WHO fungal priority pathogens list to guide research, development and public health action

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Abbreviations and acronyms

AG	Advisory Group
AMR	antimicrobial resistance
ANZMIG	Australia & New Zealand Mycoses Interest Group
BWS	best-worst scaling
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease
CT	computed tomography
DCE	discrete choice experiment
EAR	emerging antimicrobial resistance
EARS-Net	Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ECMM	European Confederation of Medical Mycology
ESCMID-EFISG	European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group
EML	WHO Essential Medicines List
GAFFI	Global Action for Fungal Infections
GAP	Global Action Plan (on AMR)
GLASS	WHO Global Antimicrobial Resistance and Use Surveillance System
HSCT	haemopoietic stem cell transplantation
IA	invasive aspergillosis
ICU	intensive care unit
IFD	invasive fungal disease
IPC	infection prevention and control
IRIS	immune reconstitution inflammatory syndrome
ISHAM	International Society for Human & Animal Mycology
LMIC	low- and middle-income country
MALDI-TOF	matrix-assisted laser desorption/ionization time of flight
MCDA	multicriteria decision analysis
MEC	minimum effective concentration
MIC	minimum inhibitory concentration
MRC	Medical Research Council Centre
MSGERC	Mycoses Study Group Education and Research Consortium
PCR	polymerase chain reaction
PJP	*Pneumocystis jirovecii* pneumonia
R&D	research and development
ReLAVRA	The Latin American and Caribbean Network for Antimicrobial Resistance Surveillance (Spanish acronym)
TB	tuberculosis
US CDC	United States Centers for Disease Control and Prevention
WHO	World Health Organization
WHO BPPL	WHO bacterial priority pathogens list
WHO FPPL	WHO fungal priority pathogens list
WHO AG FPPL	WHO Advisory Group on the FPPL

Executive summary

Infectious diseases are among the top causes of mortality and a leading cause of disability worldwide. Drug-resistant bacterial infections are estimated to directly cause 1.27 million deaths and to contribute to approximately 4.95 million deaths every year, with the greatest burden in resource- limited settings.

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.

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). The WHO FPPL 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 prioritization process focused on fungal pathogens that can cause invasive acute and subacute systemic fungal infections for which drug resistance or other treatment and management challenges exist. The pathogens included were ranked, then categorized into three priority groups (critical, high, and medium). The critical group includes *Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus* and *Candida albicans*. The high group includes *Nakaseomyces glabrata (Candida glabrata)*, *Histoplasma* spp., eumycetoma causative agents, Mucorales, *Fusarium* spp., *Candida tropicalis* and *Candida parapsilosis*. Finally, pathogens in the medium group are *Scedosporium* spp., *Lomentospora prolificans*, *Coccidioides* spp., *Pichia kudriavzeveii (Candida krusei)*, *Cryptococcus gattii*, *Talaromyces marneffei*, *Pneumocystis jirovecii* and *Paracoccidioides* spp.

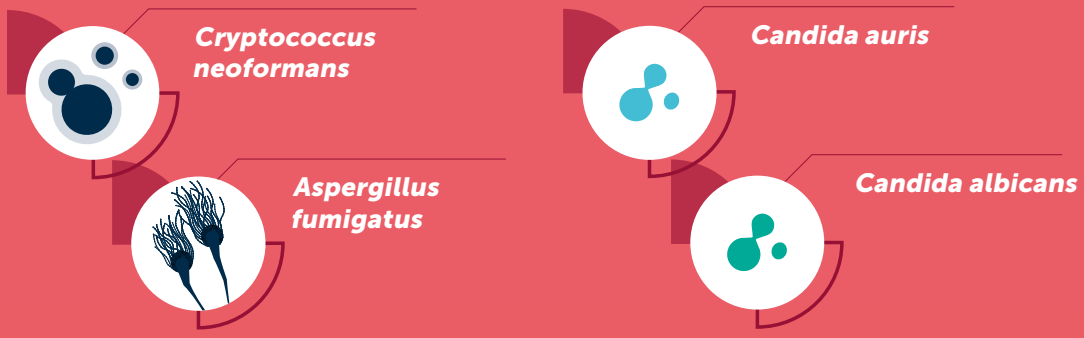
This document proposes actions and strategies for policymakers, public health professionals and other stakeholders, targeted at improving the overall response to these priority fungal pathogens, including preventing the development of antifungal drug resistance. Three primary areas for action are proposed, focusing on: (1) strengthening laboratory capacity and surveillance; (2) sustainable investments in research, development, and innovation; and (3) public health interventions.

Countries are encouraged to improve their mycology diagnostic capacity to manage fungal infections and to perform surveillance. In most contexts, this might require a stepwise approach. There is a need for sustainable investments in research, development, and innovation. More investments are needed in basic mycology research, R&D of antifungal medicines and diagnostics. Innovative approaches are needed to optimize and standardize the use of current diagnostic modalities globally. In addition, public health interventions are needed to highlight the importance of fungal infections, including through incorporating fungal diseases and priority pathogens in medical (clinical) and public health training programmes and curricula at all levels of training. Similarly, collaboration across sectors is required to address the impact of antifungal use on resistance across the One Health spectrum.

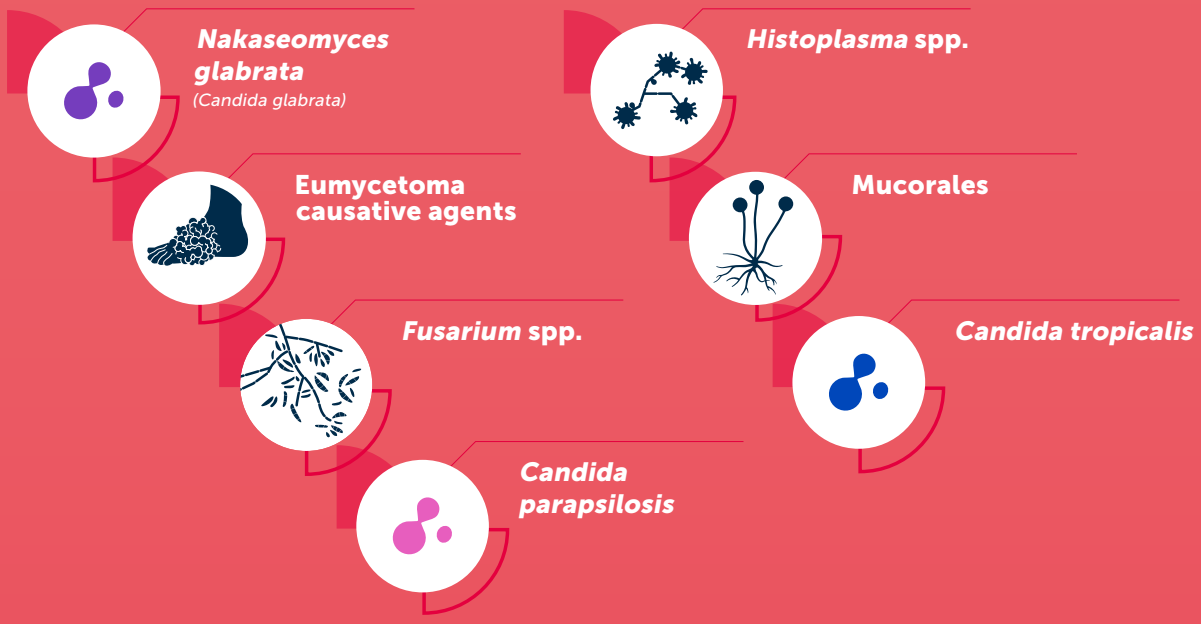
Finally, regional variations and national contexts need to be taken into consideration while implementing the WHO FPPL to inform priority actions.

Fig. 1. WHO fungal priority pathogens list (WHO FPPL)

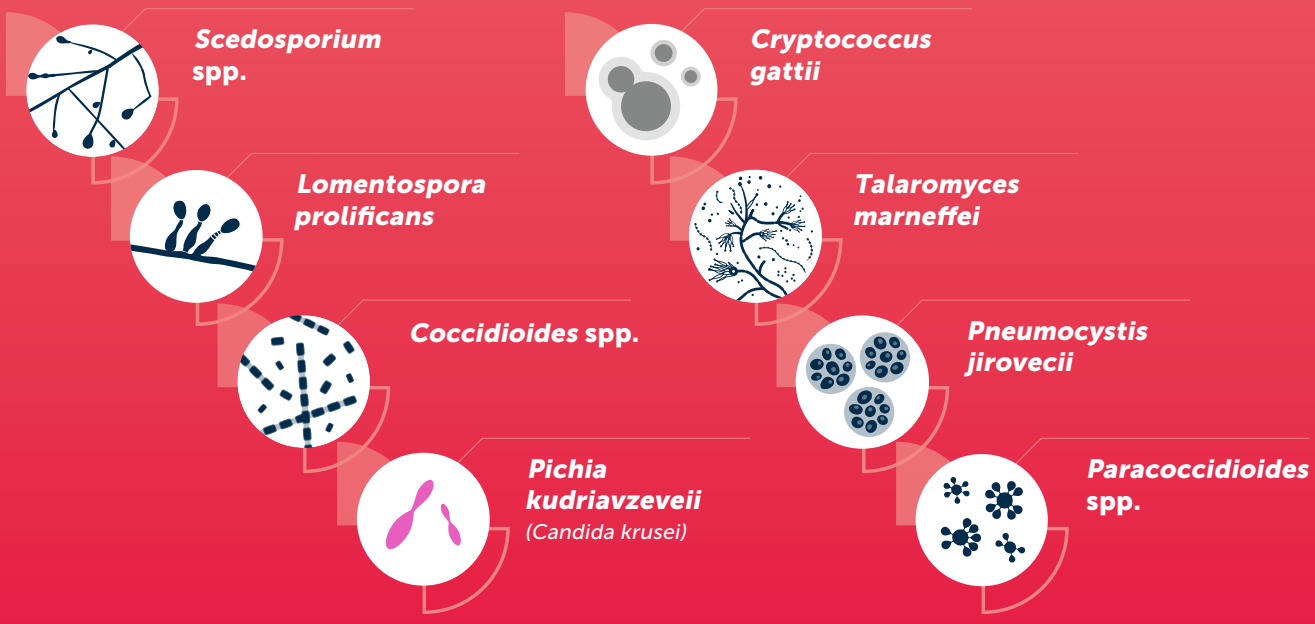
Critical Priority Group



High Priority Group



Medium Priority Group



1. Background

Fungal pathogens and infections are an increasing global public health concern. People most at risk are those with underlying health problems or a weakened immune system, such as chronic lung disease, prior tuberculosis (TB), HIV, cancer, and diabetes mellitus. Critically ill patients in an intensive care unit (ICU), patients undergoing invasive medical procedures and receiving broad-spectrum antibiotics, and those taking immune-suppressing medicines are also at risk *(1)*.

