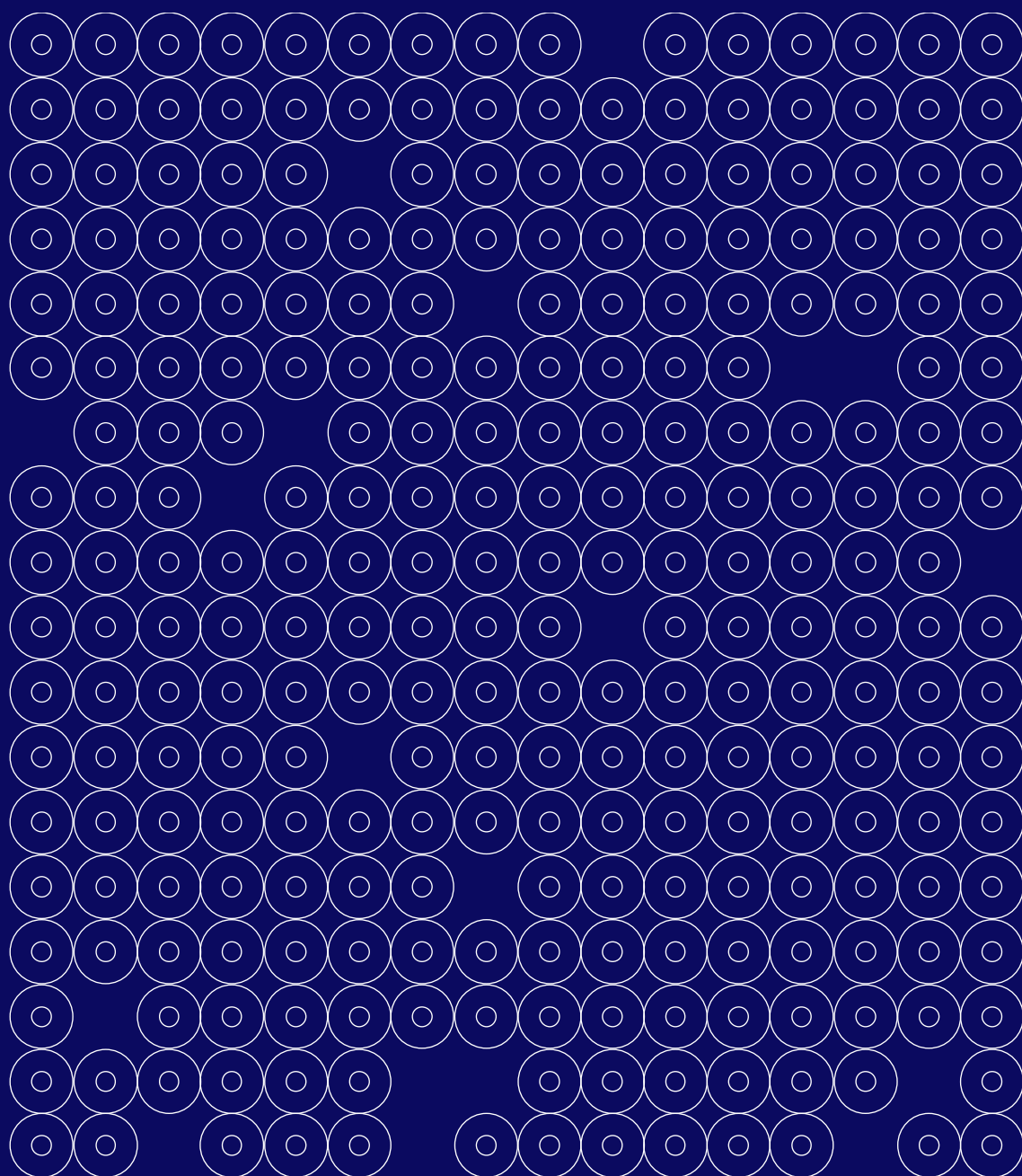


# Tackling the emerging threat of fungal drug resistance

Live webinar 23 June 2022

CSA DESIGN OH AMR



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# Introduction

The live webinar “Tackling the emerging threat of fungal drug resistance” was organised on 23 June 2022 by the Coordination and Support Action (CSA) DESIGN One Health AntiMicrobial Resistance (DESIGN OH AMR). The webinar was carried out by JPIAMR together with the Chief scientist office, Israel ministry of health (CSO-MOH).

## Background and objectives

Invasive fungal infections pose an increasing threat to public health and are an under-recognized component of antimicrobial resistance, which is an emerging crisis worldwide. Resistance of pathogenic fungi to all licenced systemic antifungals has been documented, therefore Global efforts are required to support and direct the research and development of new therapies and interventions.

