

# **FIRST MEETING OF THE WHO ANTIFUNGAL EXPERT GROUP ON IDENTIFYING PRIORITY FUNGAL PATHOGENS**

Meeting Report



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# 1. Introduction

This document includes the report and the minutes of the first meeting of the antifungal expert group convened by the World Health Organization (WHO) to develop a priority pathogens list for fungal infections of public health importance and to define the research & development (R&D) priorities. To allow full participation of experts from all parts of the world, the meeting took place virtually in two parts on 7 and 9 April 2020. The Global Action Plan<sup>1</sup> (GAP) on Antimicrobial Resistance (AMR) objective five calls for an increase of sustainable investment in new medicines, diagnostic tools and other interventions. In response to that, in 2017 WHO developed the Priority list of antibiotic-resistant bacteria<sup>2</sup> to guide R&D of new antibiotics for drug resistant bacterial infections, including tuberculosis. Since then, WHO has been reviewing the clinical antibacterial pipeline<sup>3</sup>, and since 2019, the preclinical pipeline<sup>4</sup>, on an annual basis to see to what extent global R&D efforts for new antibacterial agents are responding to the antibiotic-resistance priority pathogen list (Figure 1).

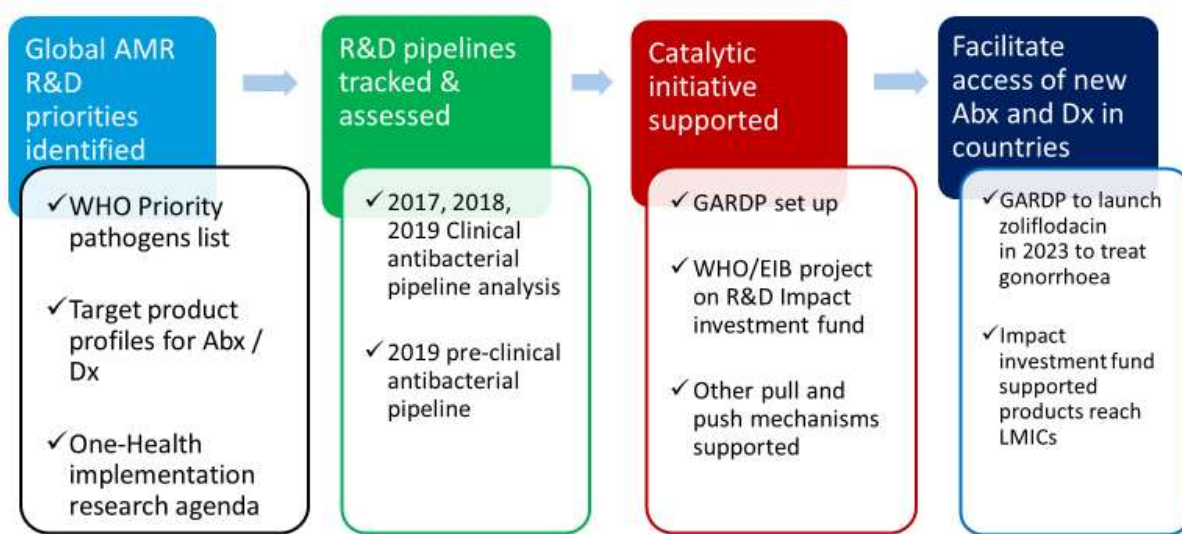


Figure 1. Presentation slide from the meeting on WHO's work on R&D priority setting for AMR

<sup>1</sup> Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015  
<https://www.who.int/antimicrobial-resistance/global-action-plan/en/>, accessed 15/04/2020

<sup>2</sup> Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017  
[https://www.who.int/medicines/areas/rational\\_use/prioritization-of-pathogens/en/](https://www.who.int/medicines/areas/rational_use/prioritization-of-pathogens/en/), accessed 15/04/2020

<sup>3</sup> 2019 antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health Organization; 2019 <https://apps.who.int/iris/handle/10665/330420>, accessed 15/04/2020

<sup>4</sup> Antibacterial agents in preclinical development: an open access database. Geneva: World Health Organization; 2019 <https://apps.who.int/iris/handle/10665/330290>, accessed 15/04/2020

Recognizing the public health threat of the global increase in burden of disease of fungal infections, coupled with existing treatability and resistance issues (both intrinsic and acquired), WHO is extending its efforts to develop a priority fungal pathogens list of public health importance and identify R&D priorities and gaps.