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, such as chemotherapy and immunotherapy for cancer, and solid organ transplantation. New groups at risk of IFD are constantly being identified. Examples include patients with chronic obstructive pulmonary disease (COPD), liver or kidney disease, viral respiratory tract infections such as influenza and those with prior non-tuberculous mycobacterial 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 *(2)*. Finally, there is evidence to suggest that both the incidence and geographic range of fungal infections are expanding globally due to climate change *(3, 4)*.

The underrecognized and emerging global health threat of invasive fungal diseases is compounded by the rapid emergence of antifungal resistance and, in many settings, limited access to quality diagnostics and treatment *(5, 6)*. Antifungal resistance has major implications for human health. It generally leads to prolonged therapy and hospital stays, and an increased need for expensive and often highly toxic second-line antifungal medicines. These medicines are often unavailable in low- and middle-income countries (LMICs) *(7, 8)*, which can contribute to increased mortality. The challenges posed by the multidrug-resistant pathogen *Candida auris* highlight these issues: not only does *C. auris* cause increased morbidity and mortality for affected individuals but the pathogen is also difficult to eradicate from hospitals, even with intensive infection-prevention strategies *(9, 10, 11, 12)*. Its detection in the hospital environment may result in prolonged ward closures. The emergence of resistance is partly driven by inappropriate antifungal use across the One Health spectrum *(13)*. For example, agricultural use is responsible for rising rates of azole-resistant *Aspergillus fumigatus* infections, with azole-resistance rates of 15–20% reported in parts of Europe and over 80% in environmental samples in Asia *(9, 14, 15, 16)*.

Currently, only four classes of systemic antifungal medicines (azoles, echinocandins, pyrimidines and polyenes) are used in clinical practice, and only a few others are under development *(17, 18, 19, 20)*. Although existing antifungal medicines are effective, they are associated with a plethora of adverse effects. The use of these medicines also requires expertise, and drug–drug interactions are particularly common *(21)*. Such interactions, along with the requirement for lengthy courses of therapy, further impact patient safety and prognosis.

Additionally, affordable access to quality medicines and diagnostic tests is unevenly distributed. This is especially acute in low-resource settings, where the disease burden is highest *(1)*. As a result, many fungal infections go undiagnosed and untreated. Causative pathogens are rarely confirmed microbiologically, and in most settings, surveillance data are of low quality or absent.

Despite posing a growing threat to human health, fungal infections receive very little attention and resources globally *(1)*. This all makes it impossible to estimate the exact burden of fungal infections and consequently difficult to galvanize policy and programmatic action.

In 2017, WHO developed its first bacterial priority pathogens list (WHO BPPL) in the context of increasing antimicrobial resistance (AMR). The aim of the WHO BPPL was to guide private and public investment into the development of new antibiotics by identifying research and development (R&D) priorities *(22)*. Since the WHO BPPL was launched, WHO has regularly used the list to analyse the antibacterial development pipeline *(23, 24)*. These analyses have shown that the WHO BPPL has been instrumental in informing research and investment decisions. Importantly, the list has also emerged as a valuable tool for raising AMR awareness and informing surveillance measures, infection prevention and control (IPC) interventions, and antimicrobial stewardship guidance. Inspired by the WHO BPPL, WHO developed the first fungal priority pathogens list (WHO FPPL).

2. Aims

In response to the rising threat of fungal infections, combined with existing and emerging resistance and treatability issues, 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.

3. 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. Similar assessments in the future could include other fungi with important economic and health consequences, particularly those causing mucosal, skin and eye infections.

4. Target audience

The target audience for this document includes but is not limited to:

- National and subnational policymakers in the Ministries of Health or equivalent authorities responsible for infectious diseases and AMR monitoring, and developing and implementing infection prevention and control interventions, national actions plan, and public health policies.
- Medical mycologists, public health researchers, general practitioners, and other healthcare providers.
- Healthcare, infectious diseases, medical mycology, and public health professional societies.
- The pharmaceutical and diagnostics industry, academic and public health research institutions.
- Research funders and public–private partnerships which invest in basic research, and the development, and implementation into practice of new antifungal agents and diagnostics.

5. Approach

The heterogeneity of communicable diseases makes it difficult to prioritize pathogens globally *(25)*. Fungal infections, with their complex epidemiology, risk factors, variable global distribution, and disease dynamics, are no exception. 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 azole-resistant *Aspergillus fumigatus (26)*. 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. In 2017 WHO successfully used multicriteria decision analysis (MCDA) to develop the WHO bacterial priority pathogens list *(27)*, and a similar approach has been adopted for the WHO FPPL *(18)*. MCDA makes it possible to combine a diverse range of criteria, qualitative and quantitative evidence, along with the experience and expertise of stakeholders. In addition, MCDA is reproducible, enabling regular reviews of the list to be performed based on new evidence.

The process began by selecting 19 pathogens to prioritize, based on 10 assessment criteria (Tables 1, 2). The list of pathogens and criteria was determined in consultation with the WHO Advisory Group on FPPL (WHO AG FPPL), relevant WHO programmes and regional offices. WHO commissioned 19 systematic reviews of the literature to describe the pathogens with reference to these criteria (Table 2).[1]

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 *(28,29)*. 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. Participants were recruited by WHO via country and regional offices, medical mycology societies and social media. Ultimately, 376 respondents from across the globe participated.

Next, the perceived public health importance of each pathogen was determined using best-worst scaling (BWS). 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. 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. 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 (Figs. 1, 2).

[1] Diagnostic and treatment criteria were not included in the systematic reviews but were determined through an alternative approach.

6. Key findings

The MCDA approach used in the prioritization comprised a DCE global survey focused on R&D, and a BWS global surveys on public health importance. The approach considers a diverse range of criteria, qualitative and quantitative evidence, along with the expertise of stakeholders. Thus, the prioritization process revealed important findings that should inform the use of the WHO FPPL.

First, public health importance is a strong determinant of priority. For the overall ranking of pathogens, BWS survey respondents favoured public health importance over unmet R&D need. Furthermore, apart from antifungal resistance, disease-burden-related criteria (mortality, annual incidence, and morbidity) had the highest weights for relative importance in the R&D DCE survey. These features are reflected in the overall ranking, where the 4 'critical threat' pathogens are those ranked highest for perceived public health importance (*Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus* and *Candida albicans*).

Second, antifungal resistance is a top priority. Of all 10 criteria in the DCE on R&D, respondents gave the highest weighting to antifungal resistance. As a result, fungal pathogens that are highly antifungal resistant ranked top in terms of R&D need (e.g. *Lomentospora prolificans*, *Fusarium* spp., Mucorales, and *Scedosporium* spp.).

Third, the systematic reviews revealed major knowledge gaps on the global burden of fungal infections and antifungal resistance. All 19 pathogens included in the prioritization lacked comprehensive data on the burden of disease, especially data relating to morbidity. Although many papers reported susceptibility data from ad hoc laboratory surveillance projects, formal surveillance and data linkage to clinical outcomes were lacking. Furthermore, susceptibility was reported very inconsistently, making comparisons over time or between geographic areas difficult. Susceptibility data were less common from LMICs, likely due to limited access to medical mycology laboratories in resource-limited settings.

Finally, fungal pathogens distribution and epidemiology vary significantly by region. Some pathogens are global, whereas some are endemic to certain areas. The systematic reviews pointed to major variations in the incidence and prevalence of fungal conditions, partly related to underlying disease and local clinical practice. The prevalence of antifungal resistance also varies considerably. Therefore, regions and countries are encouraged to contextualize these findings at the regional, subregional, or country level to inform local priorities in terms of public health importance and potentially R&D.

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.

Table 2. Prioritization criteria, definitions and levels

Criterion	Definition/description	Level value
Deaths	Average case fatality rate	**Low:** < 30% **Medium:** 30–70% fatality **High:** > 70% **Unknown:** no reliable data
Annual incidence	Number of new cases per million population each year	**Low:** < 2/million **Medium:** 2–50/million **High:** > 50/million **Unknown:** no data available
Current global distribution	Extent of geographic distribution across the globe	**Localized** in ≤ 2 WHO regions **Globally distributed** in ≥ 3 WHO regions **Unknown:** due to inadequate data
Trends in last 10 years	Evidence of change in incidence/prevalence patterns	**Stable:** no evidence of increasing incidence/prevalence **Increasing:** evidence of increasing incidence/prevalence **Unknown:** due to inadequate data
Inpatient care	Average length of hospital stay required for treatment following initial diagnosis	**Low:** < 2 days **Medium:** 2 days to 2 weeks **High:** > 2 weeks **Unknown:** no data available
Complications and sequelae	Proportion of patients suffering long-term complications of disease	**Low:** expected to affect a minority of patients (e.g. < 10%). **Medium:** expected to affect a significant proportion of patients (e.g. 10–50%). **High:** expected to affect the majority of patients (e.g. > 50%).
Antifungal resistance	Rate (or level) of acquired or intrinsic resistance to antifungal treatment	**Low:** < 10% acquired or intrinsic resistance for all four classes of antifungals. **Medium:** acquired or intrinsic resistance (> 10%) described for agents from one to two classes of antifungals. **High:** acquired or intrinsic resistance (> 10%) described for agents from three to four classes of antifungals. **Unknown:** no reliable data available
Preventability	Transmission/ acquisition dynamics and availability of evidence-based, effective preventive measures	**Low:** transmission/acquisition dynamics well described, and preventive measures ineffective or of low-quality evidence, and/or not widely available or difficult to implement. **Medium:** transmission/acquisition dynamics are not well described, but preventive measures based on moderate or high-quality evidence are available and effective. **High:** transmission/acquisition dynamics are well described, and preventive measures based on moderate or high-quality evidence are universally available and effective. **Unknown:** transmission/acquisition dynamics not well described. No preventive measures described.
Access to diagnostic tests	Availability of diagnostics	**Low:** diagnostics are not available in reference laboratories. **Medium:** diagnostics are available in institutional or reference laboratories but not universally available due to cost, distribution or technical issues. **High:** diagnostics are available and have been successfully implemented in institutional diagnostic laboratories, in at least one but not all high-burden/low-resource settings where disease occurs. **Very high:** diagnostics are universally available in institutional diagnostic laboratories where disease occurs.
Evidence-based treatments	Treatment options are evidence based and accessible	**Very low:** treatment based on expert opinion with limited evidence. **Low:** peer-reviewed, high-quality guidelines available, but first-line treatment options are unaffordable, toxic or unavailable where disease occurs. **Medium:** peer-reviewed, high-quality guidelines with at least one first-line treatment option which is affordable, non-toxic and available where disease occurs. **High:** peer-reviewed, high-quality guidelines with at least one first-line treatment option which is affordable, nontoxic and available where disease occurs, and includes specific recommendations for all main host groups, including paediatrics.