The goal of this consultation webinar is to identify opportunities and priorities in fungal resistance research, to form the basis for future collaborations between the antibacterial and antifungal research communities, with regard to the preparation for the candidate One Health AMR partnership.

### *Specific aims*

- Present and discuss the emerging threat of fungal drug resistance
- Raise awareness on antifungal resistance research
- Identify critical needs, gaps and opportunities
- Build on experiences with antibiotics
- Connect between the bacterial and fungal research communities

## Organisation

The webinar was organised and delivered by the Chief scientist office, Israel ministry of health (CSO-MOH) with support of an organising committee made up of representatives from MRC, ANR and JPIAMR secretariat. Prof Micha Fridman from Tel Aviv University chaired the event.

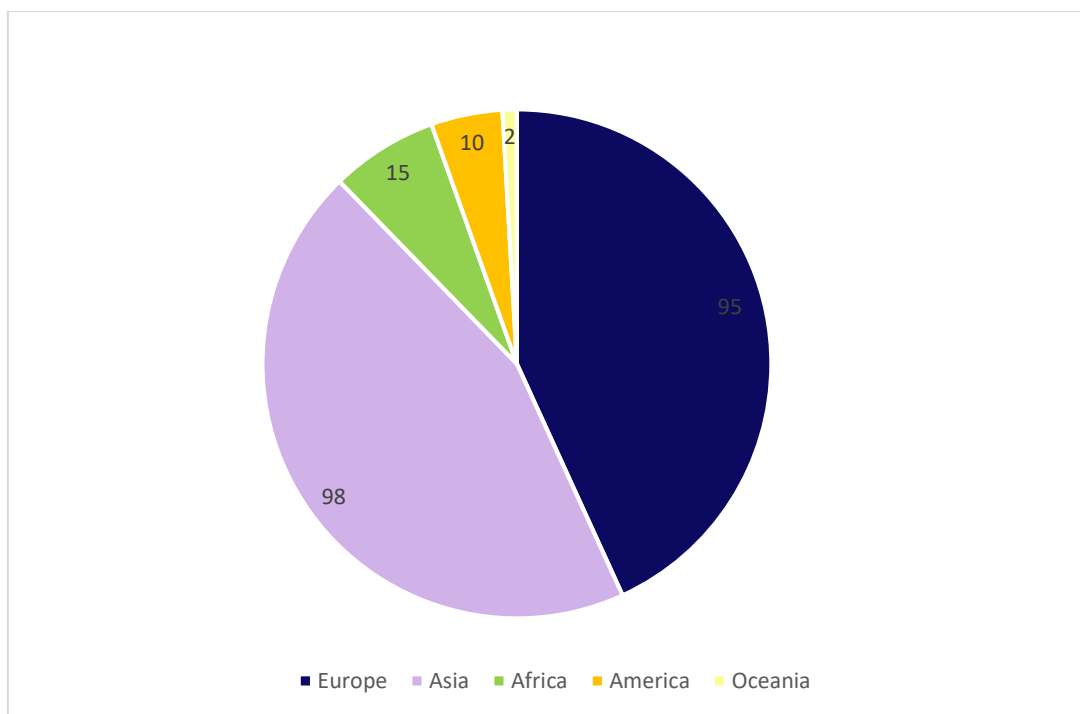
The webinar consisted of two scientific sessions. The first session included a series of five expert talks on the different aspects of fungal resistance taking into account the article published following JPIAMR initial fungal resistance consultation (Fisher M. et al, 2022). The second session consisted of a panel discussion about the gaps and opportunities in fungal drug resistance and the different ways to connect between the antifungal and antibacterial scientific communities. The chair led the panel discussion and promoted active participation from the audience.

## Key figures

- Webinar agenda – see Annex I
- 220 registered from 5 continents (Figure 1) and 39 countries (Figure 2)
- The Number of attendees logged to the webinar peaked at 140

This report provides:

- Short summaries of the sessions of the webinar
- Summaries of the major points raised in the presentation
- List of questions presented to the experts and the answers
- Summary of the gaps, needs and opportunities in fungal drug resistance with an eye to the future based on the webinar discussions.
- The Webinar recording is available [here](#).
- Presenting the experts – see Annex II
- Organising committee – see Annex III



**Figure 1.** Geographic distribution of the registered attendees by continents.



## Scientific sessions

### Session 1 – Expert lectures

The webinar was opened by welcome remarks from Prof. Avi Israeli, the chief scientist of the Israeli ministry of health. Prof. Judith Berman who was supposed to chair the webinar could not for medical reasons, and thus Prof Micha Fridman chaired the webinar. The first session included five lectures:

**Dr. Laura Plant** gave some background information to understand the context of the webinar. The Coordination and support action DESIGN OH- AMR is in charge of preparing the groundwork for the launch of the candidate One-Health AMR partnership expected in 2025. This webinar is included in a series of different consultations feeding the drafting of the Strategic Research and Innovation Agenda of the candidate partnership. The webinar will support this process by identifying gaps and needs in the area of fungal drug resistance.

