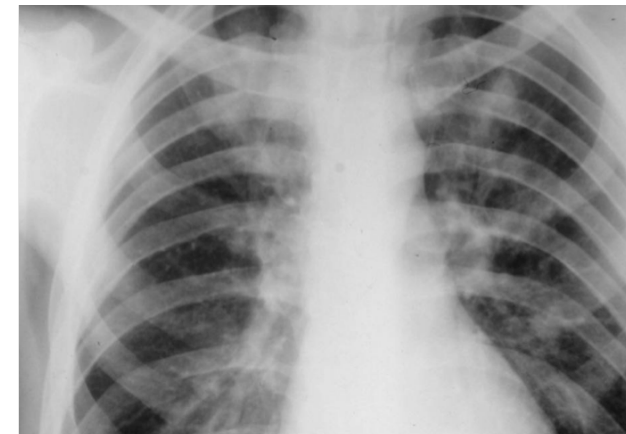
*Pneumocystis jirovecii* is a human-only pulmonary pathogen transmitted early in life and then repeatedly. Immunity is limited and immunosuppressed patients are susceptible to infection from new genotypes. It is not culturable and so is diagnosed by PCR (>95% sensitivity) or microscopy (75% sensitivity) on respiratory specimens, or circulating B-D-1,3 glucan levels. Patients often have distinctive findings on chest CT scan. Prophylaxis with cotrim is effective, but protection is not complete. The survival rate in HIV patients with good treatment is 70-90%, but only 50% in non-HIV patients. Corticosteroid adjunctive therapy reduces mortality in HIV patients but not in HIV negative people.

Invasive aspergillosis (IA) in HIV patients is more commonly found in those on corticosteroids or with neutropenia but occurs at any level of CD4 count. It is usually a subacute illness occurring over 3-12 weeks. The diagnosis can be difficult as the radiological and clinical features are similar to other infections, especially TB. It is often mistaken for tuberculosis, as cavitation is common on chest imaging. *Aspergillus* antigen, possibly *Aspergillus* antibody, and lung biopsy are the usual means of establishing the diagnosis. Many autopsy series have found about ~4% of deaths are attributable to IA (range 0-12%).

See Appendix 1 for data from Latin America.



**Dr Miguel Trelles**, overviewed the value of radiology for the diagnosis of fungal infections, including this example of *Pneumocystis* pneumonia in AIDS showing the characteristic ground glass appearance.



Bilateral patchy infiltrates of invasive aspergillosis in AIDS from the USA, with cavitation evident in left mid zone. **Dr David Denning**.

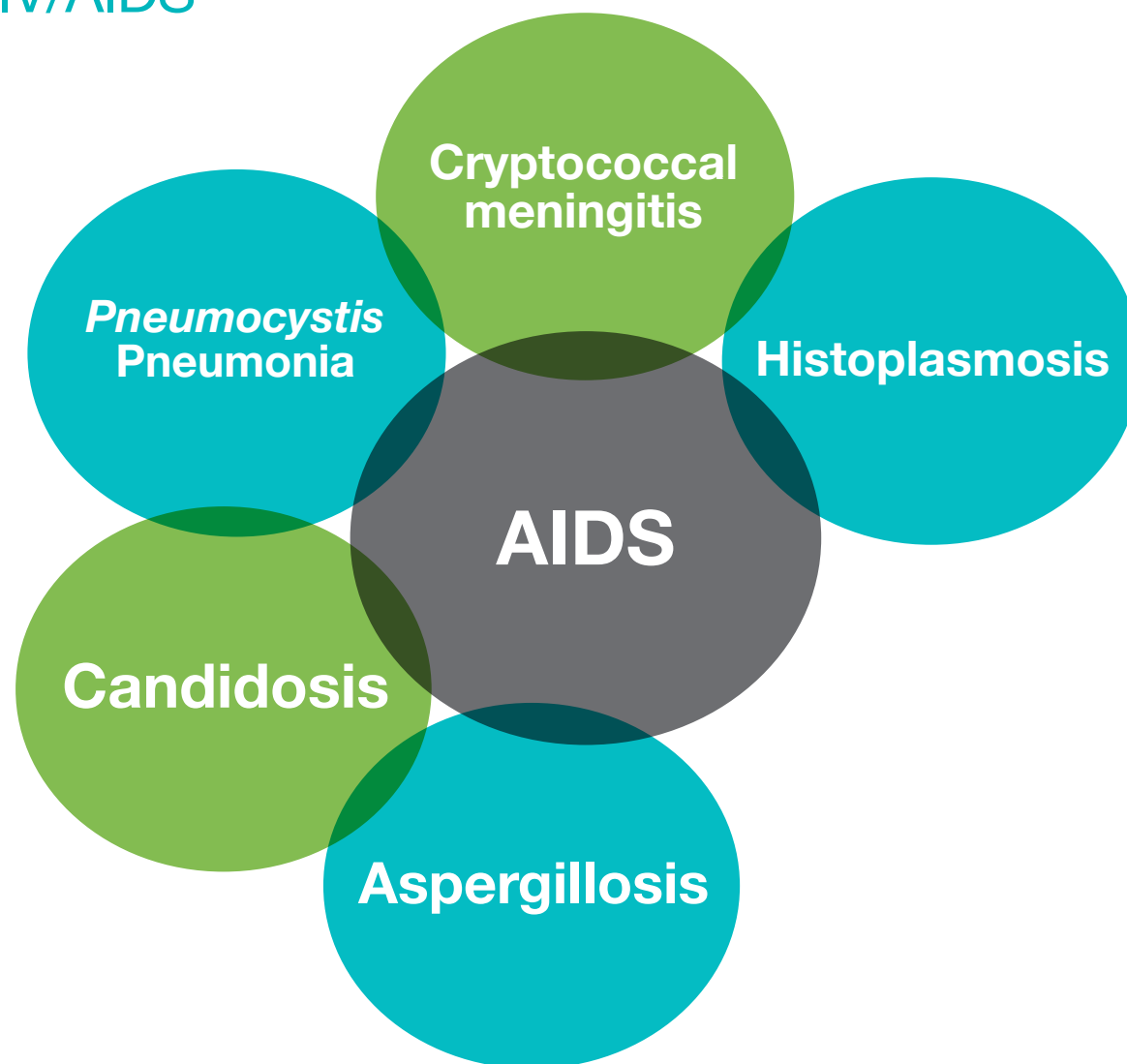


Oral lesions of disseminated histoplasmosis in AIDS in Brazil. **Dr Jose Vidal**.



Disseminated cryptococcosis in AIDS with multiple skin lesions in Brazil. **Dr Jose Vidal**.

## HIV/AIDS



**Figure 5.** The most important fungal infections occurring in patients with HIV/AIDS. Overall these infections lead to nearly 50% of the deaths from AIDS worldwide.