WHO: World Health Organization.

7. Final ranking of pathogens

The 19 fungal pathogens included were ranked and categorized into three priority groups based on their numerical scores, and consensus discussions among the WHO AG FPPL (Table 3).

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

The relative importance weight of each criterion for R&D priorities ranking varied considerably. The most important was antifungal resistance (38.5%), followed by deaths (13.9%), evidence-based treatment (11.9%), access to diagnostics (10.4%), annual incidence (8.5%) and complications and sequelae (8.4%). The remaining criteria had a relative importance of less than 5%.

Annex 1 shows the ranking for each of the 19 pathogens based on the DCE for R&D need, the BWS for perceived public health importance and finally a combined ranking. Respondents in the BWS assigned a relative importance weights of 0.48 for R&D need and 0.52 for public health importance. These weights were used to determine the overall ranking.

There are notable and understandable variations in ranking for some pathogens. For example, *Lomentospora prolificans* was ranked top for R&D need due to lack of effective treatment options but was ranked low for perceived public health importance due to its rarity. Overall, it ranked 13th. In contrast, *Aspergillus fumigatus* and *Candida albicans* were ranked lower for unmet R&D need but ranked highly for their public health burden. Overall, they both ranked in the top four (Annex 1).

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.

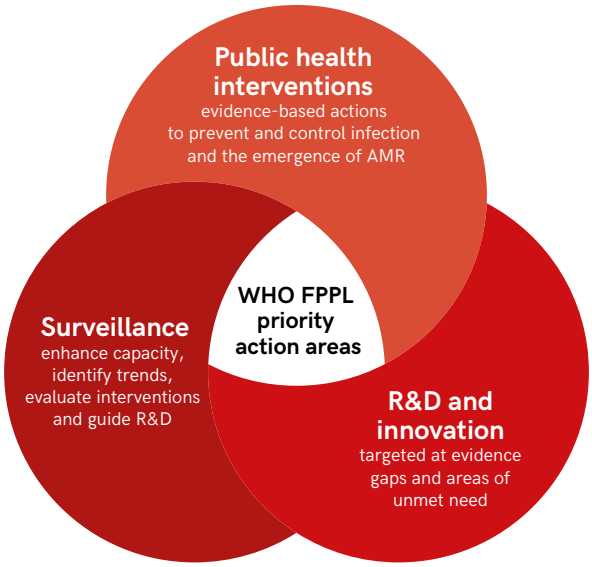
8. Important considerations and limitations

- Some pathogens are confined to certain geographical areas and thus are not considered a priority on a global scale (e.g. *Paracoccidioides* spp.). However, in areas where they are endemic, they are associated with a significant burden of disease. As such, these pathogens should be assessed independently and must be considered in the local context. Regions and countries are encouraged to contextualize these findings at the regional, subregional or country level to inform local priorities in terms of public health importance and potentially R&D.
- This is also the case for specific populations. For example, *Pneumocystis jirovecii* is one of the main pathogens causing opportunistic infections in people living with HIV/AIDS, but it ranked low in the global list. For populations at high risk of specific infections (e.g. cancer and immunosuppressed patients, and newborns with HIV infections) both the list, and the interventions outlined in this document must be contextualized and implemented accordingly.
- The MCDA approach made it possible to combine multiple types of criteria (qualitative vs quantitative) and evidence (systematic review vs expert opinion). Future iterations of the list are likely to be informed by stronger, more robust evidence generated in response to the recommendations in this report.
- The predefined criteria and levels were based on the scoping literature reviews and expert opinion from the WHO AG FPPL and were defined before the systematic reviews were conducted. Some criteria levels did not describe any of the pathogens. Although sensitivity analyses showed that these features of the data have minimal impact on the overall ranking, future iterations will build on the evidence collected in this exercise to further optimize criteria and refine levels.
- Combining the rankings of unmet R&D need and perceived public health importance is challenging. Two different surveys were conducted to assess each of them separately. The perceived public health importance on overall ranking was determined from the BWS survey among a smaller group of highly experienced mycologists. Geographic representativeness was observed during recruitment of participants.
- Evidence from the systematic review was minimal for some criteria in the MCDA-DCE. For example, many pathogens lacked data on complications and sequelae of infection and duration of inpatient care. Where data gaps were found, expert consensus was used to profile the pathogens. Therefore, some of the findings may be subject to bias.
- Large multinational prospective cohort studies are needed to fill the gaps on burden of disease criteria. In addition, quality surveillance data on antifungal resistance, and evidence on IPC measures are needed to better inform future iterations of the WHO FPPL.
- The systematic reviews that informed the criteria used in the MCDA-DCE were limited to peer-reviewed publications in English within the last 10 years (2011–2021). It is likely that more data exist, some in other languages, which could have influenced the strength of the evidence. For example, public health reports from individual countries on specific infections were not identified or included unless published in peer-reviewed journals in English. Future iterations should include other data sources (e.g. conference abstracts, grey literature), and non-English publications, especially for endemic mycoses.
- Sensitivity analyses showed that the overall ranking of fungal pathogens was robust and minimally affected by the country of origin of the respondents (LMIC vs. high-income countries) or by changing the levels of the criteria.
- Attempts to ensure representativeness of the surveys were successful. Of note, females made up 45% (n = 181/401), and 55% (n = 27/49) of the respondents to the MCDA-DCE and the BWS surveys, respectively. 42% (168/401) of the respondents worked in LMICs, or primarily in a language other than English.

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

The WHO FPPL 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. Currently, there is a clear need for an evidence base to inform public health interventions – both in terms of disease impact and improved delivery of care. To address this need, three key broad areas for action were identified: improved surveillance, targeted support for R&D and innovation, and enhanced public health interventions. These inter-linking action areas build on and reinforce each other (Fig. 2).

Fig. 2. Proposed priority areas for action



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

9.1. Surveillance

Context. Closing the large knowledge gaps identified in burden, both of disease and antifungal resistance, will require coordinated investment in both laboratory-based and clinical surveillance. This must happen at the national, regional, and international levels.

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. While many first-line tests (e.g. microscopy and culture) can be readily implemented in standard microbiology laboratories, access to these tests is still limited in many countries around the world. Other tests such as MALDI-TOF (matrix-assisted laser desorption/ionization time of flight) mass spectrometry systems, real-time PCR (polymerase chain reaction), and antifungal therapeutic monitoring are currently too costly and limited mostly to high-income settings. Addressing this limitation requires a stepwise approach, for example as described in a 2015 report by Global Action for Fungal Infections *(30)*.

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. In 2019 the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) initiated a global collaborative effort to compile available data on fungal infections, expanding its original scope from bacterial infections to include fungi. The first pathogen(s) included in the pilot phase are *Candida* spp., focusing on bloodstream infections in hospitalized patients *(31)*.

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. Such diagnostic tools include imaging tests (e.g. CT and MRI), advanced sampling (e.g. bronchoscopy, CT guided biopsy) and other technologies for accurate diagnosis.

Finally, diagnostic capacity underpins antibiotic, and antifungal stewardship. Accurate diagnoses promote the rational use of antifungal agents and reduce unnecessary empiric antimicrobial use *(32)*. Access to quality diagnostics for fungal diseases is essential part of the WHO AMR agenda (Box 1).

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**.

AMR: antimicrobial resistance; COPD: chronic obstructive pulmonary disease; EAR: emerging antimicrobial resistance; EARS-Net: Antimicrobial Resistance Surveillance Network; FPPL: fungal priority pathogens list; GLASS: Global Antimicrobial Resistance and Use Surveillance System; IFD: invasive fungal disease; ReLAVRA: Spanish acronym of The Latin American and Caribbean Network for Antimicrobial Resistance Surveillance; TB: tuberculosis; WHO: World Health Organization.

9.2. R&D and innovation

Context. 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* spp. 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. The massive use of some antifungals (azoles) in agriculture is further compounding the problem. Novel agent classes with different targets and mechanisms of action, and better safety profiles, should be developed and strictly reserved for use in humans. This, and other outcomes, will rely on the support for basic scientific research, including the pathophysiology of fungal infections. Finally, further research and innovation are needed to optimize the way current antifungals are used, including strategies to make therapeutic antifungal monitoring more widely available and optimize combination therapies to prevent further resistance and enhance efficacy.

The availability of accurate diagnostics was considered in the MCDA and impacted the R&D ranking of pathogens. The clinical diagnosis of IFD is often challenging because presentations are nonspecific and many current tests have poor sensitivity or specificity. Even in settings with adequate diagnostic capacity, the turnaround time for confirmatory tests can be days to weeks, hindering the guidance of effective early treatment. Novel antifungals, and accurate rapid diagnostics, are urgently needed. Despite this, the R&D pipeline is hampered by the long development time associated with traditional R&D models (about 10 years), the insufficient return on investment and the scientific challenges of identifying new targets (Box 2).

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.

LMICs: low- and middle-income countries; R&D: research and development.

9.3. Public health

Context. 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.

The systematic reviews showed that strategies for IPC exist for many of the priority pathogens, albeit with varying levels of evidence and implementation. Concerted efforts must be directed to refining current strategies and implementation plans, and developing new strategies, to contain the expanding burden of disease. Investigations into the role of air quality, the built environment, coinfections and other drivers at the population level should be considered.

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.

Additionally, in many settings, health care workers are unfamiliar with fungal infections. This results in low clinical suspicion, misdiagnosis, incorrect or delayed treatment and often poor patient outcomes. To address this, fungal infections need to be mainstreamed beyond specialized training programmes as part of early and ongoing medical and public health training. In addition, management of IFD must follow a patient-centred approach that empowers at-risk groups and provides them with the tools they need to look after their own health.

Finally, policy interventions must be implemented to improve access to existing antifungal agents and diagnostics where disease burden is highest (Box 3).

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.

FPPL: fungal priority pathogens list; WHO EML: WHO essential medicines list; IFD: invasive fungal disease; IPC: infection prevention and control; LMIC: low- and middle-income country; WHO: World Health Organization.