**Dr. Ana Alastruey-Izquierdo** talked about the Fungal Priority Pathogen List by WHO: Emergence of antifungal resistance is associated with high mortality and morbidity rate. Only 4 classes of systemic antifungal drugs are available but those are associated with significant side effects. Global access to antifungals and affordable diagnostics is unevenly distributed and their availability is particularly limited in low and middle-income countries (LMIC). In terms of diagnostics, existing conventional tests are quite slow, inaccurate and difficult to implement in rural regions and LMICs. There is a need for standardization and validation of tests, especially those that can be used in routine. The WHO is developing a list of global priority fungal pathogen of public health importance. The aim is to align and inform R&D investments with identified public health needs, to analyse and monitor the antifungals in clinical development pipeline and to raise awareness of antifungal resistance and the needs for both surveillance and action. The WHO included 10 criteria to assess and prioritize pathogens including: death, inpatient care, complications and sequel, antifungal resistance, preventability, annual incidence, access to diagnostic tests, evidence based treatments, current global distribution, and trends in the last 10 years. 19 pathogens were assigned as critical, high or medium priority. Antifungal resistance is a top priority with big knowledge gaps and a one-health approach needed. Three priority areas are Public health, Surveillance and R&D. There is an urgent need to develop new antifungals and to improve existing therapies and diagnostics.

**Prof. Paul E. Verweij** reported about diagnostics and surveillance of fungal resistance - current and future directions. There is a lack of fungal resistance surveillance programs worldwide and only a low number of reports on fungal resistance exist. There is a need to set-up efficient surveillance program. In particular, there is a need to monitor trends (new patient groups, new pathogens, new resistance variants, intervention). Future antifungal surveillance activities should include species identification, in vitro susceptibility testing, and definition of the methods to be used. The laboratory performing tests should increase their capacity and expertise on fungi. Reference labs, clinical excellence centers as well as public health institutes should be involved in

surveillance activities. For antifungal resistance, it appears critical to develop a one-health approach through the involvement of agricultural and veterinarian research groups, integration of fungicide exposure information and a data management plan. Getting the stakeholders together should be a priority.

**Dr. Tihana Bicanic** presented the current and upcoming antifungal drugs. Tihana gave a list of drugs that are currently in clinical trials. The classes and targets of antifungal drugs used alone or in combination include: 1) Polyenes (Amphotericin B): targets cell membrane, 2) Azole: Targets cell membrane (Fluconazole voriconazole) 3) Echinocandins: target enzyme B fluca- synthetase involved in cell wall synthesis, 4) Others (Flucytosine): Target DNA/RNA synthesis and drugs used in combination. Fungi are one-step behind regarding the development of antimicrobial agents and the development of various routes of resistance compromise the efficacy of the current drugs. An ideal antifungal drug would be applied orally, cidal (kills fungal/fungal target), kill both yeast and moulds, be well tolerated by patients, with a low resistance rate, a moderate cost and a high availability. New and upcoming therapeutic strategies for Antifungal resistance include: 1) Same target – new drug 2) New targets 3) Other modes of delivery: inhaled drugs, which can reach high concentration in lungs 4) Novel formulations: oral 5) Combination of antifungal therapies to increase efficacy and reduce resistance. Ongoing clinical trials are on-going with various antifungal drugs with different antifungal therapeutic strategies both alone or in combination treatment.

**Prof. Matthew Fisher** gave an overview on how environment and One-Health transmission contribute to the emergence of antifungal resistance: Humanity has a history of combating fungal diseases and fungal fight back by developing resistance. The wide use of fungicides, such as Azoles, with a broad-spectrum in both humans and plants increased resistance to antifungal agents. For this reason, it is important to better specify to what extent the use of fungicides in the environment is linked to resistance in patients. The presence of resistance genes in patients that never received azoles confirms that environment actively contributes to the transmission of resistance genes. In addition, genome sequencing of UK diverse samples in environment and patients confirm that resistance genes have been acquired through the environment. How does this transfer occur? There are multiple changing extrinsic factors with broad variables: use of fungicides, climate changes, new patient groups with antifungal resistance (for example, patients with serious Covid-19 experienced fungal infections resistant to antifungal treatment). One health approach is absolutely needed to better understand the spread of antifungal resistance from the environment to patients and a greater collaboration between agriculture and public health should be expected.