**Dr Tom Chiller** (CDC USA) sets out the progress made in the rapid diagnosis of cryptococcal meningitis and disseminated histoplasmosis in AIDS.



**Professor Carlos Arturo Alvarez**, Colombia, outlining how healthcare is delivered in Latin America and the Caribbean.



**TB-like fungal diseases**

Countries in the Americas notified 198,214 pulmonary TB cases in 2018 of which 79% were bacteriologically confirmed (41,625 were not) (WHO TB report, 2019). Of these ~200,000 cases, about 20,000 were in HIV-infected people, and 4,800 cases were MDR or rifampin resistant. A systematic review of the outcome of pulmonary TB pre-chemotherapy found a 70% mortality in smear positive cases without treatment and a 20% mortality in smear negative, culture positive cases (Tiemersma, 2011).

Several fungal infections of the lung can mimic TB, including aspergillosis, coccidioidomycosis, histoplasmosis, cryptococcal pneumonia (Wong, 2007) and paracoccidioidomycosis and indeed can occur together (Denning & Chakrabarti, 2017). Misdiagnosis and inappropriate treatment of TB is probably common across the world, but in Latin America the differential diagnosis is especially broad because of the endemic mycoses present. Those patients who are not bacteriologically confirmed are more likely to have a fungal disease than those that are confirmed (Oladele, 2017). In Guatemala, in those with HIV/AIDS, many cases of disseminated histoplasmosis were initially diagnosed as TB and inappropriately treated, and in some cases patients have both diseases (Samayoa, 2020). No surveys or studies of the size of this problem have been done in Latin America in those without HIV/AIDS.

All these TB-like fungal lung diseases are best diagnosed with specific antibody tests, and some of these are not available in many parts of Latin America or poorly validated.



Pulmonary tuberculosis.



Chronic pulmonary aspergillosis.

Additional details and estimated burden by country in Appendix 1.

### Serious hospital-acquired fungal infection – invasive candidiasis and invasive aspergillosis

By far the commonest life-threatening fungal infections in hospitals are invasive candidiasis and aspergillosis. The former is manifest primarily as *Candida* bloodstream infection (candidaemia) but includes deep-seated infections such as intra-abdominal candidiasis and disseminated infections in the eye, heart valve, brain, vertebral column and other organs. There are estimated to be about 60,000 instances of *Candida* BSI annually, comprising ~40% of all cases of invasive candidiasis (150,000) in Latin America and Caribbean (see Appendix 1 for details). Intra-abdominal candidiasis includes peritonitis and localized abscesses after liver or pancreas transplantation, after abdominal surgery for a perforated bowel, complicating pancreatitis, and *Candida* peritonitis from peritoneal dialysis. About 30% of *Candida* BSI occurs in intensive care. Blood cultures are only positive in about 40% of patients with invasive candidiasis, the remainder are diagnosed with B-1,3-D-glucan, PCR or cultures obtained by percutaneous aspiration or drainage procedures.

Untreated invasive candidiasis is nearly 100% fatal. Success of treatment of invasive candidiasis is time dependent. Earlier antifungal treatment based on suspicion yields about 80% survival, whereas when treatment is started when blood cultures have turned positive, survival falls to about 55%. Faster and more sensitive diagnosis is required. Azole resistance is more common than previously, so fluconazole therapy is ineffective.

Invasive aspergillosis is most familiar to clinicians in highly immunocompromised patients such as those with leukaemia and after transplantation. Increasingly invasive aspergillosis is seen in those who are less immunocompromised such as those in intensive care, admitted to hospital with COPD and those with immunological disorders such as rheumatoid arthritis, systemic lupus erythematosus and others. Very high attack rates have recently been diagnosed in those with influenza artificially ventilated in ICU (~20%). Over 85% of cases affect the lungs, but brain involvement is even more serious. The number of annual cases is estimated to be between 68,000 and 188,000 in Latin America and the Caribbean (Appendix 1).

The infection is 'quiet' until the later stages, so clinical training will allow earlier recognition, *Aspergillus* biomarkers and imaging are very important for early diagnosis. Outside leukemia and transplant units in most hospitals, most cases are missed and have a 100% mortality. The earlier the diagnosis, the greater the hope for survival, which is over 50% in the best institutions. *Aspergillus* antigen is the key diagnostic, with its sensitivity greatest on bronchoscopy washings taken as treatment is started. Some species of *Aspergillus* are azole or amphotericin B resistant and acquired azole resistance in *Aspergillus fumigatus* is increasing in the community.



Invasive aspergillosis in a neutropenic patient, showing the characteristic halo sign of ground glass surrounding the nodular areas. **Dr Miguel Trelles.**



**Professor Eduardo Ticona**, Peru, making a point about clinical care.

### Neglected tropical fungal diseases

The WHO has listed mycetoma and chromoblastomycosis as Neglected Tropical Diseases (WHO, 2019), and recently adopted sporotrichosis and paracoccidioidomycosis in addition. However the WHO is not funded to address these infections and epidemiological data is lacking in many parts of Latin America and the Caribbean.

The ongoing outbreak of cat-associated sporotrichosis in Brazil, spreading to neighbouring countries was discussed by the participants. Public health institutions and the Ministry of Health in Brazil have initiated control of this outbreak, but suitable tools other than awareness combined with early diagnosis and therapy are not available. The optimal means of diagnosing these infections has recently been published via a GAFFI inspired collaborative exercise (Hay, 2019), noting that the sensitivity of histopathology and culture are lower for sporotrichosis in immunocompetent people than for mycetoma and chromoblastomycosis. For paracoccidioidomycosis, serology is also important in diagnosis (Griffiths, 2018), but there are no tests commercially available.

Additional data can be found in Appendix 2 and linked here:

[www.gaffi.org/where/neglected-fungal-diseases](http://www.gaffi.org/where/neglected-fungal-diseases)

### Neglected skin fungal tropical diseases

The burden of fungal NTDs is not well established in Latin America and the Caribbean, but recent data include:

- Mycetoma - increase in eumycetoma (fungal cases) compared with actinomycetoma (bacterial cases), in Brazil.
- Chromoblastomycosis - most cases are reported from Brazil where the population prevalence is 3/100,000. The mean annual incidence of cases in Brazil varied from 6.4/year in Paraná to 2.6/year in Rio Grande do Sul.
- Sporotrichosis - prevalence ranges from 0.1% to 0.5% in some Latin American countries, where endemic.
- Paracoccidioidomycosis - Overall annual incidence of 1-4/100,000 inhabitants per year in geographic areas with stable endemicity, and 9-40/100,000 in hyperendemic areas.