References

1. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases – estimate precision. J Fungi (Basel). 2017;3(4).
2. Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? Lancet Respir Med. 2021;9(8):e77.
3. Wu X, Lu Y, Zhou S, Chen L, Xu B. Impact of climate change on human infectious diseases: Empirical evidence and human adaptation. Environ Int. 2016;86:14-23.
4. Nnadi NE, Carter DA. Climate change and the emergence of fungal pathogens. PLoS Pathog. 2021;17(4):e1009503.
5. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Science translational medicine. 2012 Dec 19;4(165):165rv13-.
6. Denning DW. Antifungal drug resistance: an update. Eur J Hosp Pharm. 2022;29(2):109–12.
7. Pfaller MA. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. Am J Med. 2012;125(1 Suppl):S3–13.
8. van der Linden JW, Snelders E, Kampinga GA, Rijnders BJ, Mattsson E, Debets-Ossenkopp YJ et al. Clinical implications of azole resistance in *Aspergillus fumigatus*, The Netherlands, 2007–2009. Emerg Infect Dis. 2011;17(10):1846–54.
9. Calvo B, Melo AS, Perozo-Mena A, Hernandez M, Francisco EC, Hagen F et al. First report of *Candida auris* in America: clinical and microbiological aspects of 18 episodes of candidemia. J Infect. 2016;73(4):369–74.
10. Chowdhary A, Sharma C, Meis JF. *Candida auris*: a rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. PLoS Pathog. 2017;13(5):e1006290.
11. Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender NP et al. Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis. 2017;64(2):134¬–40.
12. Rudramurthy SM, Chakrabarti A, Paul RA, Sood P, Kaur H, Capoor MR et al. *Candida auris* candidaemia in Indian ICUs: analysis of risk factors. J Antimicrob Chemother. 2017;72(6):1794–801.
13. Rhodes J, Abdolrasouli A, Dunne K, Sewell TR, Zhang Y, Ballard E et al. Population genomics confirms acquisition of drug-resistant *Aspergillus fumigatus* infection by humans from the environment. Nat Microbiol. 2022;7(5):663–74.
14. Duong TN, Le TV, Tran KH, Nguyen PT, Nguyen BT, Nguyen TA et al. Azole-resistant *Aspergillus fumigatus* is highly prevalent in the environment of Vietnam, with marked variability by land use type. Environ Microbiol. 2021;23(12):7632–42.
15. Zhou D, Korfanty GA, Mo M, Wang R, Li X, Li H et al. Extensive genetic diversity and widespread azole resistance in greenhouse populations of *Aspergillus fumigatus* in Yunnan, China. mSphere. 2021;6(1):e00066-21.
16. Vermeulen E, Lagrou K, Verweij PE. Azole resistance in *Aspergillus fumigatus*: a growing public health concern. Curr Opin Infect Dis. 2013;26(6):493–500.
17. Osherov N, Kontoyiannis DP. The anti-*Aspergillus* drug pipeline: is the glass half full or empty? Med Mycol. 2017;55(1):118–24.
18. Hoenigl M, Sprute R, Egger M, Arastehfar A, Cornely OA, Krause R et al. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. Drugs. 2021;81(15):1703–29.
19. Perfect JR. The antifungal pipeline: a reality check. Nat Rev Drug Discov. 2017;16(9):603–16.
20. Denning DW, Bromley MJ. Infectious disease. How to bolster the antifungal pipeline. Science. 2015;347(6229):1414–6.
21. Niazi-Ali S, Atherton GT, Walczak M, Denning DW. Drug–drug interaction database for safe prescribing of systemic antifungal agents. Ther Adv Infectious Dis. 2021;8:1–9.

22. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.

23. Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health Organization; 2019 (https://www.who.int/publications/i/item/9789240000193, accessed 2 June 2022).

24. Antibacterial agents in preclinical development: an open access database. Geneva: World Health Organization; 2019 (WHO/EMP/IAU/2019.12; https://www.who.int/publications/i/item/WHO-EMP-IAU-2019.12, accessed 2 June 2022).

25. Krause G. How can infectious diseases be prioritized in public health? A standardized prioritization scheme for discussion. EMBO Rep. 2008;9 Suppl 1:S22–7.

26. Antibiotic resistance threats in the United States, 2019. Atlanta (GA): Centers for Disease Control and Prevention; 2019.

27. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.12; https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12, accessed 2 June 2022).

28. Thokala P, Devlin N, Marsh K, Baltussen R, Boysen M, Kalo Z, et al. Multiple criteria decision analysis for health care decision making – an introduction: report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value Health. 2016;19(1):1–13.

29. Tervonen T, Gelhorn H, Sri Bhashyam S, Poon JL, Gries KS, Rentz A, Marsh K. MCDA swing weighting and discrete choice experiments for elicitation of patient benefit-risk preferences: a critical assessment. Pharmacoepidemiol Drug Saf. 2017;26(12):1483-1491.

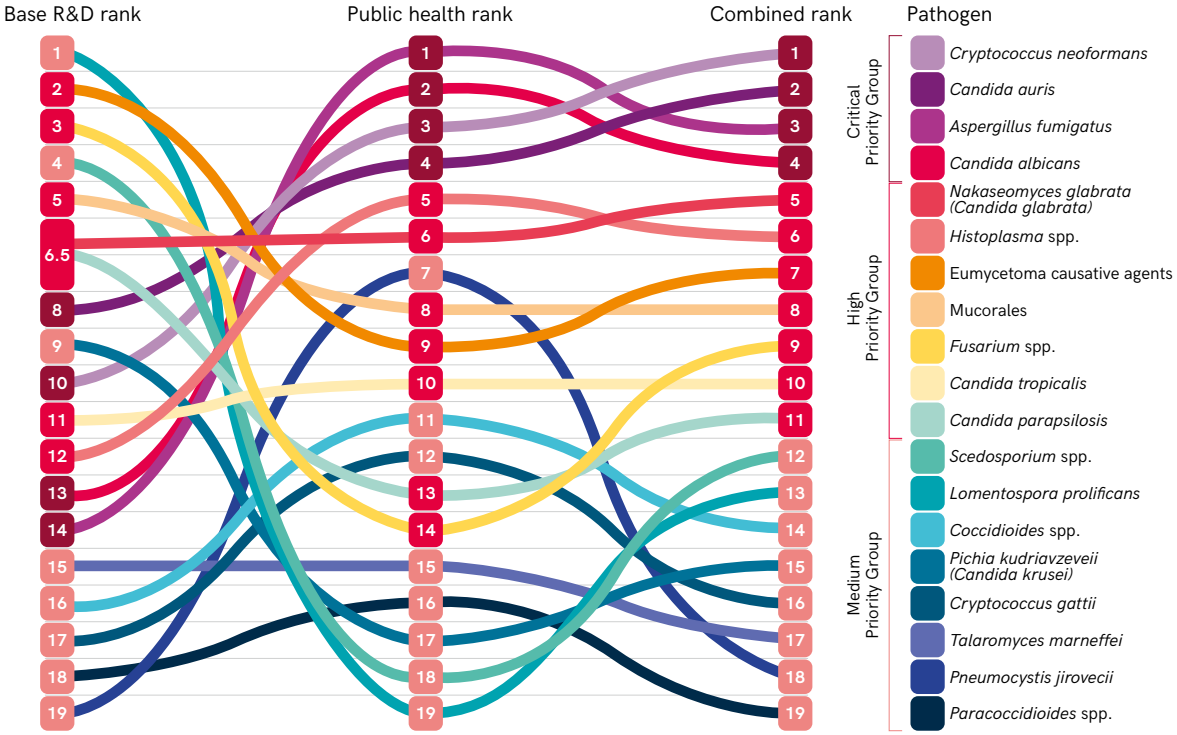
30. Global Action For Fungal Infections. "95-95 by 2025. Improving outcomes for patients with fungal infections across the world; A roadmap for the next decade." Meeting Seattle, USA, February 2015; Report May 2015 http://www.gaffi.org/roadmap/

31. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2020. Geneva: World Health Organization; 2020.

32. Denning DW, Perlin DS, Muldoon EG, Colombo AL, Chakrabarti A, Richardson MD et al. Delivering on the antimicrobial resistance agenda not possible without improving fungal diagnostic capabilities. Emerg Infect Dis. 2017;23:177–83.

Annex 1. Overall pathogens ranking across the MCDA stages

Overall pathogens ranking across the MCDA stages



Plot showing how pathogens were ranked across three stages of MCDA. From left to right: 1. pathogen ranking based on DCE survey for R&D priorities; 2. pathogen ranking based on BWS scaling survey for public health importance; 3. overall combined ranking. Respondents in the BWS applied the relative importance weights of 0.48 for R&D need and 0.52 for public health importance. These weights were used to determine the overall combined ranking. BWS: best-worst scenario; DCE: discrete choice experiment; MCDA: multicriteria decision analysis; R&D: research and development; spp.: species.

Annex 2. Brief description of each fungal pathogen

(Note: the following description is based on the systematic reviews and evidence extracted to support the prioritization process)

Cryptococcus neoformans

Key facts

- *Cryptococcus neoformans* is an opportunistic fungal pathogen. Cryptococcosis is acquired through the respiratory route when fungi are inhaled from the environment.
- Cerebral cryptococcosis is a life-threatening disease with high mortality despite antifungal therapy.
- Although treatment guidelines are well established for major risk groups (HIV patients), recommended antifungals are unavailable in many countries, and no clear guidelines for non-HIV at risk groups.

Overview

Cryptococcus neoformans is a globally distributed pathogenic yeast which lives in the environment (soil, decaying wood). After inhalation of fungal cells from the environment, *C. neoformans* can infect humans. Cryptococcosis initially affects the lungs but can spread to the central nervous system (cryptococcal meningitis) and blood (cryptococcaemia). Human-to-human transmission does not occur. Most patients are immunocompromised, and the leading risk factor is HIV infection. However, organ transplant patients and others taking medications that weaken the immune system are also at risk, and infection can occur in apparently healthy individuals. Risk factors for invasive cryptococcal disease include HIV infection, iatrogenic immunosuppression, autoimmune disease and decompensated liver cirrhosis.

C. neoformans cryptococcosis is a very serious disease, with mortality ranging from 41% to 61%, especially in patients with HIV infection. Hospital length of stay in patients with *C. neoformans* infection ranged from median of 18 to 39 days, predominantly reported for HIV-positive patients.

Complications due to *C. neoformans* infection and its treatment included acute renal impairment and raised intracranial pressure needing shunts and blindness.

Global annual incidence rates and trends over the last 10 years cannot be assessed due to a lack of studies but are expected to be consistent.

Preventability of invasive cryptococcosis is moderate as there is no vaccine, but prophylactic and pre-emptive therapy in the highest-risk groups significantly reduces the incidence of cryptococcal meningitis.

Access to diagnostics could be rapidly expanded globally, with an effective, fast, cheap and easy-to-perform lateral flow test being available.

Localized cryptococcosis can be treated with fluconazole, while severe and disseminated cases are treated with amphotericin B in combination with flucytosine followed by step-down to fluconazole. Although the treatments are included in the WHO Essential Medicines List (WHO EML), they are still unavailable in many countries. Antifungal resistance is poorly understood and there is only clinical breakpoint for amphotericin B. In addition, reduced susceptibility to fluconazole has been described.

To overcome knowledge gaps, clinical trials aimed at reducing morbidity and mortality are needed. More data on antifungal susceptibility combined with molecular typing of *C. neoformans* would allow better comparison of antifungal resistance rates for different genotypes. In vitro and in vivo synergy tests would allow expansion and optimization of current treatment options for *C. neoformans*. Prospective cohort studies aimed at evaluating long-term complications, risk factors and other clinical outcomes, together with global surveillance data, will better inform the disease burden overall as well as the molecular epidemiology of *C. neoformans* in different patient populations and regions.

