Fungus Watch

Navigating the WHO Fungal pathogen priority list

(WHO FFPL)

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- Infectious diseases are among the top causes of mortality and a leading cause of disability worldwide.

- Against the backdrop of this major global health threat, invasive fungal diseases (IFDs) are rising overall and particularly among immunocompromised populations.

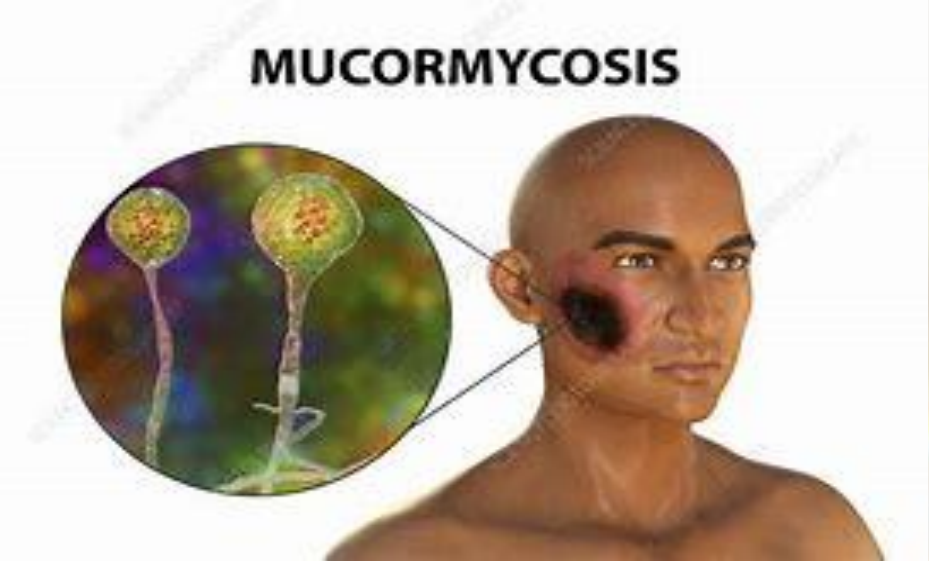
- The diagnosis and treatment of IFDs are challenged by limited access to quality diagnostics and treatment as well as emergence of antifungal resistance in many settings.

- Despite the growing concern, fungal infections receive very little attention and resources, leading to a paucity of quality data on fungal disease distribution and antifungal resistance patterns. Consequently, it is impossible to estimate their exact burden.

- Cases of invasive fungal disease (IFD) are rising as the at-risk population continues to expand. This is due to many factors, including advancements in modern medicine and accessibility to therapies and interventions that impair the immune system.

- New groups at risk of IFD are constantly being identified as patients with chronic obstructive pulmonary disease (COPD), liver or kidney disease, viral respiratory tract infections.

- The coronavirus disease (COVID-19) pandemic has been associated with an increase in the incidence of comorbid invasive fungal infections. Three groups of COVID-19 associated fungal infections; aspergillosis; mucormycosis; and candidaemia, were frequently reported, often with devastating consequences.



What is the WHO fungal priority pathogens list

- In 2017, WHO developed its first bacterial priority pathogens list (WHO BPPL) in the context of increasing antibacterial resistance to help galvanize global action, including the research and development (R&D) of new treatments.

- Inspired by the BPPL, WHO has now developed the first fungal priority pathogens list (WHO FPPL) which is the first global effort to systematically prioritize fungal pathogens, considering their unmet R&D needs and perceived public health importance.

- The WHO FPPL aims to focus and drive further research and policy interventions to strengthen the global response to fungal infections and antifungal resistance.

- The development of the list followed a multicriteria decision analysis (MCDA) approach.

- The priorit… …t can cause… …which… …challe…

Finally, regional variations and national contexts need to be taken into consideration while implementing the WHO FPPL to inform priority actions.

- This document prop… …policymakers, public health professionals and other stakeholders, targeted at improving the overall response to these priority fungal pathogens, including preventing the development of antifungal drug resistance.

Aim

WHO developed this first WHO FPPL to:

- Direct and drive research efforts towards the pathogens that pose the greatest public health threat and/or have the greatest gaps in knowledge.

- Facilitate international coordination and inform investment in R&D to discover new and optimize existing therapeutics and diagnostics, and to improve patient outcomes.