### Fungal expertise.

**Professor Alexandro Bonifaz**, Dermatology, Mexico.

**Dr Flavio Quieroz Telles**, Infectious Diseases, Brazil

**Dr Eduardo Alvarez-Duarte**, Microbiology and Mycology, Chile.

## Availability and price of medicines

Availability of affordable antifungal agents is critical for improving outcomes. There are several countries lacking some antifungals, notably liposomal amphotericin B, flucytosine and natamycin eye drops. These maps and data can be viewed at [www.gaffi.org](http://www.gaffi.org). All the data is sourced from each country.

Price is also a major consideration, especially as all the essential antifungal agents are generic. The range in price both within countries and between countries is large. This is well illustrated by itraconazole.

### WHO Essential Antifungal Medicines

Griseofulvin  
Fluconazole  
Amphotericin B  
Flucytosine  
Itraconazole  
Voriconazole  
Natamycin eye drops



Robust dialogue from **Professor Luis Cuellar**.

**Table 3. Antifungal availability and main clinical indications**

Essential antifungal	Critical need	Availability
Amphotericin B conventional	Cryptococcal meningitis, aspergillosis, histoplasmosis, resistant candidiasis	Available in all countries
Amphotericin B liposomal/lipid	Histoplasmosis, pregnancy, renal dysfunction	Not available in Ecuador, Guatemala, Costa Rica, Honduras, Nicaragua, Panama, Guyana
Fluconazole	Candidiasis, cryptococcosis, coccidioidomycosis	Available in all countries
Itraconazole	Aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis	Not available in Paraguay and possibly Bolivia
Voriconazole	Aspergillosis, rare fungal infections	Not available in Costa Rica, Dominican Republic, Paraguay and Surinam, possibly Guyana
Flucytosine	Cryptococcal meningitis, resistant candidiasis	Only available in Cuba, Colombia and Surinam
Natamycin eye drops	Fungal keratitis	Only available in Colombia, Cuba, Mexico and Argentina
Echinocandins	<i>Candida</i> infections, especially <i>C. auris</i>	Not available in Cuba, El Salvador, Paraguay, Surinam



### Training and implementation of antimicrobial stewardship teams

Antimicrobial stewardship is the science and art of ensuring that all patients get the right antimicrobial for an infection (or it is stopped if no infection), at the right dose, for the right duration, supplemented with other key actions such as surgical drainage or catheter removal. Other key elements of stewardship include policy development for prophylaxis and empirical therapy, controlling cost and education. Most successful stewardship teams comprise an experienced clinician in infectious diseases and a pharmacist, with real-time clinical microbiology input in person or electronically. Multiple publications documenting stewardship impact attest to improved clinical outcomes and reduced overall cost. In view of antifungal cost, general complexity of fungal diseases, limited knowledge of most doctors of the topic, specialized antifungal stewardship programs have been developed in many hospitals, alongside or instead of general antimicrobial stewardship. This is partly a function of available personnel with expertise.

### PAHO Strategic Fund

GFIF4 attendees learned of the potential for jump-starting their procurement of diagnostics and antifungal agents using the PAHO Strategic Fund. Started in 2000, the fund has grown to an annual turnover of \$70M, supporting 33 countries. The fund is able to negotiate competitive prices, which is particularly important in smaller countries with an uncertain burden of disease and need. All the WHO Essential systemic antifungals are available through the Fund; only topical natamycin for fungal keratitis is not. The Fund also provides technical support for planning, procurement and distribution. Purchase through the Fund provides a line of credit for governments that are not able to release funding upfront (\$18M capitalisation). Fungal disease diagnostics may also be procured through the Fund if recommended by a WHO guideline, included in the 'Essential Diagnostic List' (EDL) and of proven quality (e.g. pre-qualified by WHO).



**Dr Giovanni Ravasi** (PAHO) interacting on screening for fungal diseases in AIDS/HIV.

**Recommendations re access to antifungal treatment**

1. Availability of all antifungals included in the WHO List for Essential Medicines plus echinocandins:
  - a Registration of all antifungals in each country.
  - b Improvement of antifungal procurement at competitive prices (e.g. through PAHO Strategic Fund).
  - c Prioritize generic antifungals of assured quality.
2. Development of antifungals stewardship programs.
3. Involve pharmaceutical companies on:
  - a Registry of antifungals in Latin America and the Caribbean.
  - b Continuing education about antifungals with focus about strengths, weakness, toxicity, resistance development and interactions with other drugs.
  - c Support of stewardship programs.
  - d Education of physicians about fungal diseases.

**Key goal 2**

WHO-endorsed Essential Medicines should be made routinely available in public hospitals and AIDS-focused clinics, especially flucytosine for cryptococcal meningitis and liposomal amphotericin B for disseminated histoplasmosis. This will require accelerated registration processes in some countries, and use of the PAHO Strategic fund.

**Key priority 4**

Applications should be made to the WHO to include echinocandins as Essential Medicines.



**Ruben Ramos**, Panama, addressing concerns about AMR.



**Professor Jorge Alberto Cortes**, Colombia, summarising the fungal complications of cancer.



**Professor Donald Cole** (University of Toronto) leads breakout session.

# Flucytosine

## Availability in Latin America, 2019.

- Available
- Unavailable
- Unknown

See: <https://www.gaffi.org/antifungal-drug-maps/>



Figure 6.

## Natamycin eye drops for fungal keratitis

### Availability in Latin America, 2019.

- Available
- Unavailable
- Unknown

Fungal keratitis affects over a million eyes worldwide each year, and an estimated 19,100 or more eyes each year in Latin America and the Caribbean.

See: <https://www.gaffi.org/antifungal-drug-maps/>



Figure 7.



## Itraconazole prices

### Variability in itraconazole daily price (400mg) in Latin America, 2019

- Higher - over \$6 daily
- Medium - \$2 to \$6 daily
- Lower - under \$2 daily
- Unknown

See: <https://www.gaffi.org/antifungal-drug-maps/>



Figure 8.

## Antifungal resistance

Antimicrobial resistance (AMR) has been widely recognized as an urgent threat to public health, and, until recently, the global response has focused on pathogens other than fungi (e.g., bacteria and viruses). Although largely out of the public's view, fungi are also major causes of human disease and death, and resistance to antifungal medications is a growing problem, as it is for antibiotic drugs. Few countries have effective surveillance systems for fungal diseases, and, consequently, statistics on their incidence, resistance, and related burden of disease are limited. AMR largely arises from the excess use of antibacterial drugs, which can be partly curtailed by faster and more accurate diagnosis of both bacterial and fungal diseases.