Candida auris

Key facts

- *Candida auris* is a yeast that can produce invasive candidiasis. Invasive candidiasis by *C. auris* is a life-threatening disease with high mortality.
- *C. auris* has high outbreak potential and has already produced several hospital outbreaks.
- It is intrinsically resistant to most available antifungal medicines and some strains are pan-resistant.
- Difficult to identify by conventional techniques. Although treatment guidelines are well established, recommended antifungals are unavailable in many countries.
- Preventive measures are not well established. Overall, thermoresistant and partially resistant to commonly use disinfectants.

Overview

Candida auris is a globally distributed pathogenic yeast that can cause invasive candidiasis of the blood (candidaemia), heart, central nervous system, eyes, bones and internal organs. Invasive candidiasis is a serious nosocomial infection that especially affects critically ill and immunocompromised patients, such as cancer or bone marrow and organ transplant patients. Other risk factors include renal impairment, hospital stay longer than 10–15 days, use of mechanical ventilation, central venous catheterization, total parenteral nutrition and sepsis. Previous use of antifungal medicines, especially triazoles, is also associated with increased risk for *C. auris*. *C. auris* has emerged as a cause of hospital outbreaks. This development underscores the importance of adequate infection control preparedness to prevent the spread of *C. auris* within hospitals, although optimal prevention strategies require further study.

The overall mortality of invasive candidiasis with *C. auris* ranged from 29% to 53%. Patients with *C. auris* candidaemia had longer length of stay in hospital or ICU than those with candidaemia caused by other *Candida* spp. The median length of hospital stay was 46–68 days in adult and paediatric *C. auris* candidaemia patients, ranging up to 70–140 days.

Global annual incidence rates cannot be assessed due to the lack of studies. Trends over the last 10 years show an increase in *C. auris* due to outbreaks in many countries. Increase in the numbers of cases during COVID-19 pandemic has been reported by many countries.

Preventability of invasive candidiasis by *C. auris* is moderate. No vaccine is available. Prevention of colonization and surveillance are key in monitoring patients at risk for *Candida* infections.

Access to conventional diagnostics is moderate but overall is difficult to identify by conventional techniques. Availability and affordability of evidence-based treatments is low.

Invasive candidiasis is usually treated with echinocandins, although other antifungals such as azoles might be used following confirmation of in vitro susceptibility. Echinocandins were included in the EML in 2021. Nonetheless, they are still unavailable in many countries. In general, antifungal resistance is moderate. Resistance rates of *C. auris* to fluconazole were as high as 87–100%, while susceptibility to other azoles was variable. *C. auris* isolates showed relatively moderate resistance rates of 8–35% to amphotericin B, and a lower resistance of 0–8% to echinocandins. Unlike other *Candida*, *C. auris* has inherent resistance and in addition pan-resistant isolates have been described.

To overcome the knowledge gap, in vitro and in vivo synergies between antifungal medicines should be evaluated to optimize the current treatment regimens against *C. auris*. Effectiveness and implementation of potential preventative measures need to be explored based on the identified risk factors. Global surveillance studies could better inform the annual incidence rates, distribution and trends in other countries and regions.

Aspergillus fumigatus

Key facts

- *Aspergillus fumigatus* is a ubiquitous environmental mould that can infect humans and cause aspergillosis. It is inhaled from the environment, predominantly causing pulmonary disease, but can disseminate to other sites, such as the brain.
- Aspergillosis is a term used for a wide spectrum of infections that range from allergic reaction, colonization and semi-invasive disease to acute invasive aspergillosis.
- Azole-resistant invasive aspergillosis is a life-threatening disease with very high mortality. Emerging resistance to azoles is concerning.

Overview

Aspergillus fumigatus is a globally distributed ubiquitous environmental mould with pathogenic potential. *A. fumigatus* can produce invasive infections (invasive aspergillosis, IA), mainly in the respiratory system, but can disseminate to other organs, particularly the central nervous system. IA is a serious infection that especially affects the critically ill, those with chronic lung disease and immunocompromised patients, such as those with cancer or transplants. Risk factors for developing IA are well described and include haematological malignancy, chronic lung disease, transplantation (both solid and bone marrow), corticosteroid therapy, neutropenia and chronic liver disease.

Mortality rates in those with azole-resistant *A. fumigatus* infection are high (47–88%) and have been reported to be up to 100% in some studies. Data on overall length of stay in hospital related to IA are limited and range widely (21–532 days); there are no data on the attributable length of stay.

The prevalence of IA is geographically variable, ranging from < 1% to 5–10%; the annual incidence also varies. Azole-resistant *A. fumigatus* infection continues to increase. Trends over the last 10 years could not be established due to a lack of studies.

Preventability is high. No vaccine is available. Antifungal prophylaxis for high-risk groups can prevent IA. Screening for azole resistance is recommended even in azole-naive patients, and especially in high-risk patients such as cancer patients, patients with cystic fibrosis and those in ICU.

Access to conventional diagnostics and availability and affordability of evidence-based treatments are overall low. Azoles are the mainstay of treatment. Other effective agents, such as liposomal amphotericin B, are readily available in high-income countries, but there is limited availability in LMICs.

Antifungal resistance is on the rise. Widespread use of azole fungicides in agriculture to prevent crop losses is contributing to the rising rates of resistant aspergillosis in humans.

To overcome the knowledge gap, cohort studies or sub-analysis evaluating morbidity outcome measures such as length of stay and long-term complications, especially for azole-resistant *A. fumigatus* infections, are needed. In vitro and in vivo synergy studies would also allow optimization of treatment regimens. Global surveillance studies would better inform the distribution of azole resistance, annual incidence rates, and global distribution and trends. Effectiveness and implementation of potential preventative measures need to be explored based on global surveillance studies and other identified risk factors, especially in the setting of newer cancer treatments.

Candida albicans

Key facts

- *Candida albicans* is a fungal pathogen which can be part of the healthy human microbiome but may also cause infections of the mucosae or produce invasive candidiasis.
- Invasive candidiasis is a life-threatening disease with high mortality.
- Treatment is possible and antifungal resistance remains uncommon (low).

Overview

Candida albicans is a globally distributed pathogenic yeast. It is a common member of the human microbiota (mouth, throat, gut, vagina, and skin) and produces no harm in healthy conditions. However, it can multiply in these mucosae or invade other tissues, producing disease. In mucosae, it produces diseases such as oropharyngeal candidiasis, oesophageal candidiasis, vulvovaginal candidiasis and cutaneous candidiasis. More serious, *C. albicans* can produce invasive infections (invasive candidiasis) of the blood (candidaemia), heart, central nervous system, eyes, bones and internal organs with high mortality. Critically ill and immunocompromised patients are especially affected.

Invasive candidiasis has an overall mortality ranging from 20% to 50% despite the availability of active antifungal treatment. Length of stay in hospital is about 2–4 weeks and up to 2 months and is influenced by underlying conditions. It has been suggested that 4% of cases of invasive candidiasis develop secondary growths.

Trends in *C. albicans* over the last 10 years are stable, but in-hospital estimates of incidence and species distribution seem to indicate that infections caused by *C. albicans* are falling relative to other *Candida* species. Recent studies showing higher rates of azole resistance, especially in LMICs, raise concern that resistance is rising.

Preventability of invasive candidiasis by *C. albicans* is low. No vaccine is available. Prevention of colonization and surveillance are key in monitoring patients at risk for *Candida* infections.

Access to diagnostics is high, but availability and affordability of evidence-based treatments is unknown. Some forms of disease are difficult to diagnose, such as abdominal candidiasis whereas blood culture positivity rate is <15%. In these patients, surgical specimen is needed for conventional diagnosis.

Treatment of invasive candidiasis usually includes echinocandins followed by a stepdown to azoles when appropriate. Although echinocandins were included in the EML in 2021, they are still unavailable in many countries. Antifungal resistance is relatively uncommon. Nevertheless, resistance rates especially in non-sterile site isolates seem to be increasing, evidencing the need for more robust and systematic surveillance.

To overcome knowledge gaps, population-based estimates of the incidence of invasive candidiasis in the last 5 years are needed. Stronger data on complications, sequelae and attributable mortality, as well as mitigation strategies should be generated.

Nakaseomyces glabrata (Candida glabrata)

Key facts

- *Nakaseomyces glabrata (Candida glabrata)* is a commensal yeast which can cause invasive candidiasis.
- Mortality from invasive candidiasis due to *N. glabrata* can be as high as 20–50%.
- Preventative measures for invasive disease are not well established. Treatment guidelines are available, although AMR is increasing and poses a challenge.

Overview

Nakaseomyces glabrata (Candida glabrata) is a globally distributed commensal yeast with pathogenic potential. It is a leading cause of candidiasis, usually second only to *C. albicans* in incidence. It can cause invasive candidiasis involving the blood (candidaemia), heart, central nervous system, eyes, bones and/or internal organs. Invasive candidiasis due to *N. glabrata* is a very serious disease, with all-cause mortality at 30 days up to 20–50%. Risk factors for infection include those impacting host immunity.

Little has been reported about complications and sequelae of infection. There are also few data to estimate impact on length of hospital stay, although this is likely similar to other *Candida* species where durations of 2–8 weeks are frequently described. Stay directly attributable to infection is unclear.

Trends over the last 10 years reveal that the prevalence of *N. glabrata* as a proportion of all invasive *Candida* infections is increasing.

Similar to other *Candida* spp., information on the preventability of invasive candidiasis by *N. glabrata* is limited.

Access to conventional diagnostics and availability and affordability of evidence-based treatments are unknown. Invasive candidiasis is usually treated with echinocandins, although other antifungals such as azoles might be used following confirmation of in vitro susceptibility. Echinocandins were included in the EML in 2021 but are still unavailable in many countries.

This species shows high minimum inhibitory concentrations (MICs) to azoles, and in recent years echinocandin resistance seems to have been rising. To overcome the knowledge gap, clinical trials focused on improving outcomes and preventing infection are needed. There is a major lack of data from middle- and especially low-income settings about all aspects of the pathogen. Cohort studies addressing gaps around attributable mortality, complications and sequelae, and length of hospital stay are particularly needed.

Histoplasma spp.

Key facts

- *Histoplasma* spp. are globally distributed pathogens that cause histoplasmosis. Disseminated histoplasmosis particularly affects immunosuppressed patients, but it can also infect healthy individuals.
- *Histoplasma* spp. have the potential to produce outbreaks.
- Disseminated histoplasmosis is a life-threatening disease with mortality ranging from 21% to 53% in HIV patients.
- Treatment is possible, and AMR remains moderate but is rarely measured.