- Monitor antifungal development pipeline to track trends and identify gaps.

- Define research and development (R&D) priorities to align investments and funding with identified unmet public health needs.

- Promote knowledge generation to improve global understanding of and the response to fungal infections and antifungal resistance.

- Inform and enable policymakers to design and implement measures to address IFDs and antifungal resistance.

Scope

- The list is focused on fungal pathogens responsible for acute, subacute systemic fungal infections for which drug resistance or other treatability and management challenges exist.
- The pathogens included are all associated with serious risk of mortality and/or morbidity.
- The list is mainly focused on systemic invasive infections.

Approach

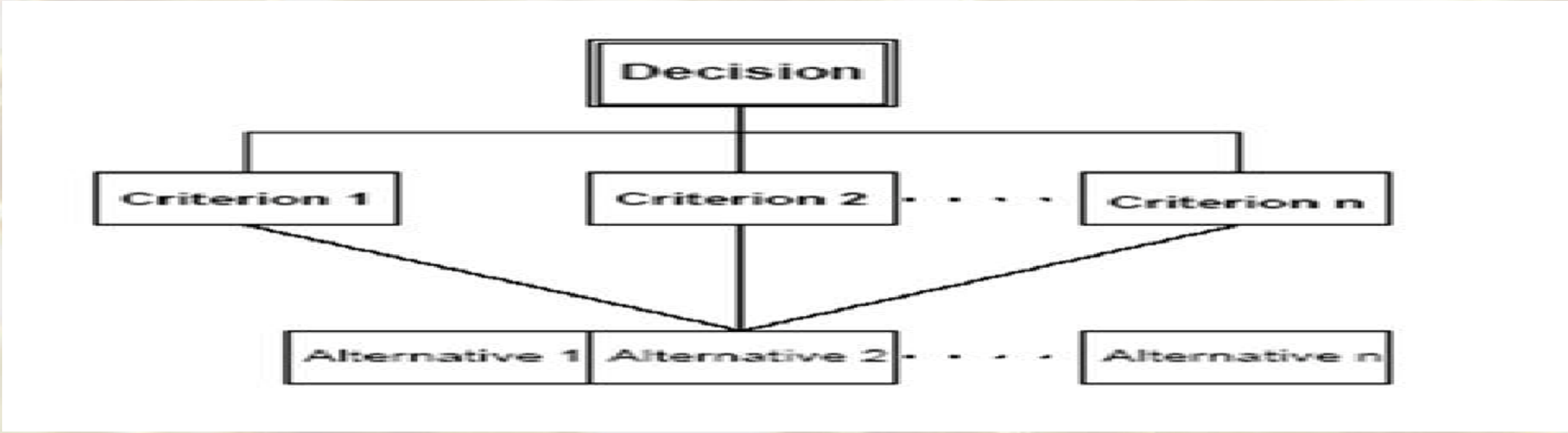
- In 2020, a scoping literature review conducted by WHO revealed that no global prioritization of fungal infection threats existed.

- Only one national infectious disease threat priority list that included fungal pathogens was identified, namely the US CDC priority threat list (2019), which highlighted three fungal “groups”: Candida auris, antifungal-resistant Candida and azoleresistant Aspergillus fumigatus.

- In addition, mucormycosis was prioritized by India in 2021 under the notifiable disease category, as a result of the world’s largest outbreak thus far, which was associated with the COVID-19 pandemic.

- Various approaches can be undertaken to develop priority lists, MCDA makes it possible to combine a diverse range of criteria, qualitative and quantitative evidence, along with the experience and expertise of stakeholders (systematic review vs expert opinion).

- In addition, MCDA is reproducible, enabling regular reviews of the list to be performed based on new evidence.



First

The process began by selecting 19 pathogens to prioritize, based on 10 assessment criteria.

The list of pathogens and criteria was determined in consultation with the WHO Advisory Group on FPPL (WHO AG FPPL), relevant WHO programs and regional offices.

WHO commissioned 19 systematic reviews of the literature to describe the pathogens with reference to these criteria.

Participants were recruited by WHO via country and regional offices, medical mycology societies and social media. Ultimately, 376 respondents from across the globe participated.