In contrast to antibacterial drugs, which have over a dozen classes, only four classes of antifungals are used to treat systemic infections: (1) azoles (e.g., fluconazole), (2) echinocandins (e.g., micafungin), (3) polyenes (e.g., amphotericin B) and (4) flucytosine. Resistance to these drugs has been found in a range of fungal pathogens, including *Candida* species, *Aspergillus* species, *Fusarium* species, and *Scedosporium* species. *C. auris* may be the first fungal pathogen to display acquired resistance to all three antifungal classes. However, given widespread use of these medications, it likely is not the last. Because of the limited number of treatment options available for fungal diseases, understanding the worldwide scope of antifungal resistance is an important step in controlling its spread.

The *Candida* species distribution has shifted, favoring species with increased resistance to antifungal drugs. In many countries with available data, *C. albicans* was once the dominant *Candida* species causing invasive infections, but now only accounts for a minority of invasive infections. Meanwhile, candidiasis due to the more commonly resistant *C. glabrata* is increasing.

*C. glabrata* is often resistant to fluconazole, previously the first-line treatment for invasive candidiasis, and some strains have become resistant to echinocandins, which have become first-line therapy, following the emergence of fluconazole resistance. In certain tropical countries like India, *C. tropicalis* instead of *C. glabrata* is the prevalent agent among non-*albicans* *Candida* species and comparatively higher resistance to fluconazole has been reported in *C. tropicalis* blood isolates. In contrast to other parts in the world, *C. parapsilosis* is very prevalent in Latin American, and distributed among all age groups.



**Dr Jeannete Zurita**, Ecuador, explaining the scale of the antifungal resistance problem in Latin America.

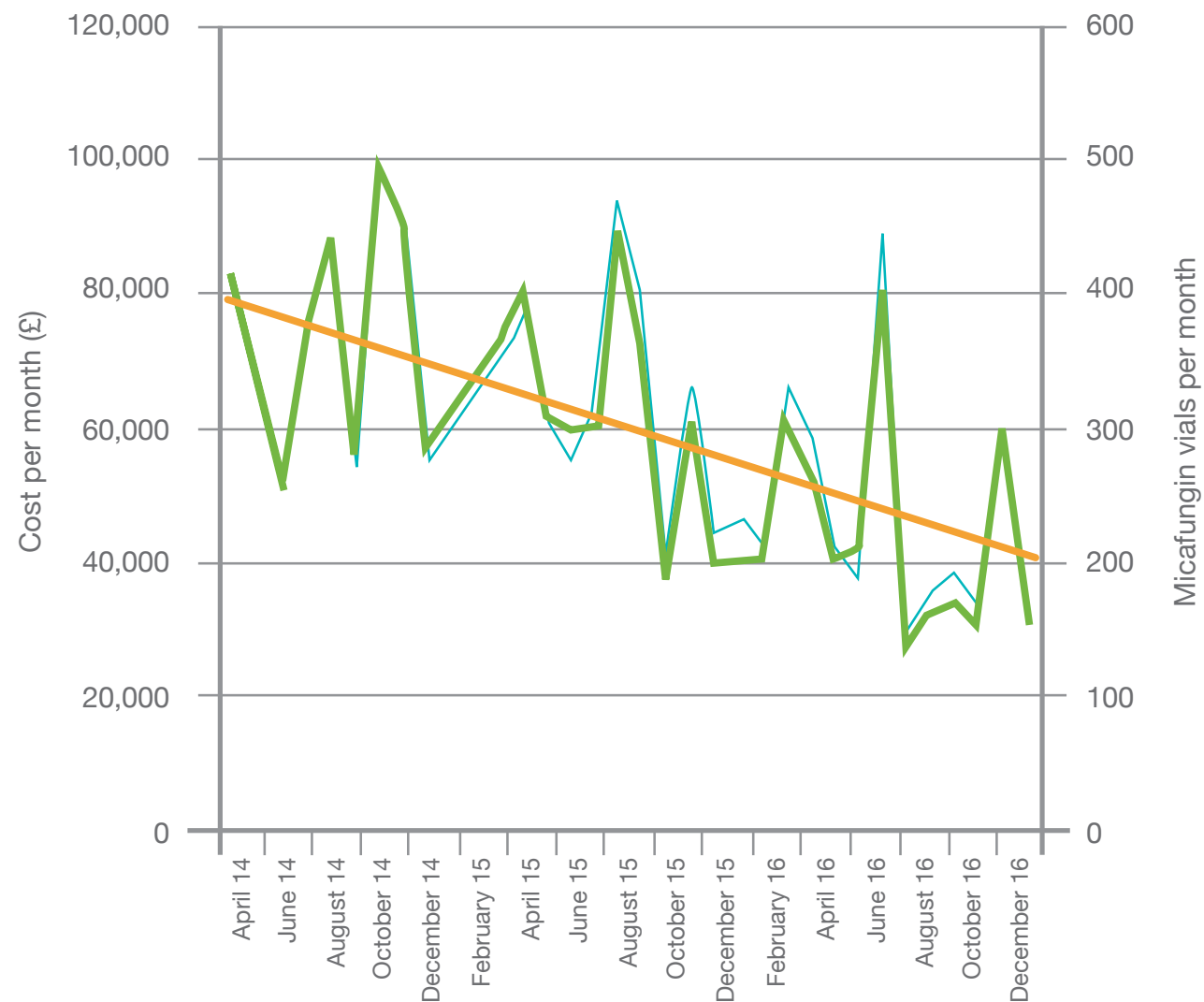


Breakout session on public health reference laboratory testing.

## Glucan testing reduces antifungal use

Investment in glucan testing was only 10% of overall savings, so highly cost effective.

50% reduction 



**Figure 9.** Rautemaa-Richardson R et al, J Antimicrob Chemother 2018;73:3488

### Challenges in antifungal drug resistance surveillance

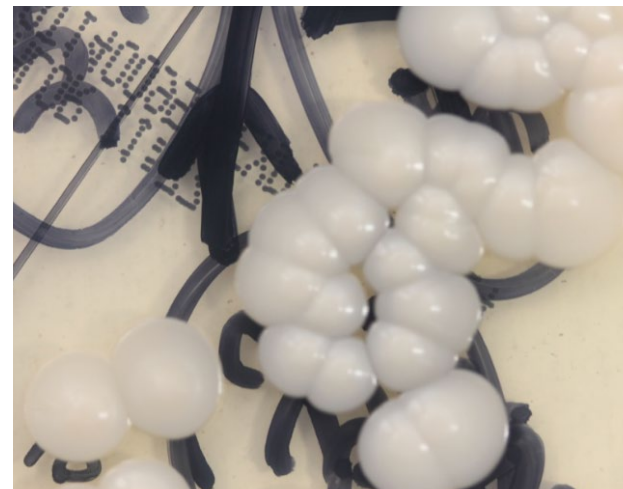
Limited resources have been allocated toward evaluating and reducing antifungal drug resistance, and few countries are performing surveillance. Little information exists about the population prevalence or clinical incidence of antifungal resistance in most of Asia and Africa, as well as parts of Latin America. Available data are often single center reports, which may bias results towards certain patient populations, especially those with a referral population of patients with severe underlying medical conditions and those in well-resourced healthcare centers.