Overview

Histoplasma spp. are globally distributed dimorphic fungi that live as a mould in the environment (soil, and bird and bat droppings) and as a yeast-like form at human body temperature. Histoplasmosis mainly affects the lungs and can expand to the central nervous system, the blood and other parts of the body. It cannot be transmitted between patients (no human-to-human transmission).

Most people that inhale *Histoplasma* spp. do not get ill. Healthy patients usually recover without medication. However, critically ill and immunocompromised patients, such as HIV, cancer and organ transplant patients, may develop severe forms of the disease. A CD4 T-cell count ≤ 50–75 cells/µL is a risk factor for AIDS patients.

Mortality rates in HIV/AIDS patients ranged from 21% to 53%, while lower rates (9–11%) were found in immunosuppressed patients and solid organ transplant recipients. One study reported a mortality rate of 2.7% in children with histoplasmosis. Length of stay in hospital is about 5–7 days in adults and children, with large variability. An average of a month stay was observed in patients with fungal meningitis. The incidence of complications and sequelae is unknown.

Global annual incidence rates cannot be assessed due to a lack of studies. Endemic regions with high incidence in Latin America and Africa have been described, but others reported lower rates. Trends over the last 10 years are stable.

Preventability of invasive histoplasmosis is low. No vaccine is available. Early diagnosis and treatment of HIV would be expected to reduce the burden of disease, although this has not been quantified.

Access to conventional diagnostics is moderate, and availability and affordability of evidence-based treatments is low. Healthy patients usually recover without medication. For severe cases, amphotericin B followed by itraconazole is recommended. Moderate and chronic cases are treated with itraconazole.

Antifungal resistance is moderate. Breakpoints for antifungal resistance are not available. Studies are very limited, but MICs seem to be low for azoles and amphotericin B.

To overcome the knowledge gap, more studies, including in vitro and in vivo synergy tests, are needed to better inform the susceptibility profile of *Histoplasma* spp. in various patient populations and to optimize antifungal regimens. The effectiveness and implementation of potential preventative measures need to be explored based on the identified risk factors. Global surveillance studies could better inform the annual incidence rates, distribution and trends in other countries and regions.

Eumycetoma causative agents

Key facts

- Eumycetoma is a deep tissue infection associated with significant disability. It can be caused by various fungal pathogens, which enter the body through breaks of the skin.
- Global incidence is unknown. Eumycetoma is especially prevalent among the poor in LMICs and appears to have significant geographic variability.
- Behavioural interventions are best described in terms of disease prevention, but their impact has not been comprehensively assessed. Although antifungal treatments are available and resistance is not considered a major issue, amputation of the affected area is frequently needed.

Overview

Eumycetoma is a deep tissue infection caused by fungi found in soil and water. The fungi enter the body through breaks in the skin. Eumycetoma causative agents include *Madurella* spp., *Falciformispora senegalensis*, *Curvularia lunata*, *Scedosporium* spp., *Zopfia rosatii*, *Acremonium* spp. and *Fusarium* spp., although microbiological data are limited. Eumycetoma is a serious infection that especially affects the poor, with many complications and sequelae. Up to 60–80% of mycetoma patients report significant impact on their daily life, and amputation rates as high as 39% have been reported. Risk factors include being a farmer, male and young (11–30 years).

Mortality could not be fully assessed due to the lack of data, but overall is thought to be low. Prevalence varies significantly by geographic location, even within countries. Tropical settings report most cases, but there is limited surveillance data globally, and all estimates are likely a gross under-representation. Trends over the last 10 years suggest no change.

Prevention frequently consists of educational and behavioural hygiene interventions (especially the use of shoes), although data on impact and cost-effectiveness are limited.

Evidence-based treatment guidelines are also limited. There is a serious lack of microbiological data on infecting species and their antifungal susceptibility patterns to inform guidelines. Nevertheless, the evidence that exists suggests considerable heterogeneity in terms of antifungal resistance between species. Treatment is typically with long-term antifungals, and amputation is frequently required for full resolution of infection.

To overcome the knowledge gap, more information on disease burden is necessary, especially in terms of prevalence, morbidity and economic impact. Microbiological data on infecting species and their susceptibility profile are very limited, and more clinical trials to inform treatment and prevention guidelines are needed.

Mucorales

Key facts

- Mucorales is a large group of fungi consisting of different genera. Mucorales are globally distributed and cause a wide spectrum of infection termed mucormycosis.
- Mucorales particularly infect immunocompromised patients but can occur in those with poorly controlled diabetes mellitus and those who have experienced trauma, particularly skin and soft-tissue injuries.
- Invasive mucormycosis is a life-threatening disease with high mortality. Treatments such as surgery and antifungal agents are available.

Overview

Mucorales is a large group (i.e. Order) of globally distributed pathogenic moulds, including *Rhizopus* spp., *Mucor* spp., *Lichthiemia* spp., and others. They can infect the human host after spore inhalation, producing mucormycosis. Therefore, the Mucorales commonly affect the lungs and sinuses, and can spread to the eye, central nervous system and gastrointestinal tract. Fungal invasion can also occur through skin breaks and after burns or other traumatic injuries. Mucorales cannot be transmitted between patients (no human-to-human transmission). Invasive mucormycosis especially affects immunocompromised patients, such as cancer and transplant patients; it has also been well described in those with poorly controlled diabetes mellitus and those who have suffered trauma injuries. Risk factors for mucormycosis include neutropenia and diabetes mellitus. Trauma was also a risk factor for subcutaneous mucormycosis. Invasive mucormycosis is a very serious disease, with mortality ranging from 23% to 80% in adult patients, and up to 72.7% in paediatric patients. Data on length of stay in hospital are limited, but it has been reported to be about 16–17 days. The degree to which the inpatient stay is attributable to mucormycosis has not been determined.

Global annual incidence rates cannot be assessed due to the lack of studies. General population-based incidence rates were poorly described. Trends over the last 10 years show an increase.

Preventability of invasive mucormycosis is challenging. No vaccine is available.

Access to conventional diagnostics and availability and affordability of evidence-based treatments are unknown.

Antifungal resistance is difficult to determine, as clinical breakpoints have not been established. MICs for azoles are generally higher for *Mucor* spp. compared with *Rhizopus* spp. Mucorales are generally susceptible to amphotericin B, although some species/strains can have high MICs. Mucorales are inherently resistant to fluconazole, voriconazole and echinocandins.

To overcome the knowledge gap, development of better diagnostics is needed. Also, more systematic testing (including in vitro and in vivo synergy) of a larger number of isolates per species is needed to establish clinical breakpoints. The susceptibility data need to be correlated with clinical data to establish clinical breakpoints. Preventative strategies, including optimization of antifungal prophylaxis, should be explored in prospective studies, together with evaluation of morbidity outcomes. Global surveillance should generate more consistent measures of incidence rates and prevalence to allow better understanding and comparison of distribution and trends for invasive mucormycosis.

Fusarium spp.

Key facts

- *Fusarium* spp. belong to a large genus of globally distributed filamentous fungi which are found in nature and can infect humans to cause fusariosis.
- Invasive fusariosis is a life-threatening disease, with mortality ranging from 43% to 67%.
- Treatment is difficult due to innate resistance to many of the currently available antifungal agents.

Overview

Fusarium spp. are a group of pathogenic moulds. While globally distributed, they occur mostly in tropical regions. They are saprotrophs, found predominantly in soil, decomposed organic matter and plants. *Fusarium* spp. can cause invasive disease (invasive fusariosis), mainly of the respiratory system and the eyes (keratitis), but can also disseminate to the central nervous system and other organs. They are known to cause fungaemia due to their capacity for adventitious sporulation.

Invasive fusariosis is a serious infection that especially affects immunocompromised patients, such as those with haematological malignancies or post-haemopoietic stem cell transplantation (HSCT). Risk factors for invasive fusariosis include acute myeloid leukaemia, allogeneic HSCT, cytomegalovirus reactivation and presence of skin lesions positive for *Fusarium* spp. at baseline.

Mortality rates (30-day) ranged between 43% and 67% for invasive fusariosis and were especially high for infections involving *F. solani* species complex and *F. proliferatum*. There are no data on length of hospital stay for invasive fusariosis. Endogenous endophthalmitis can complicate invasive fusariosis but is uncommon (< 10%). This can rarely cause visual loss/blindness. Rarely, enucleation is required to prevent blindness.

Global annual incidence rates cannot be assessed due to the lack of studies. Trends over the last 10 years show an increase.

Preventability is low. No vaccine is available. Antifungal prophylaxis has been evaluated in a limited number of studies showing variable results.

Access to diagnostics is moderate, and availability and affordability of evidence-based treatments are low.

Antifungal resistance is high. *Fusarium* spp. seem to be inherently resistant to most antifungal agents, although no clinical breakpoints have been established. Based on MICs, susceptibility to azoles is generally lower than to other antifungal mediciness, such as amphotericin B. *F. solani* showed reduced susceptibility to azoles compared with non-*F. solani* species.

To overcome the knowledge gap, more information on mortality and complications due to invasive fusariosis is needed. Generally low susceptibility was observed for current antifungal medicines. Accordingly, synergy studies and subsequent controlled clinical studies are needed to compare and optimize current drug combinations. Given the limited treatment options, the efficacy of antifungal prophylaxis needs to be established in larger, controlled clinical trials, together with more rigorous risk factor analysis. Surveillance data are needed to understand the global distribution and trends for *Fusarium* spp. infections in various regions other than India and Brazil.

Candida tropicalis

Key facts

- *Candida tropicalis* is a yeast which can be part of the healthy human microbiome but is also capable of causing invasive infections.
- Invasive infection is life-threatening, with mortality ranging from 55% to 60% in adults and 26% to 40% in paediatric patients.
- Specific preventative measures are not well described.

Overview

Candida tropicalis is a globally distributed commensal yeast with pathogenic potential. It is a common member of human and animal microbiota and causes no harm in healthy conditions. However, like other *Candida* species, *C. tropicalis* can produce invasive infections (invasive candidiasis) of the blood (candidaemia), heart, central nervous system, eyes, bones and internal organs. Invasive disease is associated with mortality as high as 55–60% in adults and 26–40% in paediatric patients. Data on complications and sequelae of infection are notably lacking. Risk factors for infection include critical illness and decreased host immunity, and this includes patients in neonatal ICUs.

Invasive candidiasis with *C. tropicalis* has an overall mortality ranging from 55% to 60% in adults and 26% to 40% in paediatric patients. Length of stay in hospital is poorly described, although likely comparable to other *Candida* species.

Global annual incidence rates cannot be assessed due to the lack of studies. Trends over the last 10 years show an increase in *C. tropicalis*.

Access to diagnostics varies, and availability and affordability of evidence-based treatments are still limited globally.