Prioritization (assessment) criteria

- Deaths
- Annual incidence
- Current global distribution
- Trends in last 10 years
- Inpatients care
- Complications
- Antifungal resistance
- Preventability
- Access to diagnostic tests
- Evidence based treatment

Then

The weight of each prioritization criterion was then determined through a discrete choice experiment (DCE) survey, focusing on the perceived R&D need.

- DCE is a well-established methodology for determining MCDA criteria weights while minimizing bias. Due to the complexity of the questions, a minimum sample size of 300 clinicians and/or researchers with expertise in medical or public health mycology was required.

Next

- The perceived public health importance of each pathogen was determined using best–worst scaling (BWS).

- WHO invited participants based on the advice of the WHO AG FPPL, WHO regional offices, and key contacts in medical mycology societies around the world, with 49 ultimately taking part.

- For this exercise, a minimal sample size of 40 respondents with senior-level expertise and experience in medical mycology and/or public health was required.

- In both surveys, efforts were made to ensure gender balance and geographic representativeness in the respondents.

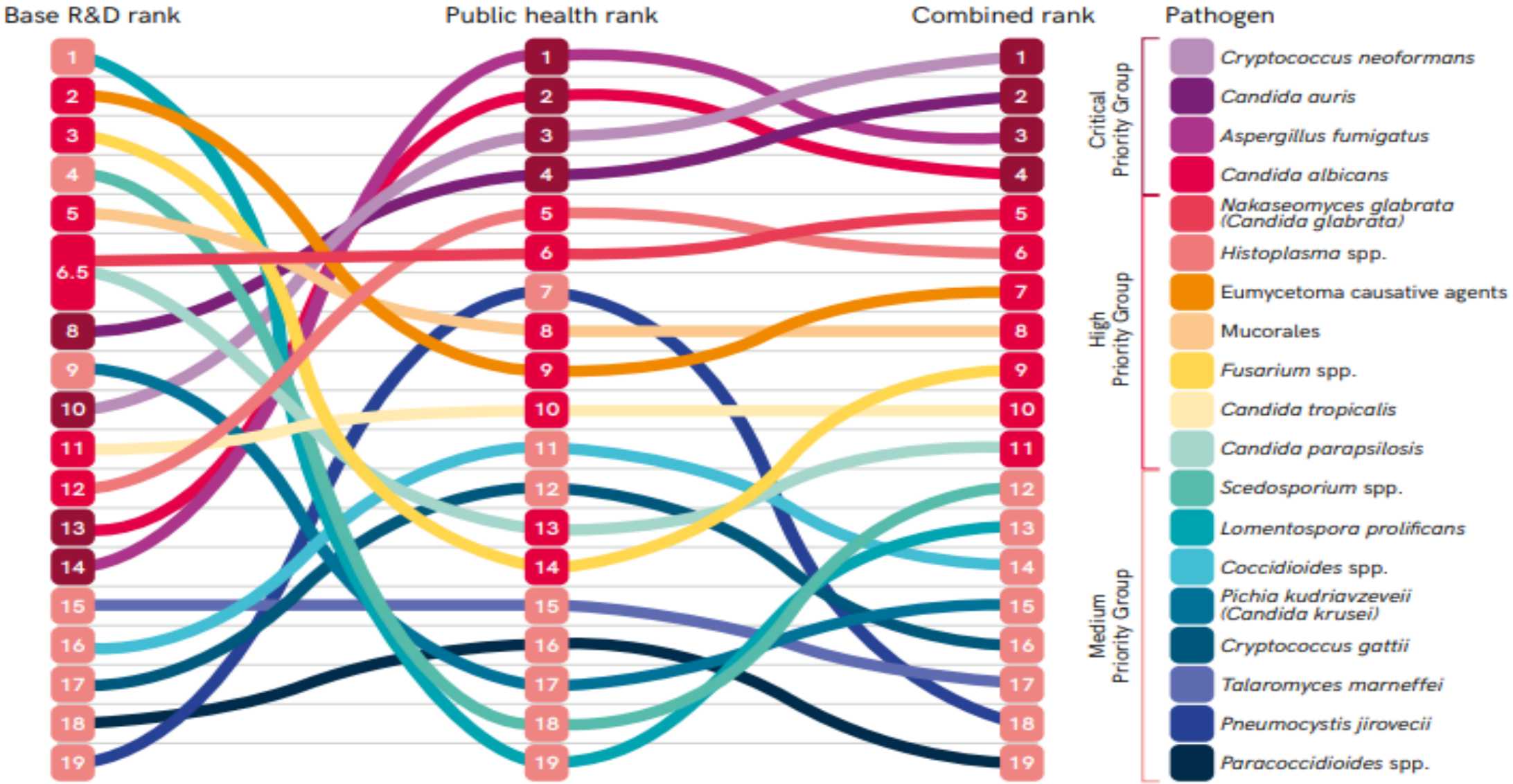
- Results from surveys were combined with the systematic reviews to produce a comprehensive ranking to guide R&D and identify strategies to prevent and control the burden of IFD and antifungal resistance