Even where antifungal resistance testing is available, which excludes most resource-poor countries, complete surveillance data may be lacking. Most available susceptibility data describe resistance among BSIs, missing roughly half of all candidiasis not diagnosed by blood cultures. This practice may underestimate resistance because these deep infections are often in body sites where bioavailability of antifungals is limited, allowing resistance to develop. Moreover, the standard design of surveillance programs is to collect the first isolate from each episode of infection, generally prior to antifungal treatment. This would not capture isolates that developed resistance after exposure to antifungal drugs. For these reasons, resistance might be more prevalent than is currently being reported. More standardized data are needed to understand the full impact that resistant *Candida* species have on patient treatment and outcome.

### *Candida auris*

The detection of *C. auris* outbreaks in several world regions over the last five years, underscores the need to ensure adequate capacity for early detection and notification of invasive fungal infections to help prevent and control transmission, particularly since molecular evidence suggests international spread. The first detected outbreak of *C. auris* in the Region of the Americas was reported in Venezuela from March 2012 to July 2013 (PAHO report, 2016; Calvo, 2016; Morales-López, 2017). In August 2016, an outbreak was reported in a pediatric intensive care unit in Colombia. Even though reporting of these kind of outbreaks is still limited, we cannot exclude the possibility that the real prevalence of this emerging multidrug-resistant yeast pathogen is underestimated in the Americas and globally (da Matta, 2017; Chowdhary, 2016).

Most *C. auris* isolates are resistant to at least one antifungal, and some are resistant to all three. Detection of clonal resistant isolates across multiple years within a healthcare facility indicates that there is no loss to fitness for becoming resistant, making rapid detection and implementation of susceptibility testing imperative. Yet, *C. auris* presents detection and susceptibility testing challenges, given its common misidentification using common biochemical laboratory methods. Data on laboratory capacities and evidence-based protocols are needed to overcome such surveillance obstacles.



*Candida auris*.



Dr Flor Urcia summarising the problem of antifungal resistance in Peru.



## WHO GLASS program

The Global Antimicrobial Resistance Surveillance System (GLASS) aims to support the implementation of the Global Action Plan on Antimicrobial Resistance (GAP-AMR) by promoting and strengthening standardized antimicrobial resistance (AMR) surveillance worldwide. GLASS combines patient, laboratory, and epidemiological surveillance data to enhance understanding of the extent and impact of AMR on populations.

In its early implementation phase (2015-2019), GLASS aims to combine data on the status of enrolled countries' AMR surveillance systems with AMR data for selected bacterial pathogens that cause infections in humans. However, recognizing the growing threat of resistant fungal infections, GLASS started a global collaborative effort to also compile available data on antifungal-resistant infections. One of the major limitations in addressing the threat of antifungal-resistant fungi is a lack of data at the global level. Few countries have effective surveillance systems for fungal diseases, and consequently, statistics on their incidence, resistance, and related burden of disease are limited. In 2019, the WHO adopted antifungal resistance surveillance in *Candida* spp. into the GLASS program.

### GLASS Fungal AMR program

As the spectrum of invasive antifungal-resistant infections is broad, the GLASS Fungal AMR effort will initially focus on invasive fungal BSIs caused by *Candida* species (spp.). BSI is one of the most common type of invasive fungal disease. Antifungal susceptibility data of invasive *Candida* isolates,

especially from patients in high-risk hospital units (e.g. intensive care units (ICUs), neonatal ICUs), that will be available through GLASS will provide an overview of the emerging resistance in *Candida* spp.

Unlike bacteria, accurate identification and antifungal susceptibility testing (AFST) of *Candida* spp. are still major challenges as many laboratories worldwide lack this capability. A fundamental limitation is that resistance breakpoints differ by individual species, with many species lacking defined breakpoints, and most laboratories rely on phenotypic *Candida* identification methods that cannot reliably differentiate uncommon species of *Candida*, including *C. auris*. Also, the databases of automated commercial microbial identification methods used in routine microbiology laboratories to identify *Candida* species may lack emerging and new *Candida* species, thus requiring molecular methods for accurate identification. The AFST expertise to perform the reference broth microdilution methods for *Candida* species is generally restricted to specialised laboratories, and breakpoints for interpreting the susceptibility by reference broth microdilution methods have been established for only the common *Candida* spp.

The Early Implementation Protocol for inclusion of *Candida* spp in the GLASS was developed to support countries to strengthen or build their national fungal AMR surveillance, and enable incorporation of AMR surveillance for invasive *Candida* infection into GLASS (WHO GLASS protocol, 2015). The protocol describes the objectives and methodology and provides details of the proposed approach and defined targets for the

surveillance of resistance in *Candida* BSIs. Using the evidence collected during the early implementation and the lessons learnt, the protocol will be finalized, and the *Candida* spp. resistance surveillance component will be fully incorporated into GLASS.

Accompanying the protocol, PAHO has developed a standardized WHONET software configuration for the collection and delivery of antifungal resistance monitoring information in *Candida* spp. at the patient level. This configuration was developed considering regional surveillance standards fully aligned with WHO's Global Antimicrobial Resistance Surveillance System (GLASS). In addition, a manual was developed for the configuration and loading of data in WHONET that includes the encryption methodology for the protection of confidential patient information.

In addition, a three-month course was provided in the Region of the Americas, training 61 professionals from 20 countries ('Standards for the diagnosis of fungal infections: from clinical suspicion to identification and sensitivity of the isolate'). The weekly course was conducted virtually through the WebEx platform for three months and practical evaluation work offline. As a final product of the course, 21 infographics, describing the standards for the diagnosis of fungal infections, have been developed that will be shared with the countries and will be available online via the PAHO website.

## Preparedness for ID and susceptibility testing of *Candida* spp.

### Species identification

While many systems reliably identify the five most common *Candida* spp., which typically comprise 80–90% of infections, the remaining isolates lack reliable identification. Therefore, national laboratories should conduct external quality assessments of the surveillance sites. Some countries have little or no access to the most reliable species identification methods. CRCs or other reference laboratories outside the country may be able to conduct limited species identification, subject to capacity and funding constraints. Even advanced laboratory methods, like matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF), may provide a “no identification” result when the species is rare, which could also prompt the use of an NRL or CRC for further species identification as needed (WHO GLASS protocol, 2015).