For several fungal diseases, effective treatment is missing altogether. Existing antifungal treatments belong to only a few classes of compounds and the pipeline for new antifungals is sparse. The process of identifying R&D gaps will also take into account possible shortcomings of the current standard of care and diagnostics. The existing treatment of certain fungal infections is challenging, including toxicity issues with long treatment courses and drug-drug interactions, amongst other concerns around the overall lack of treatment options. Availability and access to antifungal treatment and diagnostics are important components in reducing the burden of disease of fungal infections.

To support WHO's efforts on fungal infection R&D priority setting, a WHO expert group on fungal infections has been established for 2020-2021. The aim of the expert group together with WHO is to:

- develop a priority list of fungal pathogens of public health importance;
- define related R&D priorities to align R&D investments with the identified public health needs; and
- review regularly the clinical antifungal pipeline to track trends and guide R&D priorities.

This first (virtual) meeting of the antifungal expert group took place on 7 and 9 of April 2020 to discuss the methodology, pathogen selection and available evidence to begin the prioritization of fungal pathogens of global public health importance for which there is an urgent need for R&D for new treatments.

## 2. Summary of the meeting proceedings

Two virtual meetings took place with an identical agenda (Annex I). Following a short roundtable of introductions by the participants (Annex II), the meeting began with opening remarks delivered by Haileyesus Getahun (Director of WHO/AMR/GCP). He highlighted WHO's long term vision to enhance its response to address fungal infections of public health importance in the context of drug-resistance, including to guide and stimulate R&D for new treatments, diagnostics and other critical public health interventions.

Peter Beyer (senior advisor, WHO/AMR/GCP) presented the outcome of the assessment of the declaration of interests of the participants. All experts and observers were allowed to participate fully in the meeting (Annex III). The declaration of interest form of Arnaldo Colombo was outstanding; thus his participation was provisional subject to its subsequent assessment. Peter Beyer then presented an overview of WHO's work in R&D priority setting on AMR in accordance

with the Global Action Plan on AMR strategic objective five and outlined the overall aim of the informal expert group on fungal infections.

Following the opening session, two rounds of discussion took place on 1) the methodology, including criteria for the prioritization exercise of fungal pathogens of public health importance that require R&D for new treatments, and 2) the preliminary pathogen selection. At the beginning of each discussion session Laura Jung (Intern, WHO/AMR/GCP) provided a brief presentation, and Sarah Paulin (technical advisor, WHO/AMR/GCP) chaired the discussions and input by experts.

## Overview

The aim of the discussion was to seek the views of the experts on the most appropriate methodology to develop a fungal pathogen priority list to guide priority setting for R&D into new treatments. To start the discussion, WHO presented one possible option: to base the exercise on the methodology that was used for the WHO bacterial priority pathogens list<sup>5</sup> and adapt it to the specificities of fungal infections. This approach used a multi-criteria decision analysis (MCDA)<sup>6</sup>, which utilizes a list of criteria and combines evidence-based data and expert opinion. The following background work was undertaken by the WHO team in preparation for the meeting and was presented to provide a starting point for the expert group discussion:

**Initial literature review:** a literature review was conducted by the WHO team in January 2020 which identified the absence of any existing global prioritization with regard to R&D for fungal infections. It was noted that three fungal infections were included in the CDC priority threat list (2019)<sup>7</sup>.

**Preliminary selection of fungal pathogens:** an initial selection of fungal pathogens was developed by the WHO team for discussion with the experts. This selection focused on pathogens that cause invasive fungal infections and was based on the CDC Antibiotic Resistance Threats Report (2019) and expert opinion from different internal WHO departments.

**Draft selection of criteria for prioritization:** based on the criteria of the priority pathogens list for antibiotic-resistant bacteria, six criteria were initially chosen by the WHO team with relevance to fungal infections:

- a. mortality;

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<sup>5</sup> Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva: World Health Organization; 2017 [https://www.who.int/medicines/publications/WHO-PPL-Short\\_Summary\\_25Feb-ET\\_NM\\_WHO.pdf](https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf), accessed 15/04/2020

<sup>6</sup> Tacconelli E., Carrara E., Savoldi A., Harbarth S., Mendelson M., Monnet D. L. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis.* 2018 Mar;18(3):318-327, accessed 15/04/2020

<sup>7</sup> Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019 <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>, accessed 15/04/2020

- b. community burden;
- c. health-care burden;
- d. proof / prevalence of resistance;
- e. transmissibility; and
- f. treatability.