Table 1. Summary of the prioritization steps (All steps are overlapping and non-sequential)

Step 1	**Selection of stakeholder groups:** these include the WHO AG FPPL, which consists of mycology experts from all WHO regions, and participants in the Global Medical Mycology Expert Respondent Group.
Step 2	**Selection of pathogens to be prioritized:** the fungal pathogens to be prioritized were selected based on consultation and consensus.
Step 3	**Selection of criteria for prioritization:** criteria and levels for profiling fungal pathogens were selected and each criterion was defined, through an iterative process (see Table 2).
Step 4	**Systematic reviews:** 19 systematic reviews were conducted to describe each of the pathogens according to the predefined criteria and levels.
Step 5	**Assignment of levels:** based on the systematic reviews, and expert opinion where needed, levels were assigned to the criteria for each pathogen (see Table 2).
Step 6	**MCDA-DCE R&D survey:** a large DCE-based survey was conducted across six WHO regions to weight each criterion according to perceived R&D priority. The survey was available in three languages (English, French and Spanish).
Step 7	**Best-worst scaling (BWS) survey for public health importance:** a choice-based survey using BWS was conducted to estimate the weight of each pathogen according to perceived public health importance. This survey also included a question to determine the relative weights of unmet R&D vs. perceived public health importance and was used to inform the final overall pathogen ranking.
Step 8	**Final WHO FPPL:** The public health and R&D rankings were combined according to the weight assignment from step 7 to formulate the final FPPL.

WHO AG FPPL: World Health Organization Advisory Group on the Fungal Priority Pathogens List; DCE: discrete choice experiment; MCDA: multicriteria decision analysis; R&D: research and development; WHO: World Health Organization.