### Susceptibility testing

Antifungal susceptibility testing (AFST) is still a major challenge, even in the developed world. The expertise to perform the reference broth microdilution methods are generally restricted to specialized laboratories. Preferred in vitro antifungal susceptibility testing methods are the two reference microdilution methods that have been standardized by CLSI and EUCAST (EUCAST E.Def 7.3.1. 2017 and the CLSI M27-ed 4). The individual MICs can be translated into S, I, R by adoption of breakpoints ( [http://www.eucast.org/clinical\\_breakpoints/](http://www.eucast.org/clinical_breakpoints/); CLSI document M60ed1). The two standardized methods yield similar MICs for fluconazole, voriconazole, and amphotericin B, but for

other compounds the MICs can be several two-fold dilutions different. Therefore, it is crucial that MICs are interpreted adopting the breakpoints associated with the method being used, otherwise susceptibility classification might be incorrect.

Also, there has been concern regarding interlaboratory variability with caspofungin susceptibility testing when CLSI and EUCAST broth microdilution methods are used, with some laboratories reporting higher caspofungin MICs, such that isolates may falsely be classified as resistant to this echinocandin. Although this can occur when tested against any *Candida* spp., it appears to affect the testing of *C. glabrata* and *C. krusei* isolates to a greater degree. To avoid this problem, EUCAST does not recommend performing susceptibility testing with caspofungin, but instead suggests using anidulafungin and micafungin MIC results as surrogate markers to predict susceptibility or resistance to caspofungin (GLASS Early Implementation Protocol for *Candida*, 2019).



**Marlen Arce Villalobos** summarising the limited provision for fungal diagnosis in Costa Rica.

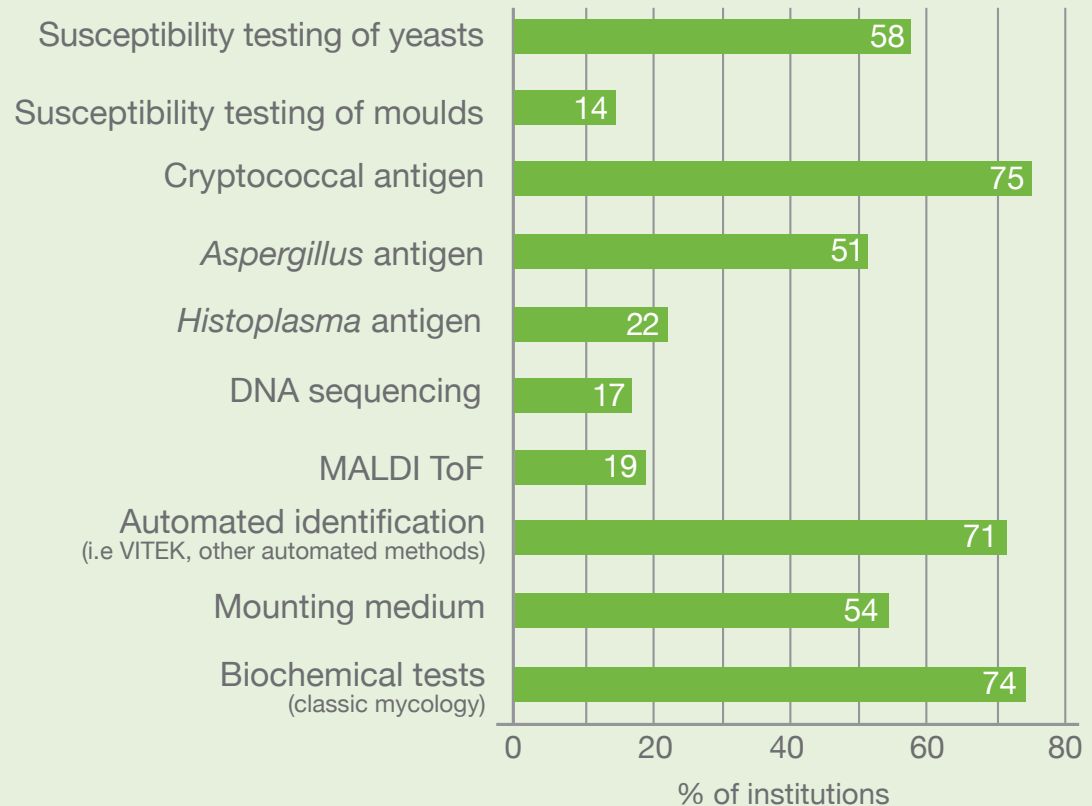
## Laboratory capabilities in Latin America and the Caribbean

A questionnaire survey of 129 centres in 24 countries determined laboratory capability for diagnosing fungal diseases.

Only 9% of centres would have the potential to apply for the minimum standards in mycology, as determined by the European Confederation of Medical Mycology.



**Dr Marina Macedo-Vinas**, Uruguay, describing the 'affordable' mycology laboratory.



**Figure 10.**

Falci DC, Pasqualotto AC. Clinical mycology in Latin America and the Caribbean: A snapshot of diagnostic and therapeutic capabilities. *Mycoses* 2019; 62:368-73

### Recommendations re laboratories and epidemiologic surveillance

1. Strengthening diagnostic capability in the region.
2. Networking of laboratories to minimise local deficiencies with a commitment to:
  - a A system to request tests and provide results by electronic means.
  - b Quick transport of clinical samples from patients to laboratories.
3. Use of current and consolidated laboratories like:
  - a Laboratories in reference hospitals.
  - b University laboratories.
4. Prioritize commercial diagnostic techniques and point of care testing.
5. Commitment to full validation of in-house diagnostic techniques.
6. Rational use of diagnostic prioritising the development of laboratories with enough workload to warrant the ongoing training of the staff and the quality of the results maintaining each test at a minimum cost.
7. Specific surveillance programs (e.g. *Candida auris*, sporotrichosis, Neglected Fungal Diseases, endemic fungal diseases, resistance to antifungals, etc.)
8. External proficiency quality control program.
9. Commitment to laboratories for techniques accreditation under ISO rules.
10. Evaluation of the need for forced declaration of some fungal diseases, especially the endemic mycoses.

### Key priority 5

Strengthening of public health for fungal diseases including a) development of specific surveillance programs to track fungal infections of public health importance, including *Candida auris*, the NTD sporotrichosis and serious endemic fungal infections and b) active epidemiology research programs, using point of care and non-culture diagnostics.

### Key priority 6

National antifungal resistance surveillance programs should be developed in public hospitals (provincial-state equivalent and above), with national reporting.



Conference in session.



Gladys Estigarribia, Paraguay, chairs Q&A session.



Dr Luis Caminero summarising the poor state of fungal diagnostics in Dominican Republic.



## Educational resources

Fungal diseases are a difficult educational subject. There are many different kinds of fungal diseases that involve several different medical specialties including dermatology, gynaecology, haematology, HIV/AIDS, infectious diseases, intensive care, ophthalmology, otolaryngology, paediatrics, pharmacy and respiratory medicine. However primary care is key, especially in rural areas or in places where there are not enough specialists, and for common, straightforward fungal disease. Ongoing training is essential to provide quality care to patients with fungal diseases. However, continuous learning for LMICs and especially for physicians or health workers living in remote areas is a challenge.