Preventability of invasive candidiasis by *C. tropicalis* is low. No vaccine is available. Infection prevention measures, including care bundles for central venous catheters, likely reduce infection rates, although the impact for this pathogen specifically is not well documented.

Antifungal resistance rates of *C. tropicalis* to azoles, including fluconazole, itraconazole, voriconazole and posaconazole, generally ranged from 0% to 20%, with some studies reporting higher resistance rates of 40–80%. For this reason, invasive disease is usually treated empirically with echinocandins. Echinocandins were included in the EML in 2021 but are still unavailable in many countries.

Overcoming the knowledge gap requires both clinical studies to improve outcomes and cohort studies or sub-analysis to evaluate morbidity outcome measures such as length of stay and long-term complications for invasive *C. tropicalis* infections. More rigorous risk factor analysis from these studies could better inform preventative measures and the need for implementation strategies. Evaluation of potential in vitro and in vivo synergy between antifungal medicines could help optimize the current treatment regimens for *C. tropicalis*. Global surveillance studies could better inform annual incidence rates, distribution and trends in other countries and regions.

Candida parapsilosis

Key facts

- *Candida parapsilosis* is a yeast which can be part of the healthy human microbiome but which also causes invasive infection. Its propensity to form biofilms makes it a particular concern for central venous catheter infections.
- Invasive candidiasis is a life-threatening disease with mortality ranging from 20% to 45%.
- Despite some challenges related to AMR, effective treatments are available. Since infection is equently associated with central venous lines, care bundles to reduce infection are important.

Overview

Candida parapsilosis is a globally distributed commensal yeast with pathogenic potential. It is a normal part of human and animal microbiota and causes no harm in healthy conditions. However, it can produce invasive infection (invasive candidiasis) of the blood (candidaemia), heart, central nervous system, eyes, bones and internal organs, especially in critically ill and immunocompromised patients, such as cancer and bone marrow or organ transplant patients. Concerns have centred around neonatal ICUs.

Invasive disease is associated with mortality ranging from 20% to 45%, despite active antifungal treatment. Data on length of stay in hospital and complications and sequelae of infection are lacking.

Global annual incidence rates cannot be assessed due to the lack of studies. Trends over the last 10 years show an increase in invasive *C. parapsilosis*. In some regions this pathogen is the primary agent for non-*C. albicans* candidaemia.

Preventability of invasive candidiasis by *C. parapsilosis* is low and poorly described. No vaccine is available. Early removal of central lines was shown to reduce incidence of infection. Also, antifungal medication is used in certain patients such as those with cancer or transplants.

Antifungal resistance is moderate. Azole resistance rates in excess of 10% were reported frequently, across multiple regions. Resistance to echinocandins, flucytosine and amphotericin was rare, but overall shows intrinsically higher MICs to echinocandins than other *Candida* species. Studies assessing biofilm mass are concerning for higher rates of resistance to all antifungal agents in biofilm situations (such as central lines, implants and prostheses). Invasive candidiasis is treated empirically with echinocandins, although other antifungals such as azoles might be used once susceptibility has been determined. Echinocandins were included in the EML in 2021 but are still unavailable in many countries.

To overcome the knowledge gap, more data from low-income settings on the incidence, prevalence among candidaemia cases and mortality are needed. Data on complications are very sparse, and it is impossible to assess the impact of this organism on long-term disability. Overall, systematic surveillance is lacking.

Scedosporium spp.

Key facts

- *Scedosporium* spp. are globally distributed fungal pathogens found in nature that can infect humans and produce scedosporiosis.
- Invasive scedosporiosis is a life-threatening disease with mortality rates as high as 42–46%.
- Treatment is threatened by high rates of AMR.

Overview

Scedosporium spp. are globally distributed opportunistic pathogenic moulds. *Scedosporium* spp. can produce invasive infection (invasive scedosporiosis), mainly of the respiratory system, but also blood, central nervous system, other organs, as well as systemic infections, which can be deadly. Risk factors for scedosporiosis include the presence of malignancy, HSCT and severe infection. Mortality rates are as high as 42–46% in adults and children. A more recent study in France reported lower mortality rates (30-day mortality of 9%, 3-month mortality of 19%) in adults and children with invasive scedosporiosis. Patient care length and complications and sequelae are unknown due to a lack of studies. Trends over the last 10 years are stable.

Preventability of invasive scedosporiosis is low. No vaccine is available. Data on preventative measures are lacking.

Access to diagnostics is moderate, and availability and affordability of evidence-based treatments are low. Invasive scedosporiosis is usually treated with voriconazole in combination with other antifungal medicines. In many cases, surgery is needed to remove the infected tissue.

Antifungal resistance is high. There are no pharmacological breakpoints. Reduced susceptibility to amphotericin B, itraconazole, isavuconazole and echinocandins is common. Voriconazole is typically the most active antifungal against these species.

To overcome the knowledge gap, studies reporting on clinical outcomes specific to invasive scedosporiosis are needed in order to better understand mortality rates, hospital length of stay, complications and sequelae. Such studies with larger patient numbers would enable more rigorous risk factor analysis to identify specific preventative strategies. In vitro and in vivo synergy testing would be beneficial to optimize current and emerging treatment options. Surveillance studies at a national or global level are needed to understand the annual incidence and global distribution of *Scedosporium* spp.

Lomentospora prolificans

Key facts

- *Lomentospora prolificans* is a globally distributed pathogen that can cause invasive lomentosporiosis in immunocompromised patients.
- Invasive lomentosporiosis is a life-threatening disease, with mortality ranging from 50% to 71% in adults and 50% in immunocompromised children.
- Treatment is threatened by high AMR rates.

Overview

Lomentospora prolificans is a globally distributed, opportunistic pathogenic mould. It can produce invasive infection (invasive lomentosporiosis) in the respiratory system, blood, central nervous system, other organs, as well as systemic infections, which are usually deadly. Invasive lomentosporiosis is a serious nosocomial infection that especially affects critically ill and immunocompromised patients, particularly those with cancer. The mortality of invasive lomentosporiosis ranges between 50% and 71% in adults and 50% in immunocompromised children. Patient care length and complications and sequelae are unknown due to a lack of studies.

Global annual incidence and trends over the last 10 years cannot be assessed due to the lack of studies.

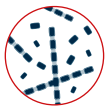
Preventability of invasive lomentosporiosis is unknown. No vaccine is available. In addition, research on the impact of different preventative measures is lacking.

Access to diagnostics is moderate, and availability and affordability of evidence-based treatments are low. Invasive infection is usually treated with voriconazole and terbinafine.

Antifungal resistance is high. Breakpoints for resistance are not defined, but all current licenced antifungals have no in vitro activity against this fungus.

To overcome the knowledge gap, larger studies are needed to better understand the outcomes assessed. Morbidity outcomes such as hospital length of stay and disability need to be defined to understand long-term effects on patients. Current antifungal medicines show low susceptibility rates based on the MIC or MEC (minimum effective concentration), and potential synergy treatment could be explored. New innovative antifungal treatments options are needed. More rigorous risk factor analysis is required to define risk factors and potential preventative strategies. Global surveillance studies could better inform the emergence pattern of the pathogen in a comparable study population.

Coccidioides spp.



Key facts

- *Coccidioides* spp. are some of the most virulent fungal pathogens. Coccidioidomycosis is acquired through the respiratory route when fungi are inhaled from the environment.
- Invasive coccidioidomycosis is a life-threatening disease, especially in vulnerable patients, but it can also infect healthy patients.
- Treatment guidelines are well established but are threatened by high rates of AMR.

Overview

Coccidioides is a genus of pathogenic dimorphic fungi distributed in the Americas, which lives as a mould in the environment (soil, etc.). After inhalation of fungal cells from the environment, *Coccidioides* spp. can infect humans. Coccidiomycosis initially affects the lungs but can expand to the central nervous system, blood, bones and other parts of the body. No human-to-human transmission has been described.

Although it can affect healthy individuals, immunocompromised patients such as cancer and HSCT or organ transplant patients are more affected. Risk factors include people of African descent, including African-Americans, increasing age (over 40–60 years old) and occupation and environmental dust and soil exposure.

Invasive coccidioidomycosis is a very serious disease, with mortality ranging from 2% to 13%. Mortality rates are higher in vulnerable patients. Hospital length of stay in patients with *Coccidioides* spp. infection ranged from a median of 3 to 7 days, with a median of 22.7 days in coccidioidal meningitis.

Global annual incidence rates cannot be assessed due to a lack of studies. Trends over the last 10 years show an increase in *Coccidioides* spp. infections.

Preventability of invasive coccidioidomycosis is low. No vaccine is available. Although many of the risk factors are non-modifiable, increased screening for coccidioidomycosis is suggested in endemic areas, especially in transplant patients, together with optimization of antifungal prophylaxis.

Access to conventional diagnostics is moderate, and availability and affordability of evidence-based treatments in most endemic areas varies.

Primary pulmonary coccidioidomycosis could resolve without antifungal treatment; however, treatment is recommended in risk groups. Disseminated coccidioidomycosis is treated with fluconazole, itraconazole or amphotericin B.

Antifungal resistance is of concern. High MICs for fluconazole and lower MICs for other azoles have been described, but data are still limited. Some studies reported variable MICs for caspofungin, and low MICs for anidulafungin and micafungin. Antifungal susceptibility testing is made even more challenging due to the danger posed by this fungus to laboratory staff.

To overcome the knowledge gap, large cohort studies to allow adequate evaluation of clinical outcomes such as mortality, length of stay and complications are needed, especially in children. Adequately powered prospective studies in larger numbers would allow better evaluation of clinical outcomes. Studies correlating antifungal susceptibility to clinical outcomes, as well as comparative trials for different antifungals, are needed to optimize treatment regimens.

Pichia kudriavzeveii (Candida krusei)

Key facts

- *Pichia kudriavzeveii (Candida krusei)* is a fungal pathogen which can cause infections of the mucosae or produce invasive candidiasis.
- Invasive candidiasis is a life-threatening disease with high mortality.
- Treatment is possible and antifungal resistance is of concern (moderate), as affordable access to effective treatment regimen is still limited.

Overview

Pichia kudriavzeveii (Candida krusei) is a globally distributed opportunistic pathogenic yeast. It is a common member of the human microbiota. However, it can invade mucosae and cause oropharyngeal candidiasis, oesophageal candidiasis, vulvovaginal candidiasis and cutaneous candidiasis. It can also cause invasive candidiasis. Invasive candidiasis is a serious nosocomial infection that especially affects critically ill and immunocompromised patients. The proportion of patients suffering from complications and sequalae is not well known due to a lack of data.

Invasive candidiasis with *P. kudriavzeveii* has an overall mortality ranging from 44% to 67% in adult patients. Limited data are available on length of stay, but it is considered comparable to invasive infections with other *Candida* spp.