Overall pathogens ranking across the MCDA stages



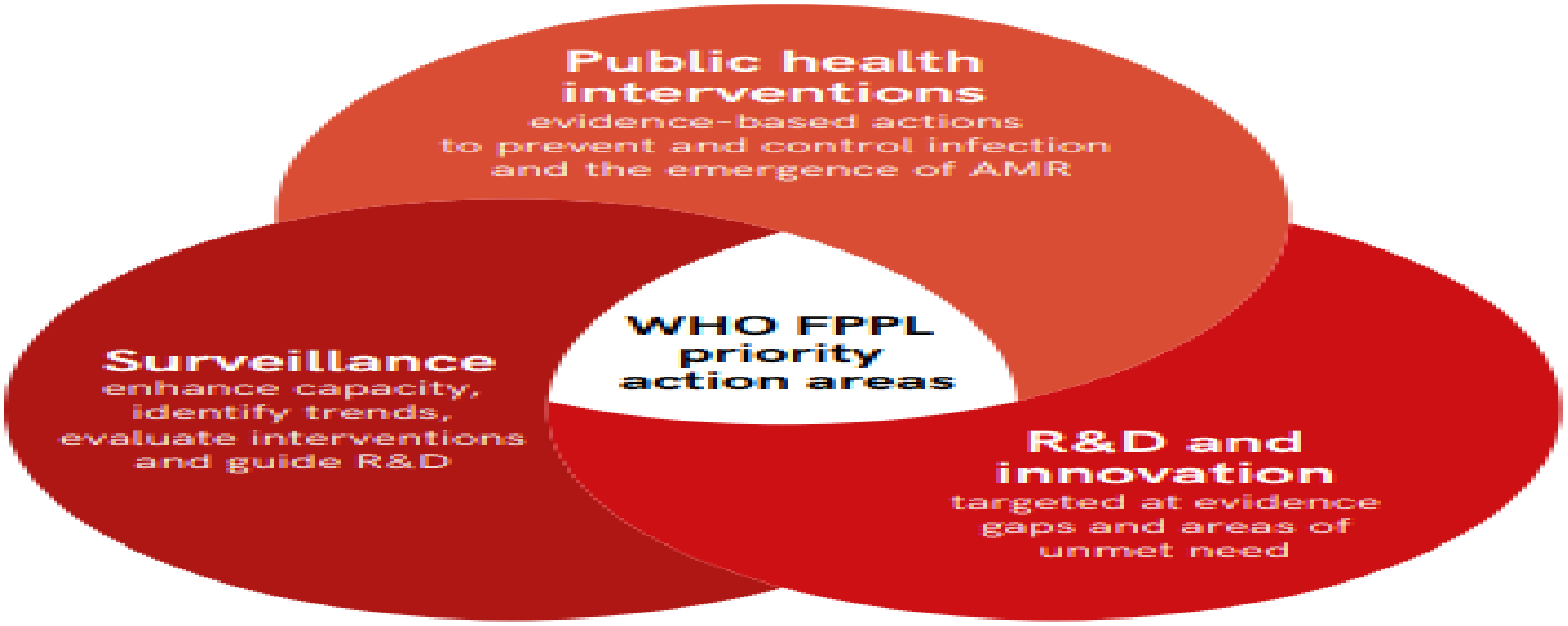
Final ranking of pathogens

Table 3. WHO fungal priority pathogens list

Critical group	High group	Medium group
 *Cryptococcus neoformans*	 *Nakaseomyces glabrata (Candida glabrata)*	 *Scedosporium* spp.
 *Candida auris*	 *Histoplasma* spp.	 *Lomentospora prolificans*
 *Aspergillus fumigatus*	 Eumycetoma causative agents	 *Coccidioides* spp.
 *Candida albicans*	 Mucorales	 *Pichia kudriavzeveii (Candida krusei)*
	 *Fusarium* spp.	 *Cryptococcus gattii*
	 *Candida tropicalis*	 *Talaromyces marneffei*
	 *Candida parapsilosis*	 *Pneumocystis jirovecii*
		 *Paracoccidioides* spp.

Implementation and use of the WHO FPPL and priority areas for action

Fig. 2. Proposed priority areas for action



AMR: antimicrobial resistance; R&D: research and development; WHO FPPL: World Health Organization fungal priority pathogens list.

Surveillance

- ✓ Achieving the goal of improved laboratory surveillance will depend on access to mycology laboratories, which are also essential for optimal patient care and overall patient safety.
- ✓ Large-scale susceptibility data collection with clinical data linkage will facilitate the development of clinical breakpoints for these fungal pathogens, many of which are not currently available.
- ✓ Improved clinical surveillance will depend on the level of knowledge and education regarding clinical presentation and risk factors for infections cause by these pathogens. Affordable access to diagnostic tools at the point of care is essential for optimal patient care, and for surveillance data generation.

Box 1: Surveillance actions, interventions and strategies

- **Build mycology diagnostic capacity** to manage fungal infections and to perform **surveillance**, starting at reference microbiology laboratories for **identification and susceptibility testing** of fungi. Such reference laboratories can perform surveillance and provide external quality assessment and training in fungal diagnosis.

- **Integrate fungal diagnostics** that are included on WHO's model list of essential diagnostics into **routine care** or **specialized laboratories** based on local epidemiology, contexts, capacity and needs. Prioritize diagnostic services to serve **populations at greatest risk** of fungal diseases (e.g., cancer, HIV/AIDS, post-TB, COPD, asthma).

- Build capacity in antifungal stewardship to **limit the inappropriate use of antifungals as well as antibiotics**. Develop **standard operating procedures** and algorithms for laboratories to **optimize the diagnosis** of fungal infections, including for pathogens with outbreak potential; build capacity for outbreak detection, reporting and response.

- Encourage the development of **networks at the national and international level** and participate in collaborative global and regional surveillance initiatives (e.g., WHO GLASS-AMR, GLASS-FUNGI, GLASS-EAR, and other regional platforms such as ReLAVRA and EARS-Net). Knowledge transfer through national, regional, and international disease registries, and other global collaborative platforms, **supports understanding of pathophysiology**, especially of rare pathogens, and will **facilitate research** into therapeutics and diagnostics.