There are courses for fungal diseases in several countries of Latin America including Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Peru, Uruguay and Venezuela. In addition, there are numerous web sites for continuous education but most of them in English. To highlight, LIFE website: <http://www.life-worldwide.org> and Microfungi: <http://www.microfungi.net> both with modules in Spanish. Guidelines are also an important tool for education and homogenization of medical practice, but their introduction is far from being perfect. Language barriers and different access to diagnostics and treatments, among countries, make the acceptance and approval of international guidelines difficult outside the high-income countries.

Attendees at the IV Global Infection Forum discussed the current educational resources available, see page 40, as well as the future opportunities that could be

developed. Information about courses to be held in the future will be available at: [www.diagnosticomicologico.com](http://www.diagnosticomicologico.com) under 'cursos' section. The following issues were identified as essential to get a good training of health professionals in fungal infections:

### 1. Establishment of a common curriculum for fungal diseases.

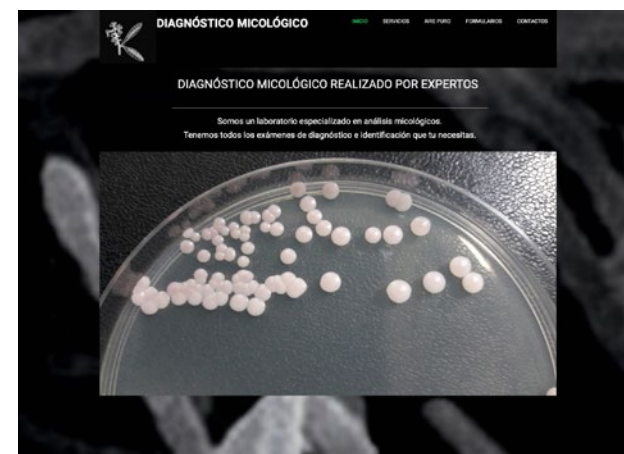
There is a clear need for agreement about the core topics that health professionals must master regarding medical mycology, especially for endemic diseases where Latin America has the greater number and variety of all continents. A common curriculum would facilitate the development of the program and its contents and provide reassurance that all health professionals get the same education on this topic.

### 2. Introduction of Guidelines in clinical practice.

It is mandatory to increase the speed of Guidelines introduction in the health sector, especially those that are global. However, in some settings it is also important to adapt and/or elaborate local guidelines that highlight the specific issues of fungal infections in the area. In any case, the guidelines should be transparent, evidence based and with full explanation about how they have been formulated. Finally, the guidelines should be a dynamic process quickly incorporating improvements as evidence is generated.



[www.microfungi.net](http://www.microfungi.net)



[www.diagnosticomicologico.com](http://www.diagnosticomicologico.com)

### Incorporation of new technologies for continuing education.

The current system for providing education does not assure the training of enough health professionals to achieve better diagnosis and treatment of fungal diseases. There are several constraints, but mainly those related to the shortage of specialized centres on fungal diseases. This means that professionals have usually to move to other locations to be trained in the subject. However, this is unavailable for the majority of them because most courses or masters programs exceed the funding available. In addition, if the trainee has a job somebody else has to take care of it. Specialized websites can help in this enterprise but to reach a good level of expertise, practical training guided by mentors is mandatory. New technologies, like the introduction of 5G technology, natural processing language and artificial intelligence can allow real training whilst the health worker is attending the patients. A way to implement these new technologies in LMICs must be found. LMICs have three main problems (i) they do not have enough experts to attend all cases; (ii) they do not have enough experts and centres to train primary care health workers to provide adequate quality and, (iii) they have a big rural population with no economic means to move towards a big city for being attended to by a specialist.

### Recommendations re continuing education.

1. Establishment of a common curriculum for fungal diseases
2. Improvement of fungal diseases training for:
  - a Primary care
  - b Specialties with fungal diseases pathology (e.g. Dermatology, HIV/AIDS, Pneumology, Haematology, Paediatrics, etc.)
  - c Laboratory personnel
3. Fast Introduction of Global Guidelines in clinical practice with evaluation of the need of local adaptation
4. Analysis and introduction of Artificial Intelligence for ongoing training

### Key priority 7

Substantial educational efforts of healthcare professionals, notably in the use of non-culture diagnostics, antifungal usage and stewardship programs, WHO Guidelines for Advanced HIV disease, cryptococcal meningitis and other international clinical and laboratory practice guidelines.

### Key priority 8

Assessment and then implementation of artificial intelligence systems to counteract the shortfall in healthcare professionals, notably in radiology, histopathology, dermatology and ophthalmology.



**Dr Ricardo Rabagliati**, Chile, airs significant concerns about training in new diagnostic technologies.



Breakout session on AMR control.

## Available courses - per country

Medical mycology courses in Latin America

See [www.diagnosticomicologico.com](http://www.diagnosticomicologico.com) under 'cursos' section for a full listing.

### Argentina

Cursos virtuales micología médica  
<https://aam.org.ar/>

Micología Médica

<https://fundacionquimica.org.ar/cursos/cursos/>

Curso teórico práctico universitario anual de micología médica

<https://fundaciontecsal.org/producto/curso-teorico-practico-universitario-anual-de-micologia-medica/>

### Brasil

Escuela altos estudios en micología clínica.

<http://www.prppg.ufpr.br/ppgmpp/index.php/2017/12/14/eae-micologia-clinica-inscripciones-abertas/>

Curso de postgrado en parasitología y micología clínica de laboratorio.

<https://www.egasmoniz.com.pt/pt-pt/ensino/iuem/cursos/p%C3%B3s-gradua%C3%A7%C3%B5es/curso-de-p%C3%B3s-gradua%C3%A7%C3%A3o-em-parasitologia-e-micologia-cl%C3%ADnica-laboratorial.aspx>

Curso de micología médica de laboratorio.

<https://www.imunomed.com.br/cursos>

### Chile

Curso teórico y curso práctico de micología médica, Instituto de Salud Pública. Laboratorio Referencia en Micología Médica.

<http://www.ispch.cl/actividadesispch>

Jornadas Nacionales Micología Médica. Universidad de Chile

[www.diagnosticomicologico.com/](http://www.diagnosticomicologico.com/)

Cursos itinerantes de micología médica.

[www.diagnosticomicologico.com/](http://www.diagnosticomicologico.com/)

### Colombia

Diplomatura de actualización en micología médica.

### Costa Rica

Maestría en microbiología con énfasis en micología médica

[http://www.sep.ucr.ac.cr/index.php?option=com\\_sppagebuilder&view=page&id=833/](http://www.sep.ucr.ac.cr/index.php?option=com_sppagebuilder&view=page&id=833/)

### Mexico

Taller de micología básica, clínica y molecular.