In addition, a criterion for the R&D pipeline analysis was suggested, to be completed once the initial list has been agreed with the experts.

**Data extraction and synthesis:** for the preliminary list of fungal pathogens and criteria, the WHO team reviewed the existing published literature and international treatment guidelines and summarized the evidence in a performance matrix, which was provided to the experts ahead of the meeting (Annex IV).

Through two subsequent sets of discussions, the participants were asked to comment on 1) the draft methodology, and 2) the selection and prioritization of fungal pathogens of public health importance.

In the first set of discussions the participants were asked to comment on the initial approach presented for the methodology and the appropriateness of MCDA with regard to fungal pathogens. The participants were also invited to provide comments on the initial list of criteria, in particular the comprehensiveness of the criteria, as well as the possibilities of weighing and stratifying the criteria.

During the second set of discussions the participants were invited to comment on a preliminary selection of fungal pathogens and to evaluate the significance of the chosen pathogens for global public health that would require urgent R&D treatments, taking into account existing resistance and treatability issues. In addition, experts were asked to suggest any additional pathogens that should be considered for inclusion in the long list from which the priorities will be identified, and how the prioritization process should be conducted.

## Summary of discussion points on the methodology

- There was overall consensus that using an adapted version of the MCDA is a good approach/starting point as it allows for a prioritization process built on both available evidence and expert opinion and can be built around the objective and parameters for this prioritization exercise to identify the R&D priorities for fungal pathogens of public health importance
- Given the considerable difference between fungal and bacterial infections, including the data available, an adapted MCDA approach is needed to the specific situation of fungal infections, including the criteria and stratification.
- There was agreement to include global and regional stratification of fungal infections of public health importance given the regional specificity of some of the fungal infections.



- The type of infection and host may need to be considered in the criteria as there is a high heterogeneity of infections caused by fungi and the prioritization exercise may need to target specific infections/syndromes to be comparable in the data set for prioritization. (The target in the priority pathogens list of bacteria was invasive infections.) Further consideration is also needed on the type of host and on immunocompromised versus not immunocompromised.
- As there is an existing treatability issue with fungal pathogens, it is preferable that both treatability and resistance are included as separate criteria for the prioritization exercise and that resistance alone should not be the overarching objective for the prioritization exercise. This would allow for the pathogen list to also identify R&D priorities for fungal pathogens independently of the prevalence of resistance.
- The treatment criterion would need to include further granularity including efficacy, accessibility (including differences of accessibility across all regions and implications on the burden of the diseases), length of treatment, toxicity, drug-drug interaction and mode of administration (IV vs. oral). It might be necessary to develop a scoring system to weigh these sub-criteria.
- It was highlighted that the data for many criteria might be difficult to obtain (e.g. community burden, mortality and resistance) in part due to diagnostic challenges in many countries/regions. Many participants were of the opinion that community burden could be excluded as a criterion because of the lack of available data. Expert opinion will likely play a larger role in this prioritization exercise than available evidence.
- The participants suggested to include an additional criterion on the public health trend/trajectory for the burden of the pathogen (important for emerging pathogens such as *C. auris*, and azole-resistant *Aspergillus fumigatus*).
- The difference between intrinsic and acquired resistance will need to be more explicitly reflected in the criteria given the significance of both for fungal pathogens and it is important to take into account that resistance breakpoints do not exist for many species and antifungals and therefore defining resistance may sometimes be difficult.
- The considerable challenge in obtaining data around the gap in diagnostics for many fungal pathogens was highlighted, and it was suggested therefore either to include diagnostics as a criterion on its own or to find another way with which to address the diagnostics gap in this project. There is a lack of standardization of susceptibility testing broadly and in many regions there is a lack of data on resistance in general.
- There was consensus that not all the criteria have the same level of public health relevance and it will be necessary to perform a weighting exercise for prioritization. Mortality, burden of disease, global and regional epidemiology, treatability and resistance were all raised as important criteria.

## Summary of discussion points on fungal pathogen selection and prioritization

There was overall consensus that the fungal pathogens initially set out by the WHO secretariat (*Candida auris*; azole-resistant *Candida spp.*; azole-resistant *Aspergillus fumigatus*; *Cryptococcus neoformans* & *gattii*; *Pneumocystis jirovecii*; *Mucorales*; and potentially *Histoplasmosis*) were all of global public health importance and should be evaluated based on limitations of treatment options due to resistance and/or existing treatability issues (e.g. *Mucorales* has limited treatment options and poor outcomes).