- Utilize epidemiological laboratory and clinical **surveillance data** along with other health care data to **quantify** the burden of IFD and **antifungal resistance** to inform public health interventions, and guide IPC measures.

- Follow a stepwise approach in implementing the FPPL beginning with top priority pathogens, starting with **data and evidence generation**, and **tailoring FPPL to regional, national, and local contexts and needs**.

Research and development

Currently, fungal infections receive less than 1.5% of all infectious disease research funding. Consequently, the evidence base is weak, and most treatment guidelines are informed by limited evidence and expert opinion.

Tackling the problems posed by IFD will require increased research funding, targeted at the key priorities, new antifungal medicines and improved diagnostics.

Pathogens with limited therapeutic options such as Lomentospora prolificans or Fusarium species were clearly prioritized for R&D. Neither currently approved systemic antifungals nor those in the clinical pipeline fully address the problems faced by health care workers, due to treatment inherent limitations, and the rising rates resistance.

Box 2: R&D and innovation actions, interventions and strategies

- Focus R&D investments on **innovative antifungal agents** (i.e. **no cross-resistance to other antimicrobial classes, new chemical class, new target, and new mode of action-no or minimal drug-drug interaction**) effective against priority pathogens.
- **Improve existing therapies** and generate new knowledge on their optimal use, including pharmacokinetics/pharmacodynamics and therapeutic antifungal monitoring. Optimize combination therapies to **prevent further resistance, enhance efficacy and minimise toxicity**.
- Support research into the development of novel, accurate **rapid diagnostics** for priority pathogens – especially **affordable point-of-care rapid screening tests**, with the potential for widespread roll-out, particularly to **LMICs**.
- Promote research to improve efficacy, efficiency and quality of **fungal identification and susceptibility testing**, including the development of rapid screening tests suitable for LMICs, and to optimize and standardize the use of current diagnostic modalities for comparison locally, regionally and globally.
- Build an evidence base for incorporating **effective clinical care** for fungal disease into **existing health systems**, with the additional aim of informing public health.
- Pursue **public–private partnerships** and **multicountry collaborative research platforms** to support development of new antifungal therapies and diagnostics.

Public health

- IFD and antifungal resistance are important global health issues that impact vulnerable populations globally.
- Public health interventions must be built on the foundation of surveillance and R&D, with some priorities outlined in this report.
- A deep, granular understanding of the dynamics of disease burden (incidence, prevalence, mortality and morbidity) and the prevalence of AMR for these priority pathogens will facilitate rational interventions.

- With respect to emerging AMR, while the focus of this prioritization was fungal pathogens in human health, environmental contamination with antifungal agents is a problem.

- Therefore, One Health approaches are required to understand and mitigate these drivers but have thus far been very limited.

- Interlinked, integrated and innovative multisectoral approaches to surveillance of AMR and antimicrobial use and consumption are needed.

Box 3: Public health actions, interventions and strategies

- Incorporate fungal diseases and FPPL in **medical (clinical) and public health training** programmes and curricula at all medical training levels.
- **Improve global coordination and action** to strengthen and align action on IFD and antifungal resistance **prevention and control**.
- Promote **existing IPC** measures and **develop new** preventive measures at both the health care facility level and in the community.
- **Adopt, adapt and modify** existing and newly developed **health system approaches** to fungal disease care delivery based on fungal diseases epidemiology and local context.
- Promote **rational use** of antifungal agents through antifungal stewardship intervention, promotion existing or development of new evidence-based treatment guidelines and assess impact on outcomes (survival, length of hospital stays, development of resistance, etc.). Ensure availability of quality antifungal drugs as per WHO EML.
- Develop mechanisms and policies to ensure **equitable, affordable access to quality antifungal agents**. Utilize the **WHO EML** and other tools to inform procurement, tailoring to local need and disease epidemiology. Provide affordable access to diagnostics at the point of care for early identification of high risk patients and to improve appropriate and effective treatment.
- Promote **collaboration across sectors** to address the impact of **antifungal use** on **resistance** across the One Health spectrum.


Thank
you!