[http://himfg.com.mx/interna/inf\\_resident/cursos.php/](http://himfg.com.mx/interna/inf_resident/cursos.php/)

### Uruguay

Especialista en micología médica y parasitología.

<https://www.universia.edu.uy/estudios/universidad-republica/especialista-parasitologia-micologia-medica/st/189276/>



Course in medical mycology lead by **Dr Eduardo Alvarez-Duarte** in Santiago Chile.



# Promoting integration of Fungal Disease into Health Systems

In addition to the direct objective of reducing premature death and improving the health of people in Latin America (SDG3), several other SDGs are addressable by implementing improvements for fungal disease diagnosis and care. These include:

- SGD1 (Promoting the health needs of the poor) - especially HIV/AIDS, TB and NTDs.
- SGD4 (Supporting high-quality education for all to improve health and health-equity) – Healthcare worker education in particular.
- SGD8 (Promoting health employment as a driver of inclusive economic growth) – directly with more laboratory personnel and expanded roles in pharmacy, radiology and information technology, and indirectly in supply chains for diagnostics and antifungal agents.
- SGD9 (Promoting national R&D capacity and manufacturing of affordable essential medical products) – notably epidemiology studies, surveillance and laboratory consumables and computers.
- SGD12 (Promoting responsible consumption of medicines to combat antimicrobial resistance) – notably widespread adoption of rapid and sensitive diagnostics, antifungal surveillance and antifungal stewardship programs.
- SGD16 (Empowering strong local institutions to develop, implement, monitor and account for ambitious national SDG responses) – notably development of critical mass in fungal disease diagnosis and management with surveillance networks.
- SGD17 (Mobilising partners to monitor and attain the health-related SDGs) – development of public health mycology, on a strong epidemiology and surveillance background.



**Figure 11.** WHO Sustainable Development Goals - Health in the SDG ERA.



To these ends, the meeting recommended some key advocacy goals related to fungal diseases as follows:

### Advocacy

1. Development of a regional report about Fungal Diseases situation in the Americas.
2. Disseminate and promote the adoption of the WHO Essential Diagnostics and WHO Essential Medicines Lists.
3. Disseminate and promote the adoption of the WHO Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy.
4. Promote 'One Health', human, animal and environmental;
5. Promote a WHO resolution about the prevention and control of fungal diseases.

There are many resources and capabilities in Latin America to address fungal diseases, and many gaps. Multiple levels of capacity strengthening with inter-country support, exchange and dialogue will contribute to improved clinical services, epidemiology research and surveillance. Examples that participants in Lima recommended and could see benefit in include:

### Horizontal Cooperation and its Strengthening

1. Disseminate and promote Regional Good Practices:
  - a Lessons learned from the FUNGIRED Guatemala project.
  - b Lessons learned from the Guatemalan Diagnostic Laboratory Hub.

2. Strengthen the cooperation and network working between:
  - a GAFFI, b PAHO/WHO, c CDC, d API, e ALM
3. Development and strengthening of Diagnostic Reference Laboratories and networks, both within countries and internationally.
4. Development of a regional PAHO Plan of Action for the prevention and control of Neglected Fungal Diseases endorsed by all Member States.
5. Development of research, audit and clinical care programs incorporating fungal disease complications and differential diagnoses for:
  - i Tuberculosis.
  - ii HIV/AIDS.
  - iii Respiratory Infections.
  - iv Neglected Diseases.
  - v Infection Control and Antimicrobial Resistance.
  - vi Epidemiologic surveillance.
  - vii Primary care.
6. WHO Collaborative Centers in Fungal Diseases and Reference hospitals for care of the most complex patients.



**Dr Jose Sanchez** summarising fungal diagnostic testing and antifungal therapy in Honduras.



**Professor Donald Cole**, Canada, summarising a discussion session on funding for improved care.

# List of abbreviations

**AI** Artificial intelligence

**AIDS** Acquired immunodeficiency syndrome

**ALM** Asociación Latinoamericana de Micología  
(Latin-American Mycology Association)

**AMR** Antimicrobial resistance

**API** Asociación Panamericana de Infectología  
(Pan-American Infectologist Association)

**ART** Antiretroviral therapy

**BSI** Bloodstream infection

**CDC** Centers for Disease Control and Prevention, Atlanta, GA, USA

**CLSI** Clinical and Laboratory Standards Institute

**CPA** Chronic pulmonary aspergillosis

**CrAg** Cryptococcal antigen tests

**CRC** Clinical Research Centre

**CSF** Cerebrospinal fluid

**EDL** Model List of Essential In Vitro Diagnostics

**EUCAST** European Committee for Antimicrobial Susceptibility Testing

**EIA** Enzyme immunoassay

**ELISA** Enzyme linked immunosorbent assay

**EQA** External Quality Assurance

**GAFFI** Global Action Fund for Fungal Infections

**HCW** Healthcare worker

**HIV** Human immunodeficiency virus

**IA** Invasive aspergillosis

**IRIS** Immune inflammatory response syndrome

**LFA** Lateral flow assay

**LFD** Lateral flow device

**LICs** Low income countries

**LIMS** Laboratory information management systems

**LMICs** Low and middle income countries

**PAHO** Pan-American Health Organisation

**PCP** *Pneumocystis* pneumonia

**PCR** Polymerase chain reaction

**SDG** Sustainable Development Goal

**TB** Tuberculosis

**WHO** World Health Organisation

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## Global Fungal Infection Forum meetings

### GFIF 1

Seattle, February 2015, 10-year GAFFI Roadmap, which resulted in the 95/95 by 2025 logo and plan: 95% of the world's population having access to fungal disease diagnostics and antifungals by 2025.

<https://www.gaffi.org/global-fungal-infection-forum/about-global-fungal-infection-forum/>

### GFIF 2

Liverpool, October 2016, consensus definition of chronic pulmonary aspergillosis for low- and middle-income countries.

<https://www.gaffi.org/global-fungal-infection-forum-2-in-liverpool/>

### GFIF 3

Kampala, April 2018, developing consensus on which diagnostics for AIDS and serious fungal diseases should be included on the WHO Essential Diagnostic List.

<https://www.gaffi.org/global-fungal-infection-forum-3-in-kampala/>

### GFIF 4

Lima, September 2019, Developing a coalition roadmap for integration of fungal disease pathways and AMR solutions into health systems in Latin America

<https://www.gaffi.org/global-fungal-infection-forum-4-in-lima/>



**GFIF 1**

Seattle, USA. February 2015



**GFIF 2**

Liverpool, UK, October 2016



**GFIF 3**

Kampala, Uganda. April 2018



**GFIF 4**

Lima, Peru. September 2019

# Supporters of the Global Fungal Infection Forum



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