- Experts were in agreement that a longer initial list of fungal pathogens be drawn up which would then be prioritized and shortened.
- There was consensus amongst the experts that *Histoplasma* should be added given its regional importance (e.g. in the Americas) and the challenges in diagnostics and treatability (e.g. reliance on amphotericin B).
- It was highlighted that resistance to dermatophytes was increasing in some countries and becoming a matter of significant concern. This poses difficulties for the management of (but not limited to) fungal keratitis and *Candida* vulvovaginitis in certain LMICs.
- Other fungal pathogens that were mentioned for consideration include *non-fumigatus Aspergillus spp.*, *Fusarium*, *Coccidioides*, *Sporothrix*, *Blastomyces*, *Chromoblastomycosis*, rare pathogens causing *Chromoblastomycosis* and mycetoma (invasive), and even rarer moulds such as *Lomentospora*, *Scedosporium* and *Talaromyces marneffeii*. It was suggested that the rare fungal infections that are either poorly treatable or untreatable could be captured in a separate group to highlight the need for compounds with activity against them.
- It was agreed that prioritization should consider not only availability of treatment, but also prevention strategies (infection prevention and control/prophylaxis), especially for pathogens with nosocomial relevance (e.g. for *C. auris*).
- Regional differences need to be considered in the global picture and pathogens both of global and regional importance should be included but stratified accordingly (e.g. regional relevance of *Coccidioides* in the Americas and *Histoplasma* in South America).
- There was a general agreement to limit the list to certain pathogens and invasive fungal infections and to consider clinical presentation as a criterion or sub-criterion. It was also suggested that the list be limited to health-care related infections due to challenges in obtaining data outside of that setting, however, no conclusion was reached on this matter.

## 3. Way forward

The discussions during the virtual brainstorming meetings provided important feedback on the project. The constitution of the expert group and the initial virtual meetings are an important starting point for the development of a priority fungal pathogen list of public health importance

to guide, but not be limited to, R&D into new antifungal treatments and diagnostics and other public health interventions. The WHO team will take on board the recommendations in developing an overall framework for the project. This will include a longer initial list of priority fungal pathogens as well as a review and update of the initial criteria and the overall methodology. The draft will be shared with the expert group for further comments. The participants are invited to provide the WHO team with any additional published data/evidence that should be included that had not already been captured in the meeting background document.

The aim is to complete these steps by Q4 2020. Subsequently, a face-to-face meeting of the expert group will be organized in Q1 2021 for finalization of the priority fungal pathogens list and subsequent clinical antifungal pipeline review to be published in Q2 2021. WHO will consult the expert group throughout the process and provide opportunities for review and feedback.

# Annex I: Agenda

Agenda Item	Presenter/Moderator
<b>Introductory session</b>	
Round table of introductions	All
Opening Remarks	Haileyesus Getahun
Conflict of interest management	Peter Beyer
Introduction to the WHO fungal pathogen project	Peter Beyer
<b>Discussion session</b>	
Methodology including criteria: introduction and input from experts	Laura Jung/ Sarah Paulin
Draft pathogen selection and prioritization: introduction and input from experts	Laura Jung/ Sarah Paulin
<b>Closing session</b>	
Way forward	Peter Beyer

## Annex II: List of Participants

Name	Affiliation	Country	Day of meeting attended
<b>Experts</b>			
Ana Alastruey-Izquierdo	Instituto de Salud Carlos III	Spain	7 April 2020
Arunaloke Chakrabarti	Postgraduate Institute of Medical Education & Research, Chandigarh	India	7 April 2020
Tom Chiller	Centers for Disease Control and Prevention	USA	7 April 2020
Arnaldo Colombo	Federal University of São Paulo	Brazil	7 April 2020
Nelesh Govender	University of Witwatersrand	South Africa	9 April 2020
Tom Harrison	St. Georges, University of London	United Kingdom	9 April 2020
Jutta Heim	Global Antibiotic Research and Development Partnership Scientific Advisory Group	Switzerland	7 April 2020
Jennie Hood (Observer)	Global AMR R&D Hub	Germany	9 April 2020
Volker Rickerts	Robert-Koch-Institute	Germany	9 April 2020
Jong-Hee Shin	Chonnam National University Medical School	Republic of Korea	9 April 2020
Tania Sorrell	University of Sydney	Australia	9 April 2020
Evelina Tacconelli	University of Verona	Italy	9 April 2020
<b>WHO</b>			
Haileyesus Getahun	WHO Headquarters		7 & 9 April 2020
Peter Beyer	WHO Headquarters		7 & 9 April 2020
Sarah Paulin	WHO Headquarters		7 & 9 April 2020
Laura Jung	WHO Headquarters		7 & 9 April 2020
Benedikt Huttner	WHO Headquarters		7 & 9 April 2020
Nathan Ford	WHO Headquarters		7 & 9 April 2020