The annual incidence is moderate; global annual incidence rates are difficult to assess due to the lack of studies. Trends over the last 10 years are considered to be stable.

Preventability of invasive candidiasis by *P. kudriavzeveii* is low. No vaccine is available. Prevention of colonization and surveillance are key in monitoring patients at risk for *Candida* infections. Reinforcement of hand hygiene on wards could be a general infection control measure to prevent infections, including *P. kudriavzeveii*.

Access to diagnostics is moderate, and availability and affordability of evidence-based treatments are low.

Antifungal resistance is moderate, as *P. kudriavzeveii* is considered intrinsically resistant to fluconazole; but resistance to other azoles and echinocandins is low (0–5%). Invasive candidiasis treatment usually includes echinocandins, although other antifungals, such as azoles, might be used. Echinocandins were included in the EML in 2021 but are still unavailable in many countries.

To overcome the knowledge gap, data on morbidity (hospitalization and disability) and annual incidence are needed. Global surveillance studies and stronger surveillance systems could better inform the distribution pattern of the pathogen in comparable study populations. Specific preventative measures based on risk factors should be explored for their potential benefit and feasibility for implementation.

Cryptococcus gattii

Key facts

- *Cryptococcus gattii* is a globally distributed fungal pathogen, traditionally described more frequently in tropical and subtropical areas, although it can adapt to different temperate settings.
- Invasive disease is life-threatening, and mortality commonly ranges from 10% to 25%. Immunocompromised individuals are at higher risk, but healthy individuals can also be affected.
- Treatment guidelines exist for *C. gattii* infection and resistance remains low, although key medicines are frequently unavailable in LMICs.

Overview

Cryptococcus gattii is a globally distributed pathogenic yeast. It is primarily found in the environment (soil, certain trees, etc.) in tropical and subtropical areas of the world. It can infect the human host after inhalation of spores. Cryptococcosis initially affects the lungs but can spread to the central nervous system (cryptococcal meningitis), the blood (cryptococcaemia) and other parts of the body. There is no human-to-human transmission. Invasive *C. gattii* cryptococcosis is a serious infection, traditionally described as affecting immunocompetent hosts (in contrast to *C. neoformans*). Risk factors include being critically ill, immunocompromised, older age and having pre-existing immunosuppression (e.g. oral corticosteroid use, organ impairment). Neurological sequelae occurred in up to 27% of patients. Immune reconstitution inflammatory syndrome (IRIS) occurred in 9.4% of patients. These complications were reported up to a year after treatment initiation.

Invasive *C. gattii* cryptococcosis is a very serious disease, with mortality reported as 43% for bloodstream infections, though based on limited data. Mortality rates for central nervous system infections and pulmonary infections ranged from 10% to 23% and 15% to 21%, respectively. Length of stay in ICU was about 9 days for adult patients in Australia. Most patients received at least 14 days of therapy requiring hospitalization.

Overall *C. gattii* accounted for 11–33% of cryptococcal infections. Distribution varies by molecular types. Overall annual incidence is low, although some endemic areas (and populations) have higher rates and outbreaks do occur. Trends of *C. gattii* over the last 10 years are unknown due to a lack of surveillance.

Preventability of invasive cryptococcosis by *C. gattii* is low. As with other fungal pathogens, no vaccine is available. Access to diagnostics is very high, with an effective, fast, cheap and easy-to-perform lateral flow test available. Invasive cryptococcosis is usually treated with liposomal amphotericin B in combination with flucytosine (severe lung infection or central nervous system), although fluconazole monotherapy can be used for asymptomatic infection or mild-to-moderate pulmonary infection). Availability and affordability of evidence-based treatments are low. Antifungal resistance is unknown. *C. gattii* isolates showed variable susceptibility data depending on the molecular type, and in general showed higher MICs to fluconazole compared with other azoles, including isavuconazole, itraconazole, posaconazole and voriconazole. MICs for amphotericin B and flucytosine were low.

To overcome the knowledge gap, stronger surveillance systems to understand the global distribution of *C. gattii* and its molecular epidemiology are needed. Such systems may allow more rigorous identification of at-risk populations, dispersion patterns and preventative measures. Better understanding of clinical manifestations and susceptibility profiles for different molecular types is needed and could potentially make it possible to individualize treatment options.

Talaromyces marneffei

Key facts

- *Talaromyces marneffei* is acquired through the respiratory route when spores are inhaled from the environment.
- Invasive talaromycosis is a life-threatening disease, particularly in adults with HIV infection, but it can also infect healthy individuals.
- Treatment guidelines are well established, but recommended antifungals are unavailable in many countries.

Overview

Talaromyces marneffei is a pathogenic dimorphic fungus endemic in South-East Asia and some areas of China. It can be found in the environment (soil, decaying wood, etc.) and may infect the human host after inhalation of spores. Talaromycosis affects the lungs but can expand to the central nervous system, the blood and other parts of the body. There is no human-to-human transmission.

Invasive talaromycosis especially affects critically ill and immunocompromised patients, such as HIV (risk factor being low CD4 count), cancer or organ transplant patients.

Invasive talaromycosis is a serious disease, and mortality ranges between 12%-21% in adults with HIV infection. Hospital length of stay in patients with *T. marneffei* was around 27 days. Complications due to *T. marneffei* infection included respiratory failure, IRIS and wasting syndrome.

Global annual incidence rates cannot be assessed due to a lack of studies. Trends over the last 10 years show an increase.

Preventability of invasive talaromycosis is low. No vaccine is available. Prevention of colonization and surveillance are key in monitoring patients at risk for *T. marneffei* infection.

Access to conventional diagnostics is moderate, and availability and affordability of evidence-based treatments are low. Invasive talaromycosis is usually treated with amphotericin B, itraconazole or voriconazole.

Antifungal resistance is low. There are no established clinical breakpoints for *T. marneffei* isolates to allow studies to define resistance rates to antifungal medicines. Fluconazole showed higher MICs compared with other azoles, such as itraconazole, posaconazole and voriconazole. Anidulafungin and caspofungin showed higher MICs.

To overcome the knowledge gap, prospective studies investigating clinical outcomes such as mortality and morbidity are needed, including paediatric patients. Antifungal susceptibility studies on a larger number of isolates are needed. Such studies should ideally investigate the correlation between in vitro susceptibility and clinical outcome to allow optimization of treatment and establishment of clinical breakpoints. More active surveillance systems are needed to estimate global distribution and trends for talaromycosis, including data on non-HIV/AIDS patients.

Pneumocystis jirovecii

Key facts

- *Pneumocystis jirovecii* is an opportunistic fungal pathogen which is acquired from person to person through the air.
- *P. jirovecii* pneumonia is a life-threatening disease, with substantial but highly variable mortality.
- Treatment is well established, but antifungals are unavailable in many countries.

Overview

Pneumocystis jirovecii is a globally distributed, opportunistic pathogenic fungus. *Pneumocystis jirovecii* pneumonia (PJP) is acquired from person to person through the air. It can be carried by healthy individuals who are asymptomatic.

Although *P. jirovecii* can affect healthy individuals, immunocompromised patients such as those with HIV, organ transplant patients and others taking medications that weaken the immune system are more affected. Risk factors for PJP include AIDS, cancer, iatrogenic immunosuppression with solid organ transplantation (especially renal), autoimmune and inflammatory disease, and nephrotic syndrome.

PJP is a very serious disease, and mortality ranges from 0% to 100% overall (highly variable). Hospital length of stay in patients with *P. jirovecii* infection ranged from 0–123 days (median of 6.6–30 days). Complications include respiratory failure, long-term graft failure and renal failure.

P. jirovecii is globally distributed, but global annual incidence rates are unknown but are expected to be consistent. Trends over the last 10 years indicate stable incidence overall but a decline in some groups, particularly in persons with HIV.

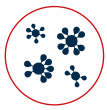
Preventability of PJP is high. No vaccine is available. Preventative measures were widely reported and consisted of drug prophylaxis, which is highly efficacious.

Access to conventional diagnostics is moderate, and availability and affordability of evidence-based treatments are high. PJP is usually treated with cotrimoxazole.

Antifungal resistance is unknown. Phenotypic susceptibility testing is not possible for *P. jirovecii*, breakpoints have not been established, and treatment is with agents different to those used for other fungal infections.

To overcome the knowledge gap, better understanding is needed of factors associated with the risk of PJP acquisition and mortality, especially in non-HIV at risk populations. The significance of molecular mutations remains to be further explored. Also, more and standardized information on annual incidence is needed.

Paracoccidioides spp.



Key facts

- *Paracoccidioides* spp. are fungal pathogens that are acquired through the respiratory route when spores are inhaled from the environment.
- Paracoccidioidomycosis is a life-threatening disease with medium mortality despite antifungal therapy. Immunocompromised individuals are at higher risk, but the pathogen can also infect healthy individuals.
- Treatment is well established, but antifungals are unavailable in many countries.

Overview

Paracoccidioides spp. are pathogenic dimorphic fungi endemic to Central and South America that live in the environment (soil). After inhalation or penetration of the skin by fungal spores from the environment, the pathogen can infect humans. Paracoccidioidomycosis mainly affects the lungs, mucous membranes and skin, and can expand to the lymph nodes and other organs of the reticuloendothelial system. Most people infected with *Paracoccidioides* spp. never develop symptoms. It cannot be transmitted between patients (no human-to-human transmission).

Risk factors include age > 40 years old and male gender.

Paracoccidioidomycosis is a serious disease. Mortality ranges from 3% to 23%, especially in patients with HIV. Hospital length of stay in patients with *Paracoccidioides* spp. infection could not be assessed due to a lack of data. Complications due to *Paracoccidioides* spp. infection and its treatment include low adrenal reserve and lymphedema.

Paracoccidioides spp. are endemic to Central and South America, but global annual incidence rates cannot be assessed due to the lack of studies. Trends over the last 10 years are stable.

Preventability of invasive paracoccidioidomycosis is low. No vaccine is available. Data on prevention strategies are lacking.

Access to conventional diagnostics is moderate, and availability and affordability of evidence-based treatments are very low.

Invasive paracoccidioidomycosis is usually treated with itraconazole, amphotericin B or cotrimoxazole.

Antifungal resistance is unknown.

To overcome the knowledge gap, larger cohort studies evaluating morbidity outcome measures such as length of stay and long-term complications of paracoccidioidomycosis are needed. There have been no antifungal susceptibility data for *Paracoccidioides* spp. in the last 10 years. Susceptibility testing with newer antifungal medicines as well as potential synergy tests should be performed to ensure evidence-based treatment regimens and optimization. Studies predominantly reported paracoccidioidomycosis in Brazil. Global surveillance studies are needed to inform incidence rates, distribution and trends in other countries and regions. These studies could also identify risk factors in different patient populations to enable tailored preventative strategies.

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