## Annex III: Declaration of Interests

The declarations of interests (DOIs) were collected and reviewed by the WHO Antimicrobial Resistance Division in collaboration with the Office of Compliance, Risk Management and Ethics following WHO standard protocol. Based on the review four candidates were not invited to join the expert group. Full participation was granted to Ana Alastruey-Izquierdo, Arunaloke Chakrabarti, Tom Chiller, Arnaldo Colombo, Nelesh Govender, Tom Harrison, Jutta Heim, Volker Rickerts, Jong-Hee Shin, Tania Sorrell and Evelina Tacconelli. In addition, Jennie Hood participated as an observer with no conflict of interest.

Two experts disclosed potential conflicts of interest which were duly considered. It was concluded that these interests did not prevent the experts from full participation in the meeting on prioritization of fungal pathogens:

- Tom Harrison - St. Georges, University of London, United Kingdom: received Gilead Investigator Award for a trial on Cryptococcal meningitis treatment in 2017.
- Ana Alastruey-Izquierdo – **Instituto de Salud Carlos III**, Mycology Reference Laboratory, Spain: received funding from F2G and Scynexis for testing MICs of two new antifungals against different fungal species in 2017.

Arnaldo Colombo's declaration of interest form was outstanding at the time of this meeting, thus his participation was provisional subject to the submission and subsequent assessment of declaration of interests.

## Annex IV: Draft performance matrix

Pathogens	Mortality	Epidemiology/ community burden	Health-care burden	Transmissibility	Current treatment available	Proof / prevalence of resistance
<b><i>Candida auris</i></b>	crude mortality 30-60% for candidemia in mostly small studies (918 cases/ 5 studies), but attributable mortality difficult to quantify due to comorbidities/ underlying disease, colonisation only doesn't seem to be associated with mortality	first detected in 2009, since then increase in cases, unequal distribution of cases by countries, all WHO regions affected, risk for infants, less than 1000 cases per country	economic burden: increased costs due to outbreak control plus subsequent costs for follow up (1 study)	nosocomial transmission likely, outbreaks possible (213 cases/ 4 studies), mechanisms still unclear, prolonged environmental persistence suggested, risk for transmission outside health-care setting not yet assessed	optimal treatment needs to be defined - empirical use of one class for first line therapy (echinocandins) (2 guidelines)	resistance common, fluconazole resistance: 90-100% (957 cases/ 5 studies), 33-35% amphotericin B resistance (86 cases/ 2 studies) frequent MDR resistance, resistance might depend on strain
<b>Azole-resistant <i>Candida</i> spp. (excluding <i>Candida auris</i>)</b>	overall 30-day mortality 12-40% for candidemia (4375 cases/ 12 studies), mean=30%, but attributable mortality difficult to quantify due to comorbidities/ underlying disease; (estimate attributable mortality for invasive candida 19-24% (313 cases/ 2 studies)), no data for resistant <i>Candida</i> spp.	regional differences for burden and distribution of <i>Candida</i> strains, incidence candidemia 8,1-8,7 per 100 000 population (2 studies), case estimates available for South America ( <i>Candidemia</i> incidence 12,1 per 100 000 population), 0,4 - 0,80 per 1000 hospital admissions (3 studies), no data for resistant <i>Candida</i>	economic burden: <i>Candida</i> colonisation and infection associated with longer hospital stays (5 to 17 days) and increased health care costs up to \$45, 000 compared to matched controls (5 studies), resistance not necessarily associated with higher costs (1 study)	low transmissibility, but horizontal transmission especially in immunocompromise, neonatal patients seems possible (239 cases/ 2 studies)	two classes for first line treatment available (echinocandins, azoles), in case of resistance: liposomal amphotericin B (2 guidelines)	low resistance rates for <i>C. albicans</i> , up to 10% or higher resistance to fluconazole for other species including <i>C. glabrata</i> , trends show that resistance has increased over last decade. Several clusters of fluconazole resistance <i>C. parapsilosis</i> bloodstream infections have been reported worldwide fluconazole resistance in <i>C. tropicalis</i> infections is also on the rise.

<b>Azole-resistant <i>Aspergillus fumigatus</i> - invasive Aspergillosis</b>	crude mortality rate between 14 and 44 % (360 737 cases/ 7 studies), mortality 4 times higher than in comparison group (154 888 cases/ 1 study), mortality higher when only proven cases are included, data from LMIC rare, in paediatric patients (98 cases/ 1 study) mortality = 31%, no data for resistant <i>Aspergillus</i>	incidence in Europe/ US between 1.1 and 4.6/ 100 000 population - trends show increase (3 studies), in high risk patient groups (chronic lung diseases, transplant recipients) 0.2- 1.6% of patients affected (2 studies) no data for LMICs, case estimates available for South America (incidence 11 per 100 000 population),	<i>Aspergillus</i> infection associated with an increased length of stay of 5 to 10 days (3 studies) and excess costs of \$15,000-\$45,000 (3 studies), costs twice as high as in matched non- <i>Aspergillus</i> patients	no human-to-human transmission, but ubiquitous in the environment - contact through inhalation	first line treatment is liposomal amphotericin B	azole resistance in 1.5- 13% of the cases (11 studies), up to 20% in high-risk patients (1 study), trends shows increase in resistance, lack of data from LMICs
	crude mortality between 10 and 55% (13986 cases / 14 studies), higher mortality rates in LMIC 31-55% (1269/6 studies),	trend: incidence is decreasing, incidence between 0.4 and 2.4 / 100 000 population (3 studies), higher incidence in HIV patients (0.04-12%), lack of data from LMIC, but more than 70% of cases expected to be in Sub-Saharan Africa. Guatemala: incidence 4.4 in HIV population (76 cases in 1732 screened)	<i>Cryptococcus</i> infection associated with increased length of stay (5 days) and higher costs (\$10, 000) compared to matched non- <i>Cryptococcus</i> patients	no human-to-human transmission, but environmental exposure (soil, wood, bird droppings)	induction: amphotericin B deoxycholate and flucytosine, followed by 8 weeks of fluconazole. Access issues. For non-HIV long therapy required. Toxicity to AMB may be a problem in LMICs with limited access to lipid formulations of AMB	overall low resistance rates (5 studies), regional higher resistance rates for fluconazole 3-11% (3 studies), trends show increase in fluconazole resistance
<b><i>Cryptococcus neoformans</i></b> <b><i>Cryptococcus gatti</i></b>						
<b><i>Pneumocystis jirovecii</i></b>	crude mortality between 9 and 34% in general hospital patients (10158 cases/8 studies), >40% in paediatric and rheumatological patients, 11-30% in HIV patients (260 cases/ 2 studies, differences between HIC and LMIC countries) mortality higher in non-HIV compared to HIV patients	incidence 1.0 -2.6 per 100 000 population, incidence 0.3 - 1.1% in transplant patients, no data for LMICs (case estimates South America = 10.6 per 100 000 population)	no comparative cost analysis	very low-grade patient-to-patient transmission in healthcare settings likely (52 cases/ 4 studies), especially in transplant recipients	first line: trimethoprim/ sulfamethoxazole, in case of treatment failure parenteral pentamidine or oral primaquine combined with IV clindamycin. Very limited data on pentamidine	large regional differences of DHPS mutations (3-55%, 7 studies), clinical significance of mutation remains unclear



<b>Mucormycetes</b>	crude mortality between 17 and 50% (12 391 cases/ 13 studies), 33-34% in paediatric patients (108 cases/ 2 studies)	incidence 0.06- 0.34 per 100 000 population 2 studies), trend: increasing, incidence 0.3-2.2% in transplant patients (US, 2 studies), high incidence in LMICs especially India, China, Mexico.	mucormycosis associated with high readmission rates (30% within one month), increased lengths of stay (10 to 26 days) and excess costs of \$30,000-\$60,000 (4 studies), costs up to 3 times higher compared to control group without fungal infection	no human-to-human transmission, but ubiquitous environmental exposure (soil, wood, bird droppings) - contact through inhalation	first line treatment: surgical debridement and antifungal (amphotericin B, liposomal /posaconazole, isavuconazole)	intrinsic resistance to voriconazole and variable to other azoles. In vitro resistant to echinocandins
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Additional fungal pathogens and criteria to be added/changes as suggested by the expert group.



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