## **Session 2 – Expert panel**

The talks were followed by panel discussion with the participation of: Prof. Tom Harrison, Dr. Neil Stone, Prof. Ronen Ben Ami and Prof. Patrick Van Dijck. The panel discussed the gaps and needs in fungal drug resistance and sought the different ways to connect between the antifungal and antibacterial scientific communities. The chair asked the following questions to the panellists:

*What are the most critical needs for fungal resistance research?*

**Ronen Ben Ami:** from a clinical perspective, testing is critical. The ability to test and diagnose *C.albicans*, *Aspergillus* and rare yeast is fundamental.

**Neil Stone:** Surveillance and detection are fundamental. There is a need for surveillance in order to detect resistance both in LMIC and in developed countries. There is a lack of access to fungal resistance testing. There is a large gap in abilities to detect resistance in Africa.

**Ana Alastruey:** Surveillance and access to LMIC should be a priority, but even in high-income countries, there is a lack of data and awareness regarding resistance to antifungals. It is important to diagnose better and earlier. International recognition of surveillance will luckily promote the development of tools that could be more accessible.

*Where do you think the gaps and opportunities are in fungal resistance research?*

**Tom Harrison:** Surveillance, rapid and sensitive diagnostics, targeted treatments, combination treatments are needed, always considering a One-health perspective. Better diagnostics would reduce antifungal drug use and reduce resistance and some efforts are ongoing to make diagnostics shortly available. Drug combination have already proven their efficacy in bacterial infections to prevent the development of second resistance. Increase in cooperation between academia and industry is needed and will enhance progress. It will also be important to seek how to simplify clinical trials to increase participation and test interventions in LMIC.

**Ana Alastruey:** Also agreed that finding ways to gather solid data and include LMIC in clinical trials should be a priority.

*Which methods and disciplines are missing or need to be developed in the next years?*

**Patrick Van Dijck:** The use of drug combination, both in human, and in animals, could be a strategy to fight against antifungal resistance. This approach has already shown its efficiency to decrease antibacterial resistance.

**Micha Fridman:** Collaboration between chemists, physicists, fungal experts and clinicians is needed to promote the development of new tools. Micha gave an example for a collaboration between himself, a chemist and Prof. Judith Berman, a fungal expert, in a project to develop chemical modifications of antifungal drugs in order to restore their efficiency in fungal infections.

*How can the public/policy/industry be made aware of the importance and danger of fungal infection?*

**Ana Alastruey:** The scientists should raise the awareness.



**Neil Stone:** Awareness is critical. The public is not aware of the danger of fungal infections. Fungi resistance kill more than malaria but receive only a small fraction of the funding. The use of social media, such as Twitter that can reach millions of people or the use of platforms to reach a wider public, funders, government and policy makers would be fundamental. The WHO list of important pathogens is a great start. The researchers should increase the awareness on the importance of fungal resistance.

**Paul Verweij:** Fungal disease have not been seen as public health threat. It is important to incorporate fungal disease in AMR programs and develop expertise.

*What can be learned and implemented from antibacterial resistance?*

**Neil Stone:** The antifungal community should not reproduce mistakes done in treating bacterial infections. In particular, it is important to consider antifungal resistance using one health approaches (including agriculture and animal).

**Tom Harrison:** It is important to avoid serial monotherapies to protect new drugs and favour combination therapy to extend the spectrum. To fight against bacterial and fungal resistance, it will be important to use rationally designed treatment based on mechanistic studies.

*How can we build connections between the fungal and bacterial resistance and between the clinical, agriculture, and research communities?*

**Patrick Van Dijck:** Separate research communities need to meet together and cooperate. Activities including researchers working on bacteria and fungi is needed to learn from each other.

**Matt Fisher:** Collaboration with the agriculture community should be extended. A panel with different expertise is needed to discuss development and overlap.

**Ana Alastruey:** JPIAMR Calls for proposals support research projects encompassing different research communities. It will be important to promote group discussion where antibacterial and antifungal resistance are discussed together.

**Laura Plant:** JPIAMR launched a network call on diagnostic and surveillance in April 2022. Researchers from the different communities can apply.

## **Conclusion**

The chair thanked the speakers for the great presentations and discussions. There is a growing need to increase the collaboration between the antibacterial and antifungal research communities and generate more platforms for collaboration between the different one-health stakeholders by initiating joint research calls and joint events such as this webinar.

# Summary of gaps, needs and opportunities in fungal drug resistance with an eye to the future

## Diagnostics

- Diagnostics is unevenly distributed, and there is a low availability particularly in LMICs
- Slow and inaccurate conventional diagnostic tests
- Need for rapid diagnostics
- Hard to implement in LMICs
- Lack of standardization and validation of tests
- Lack of routine testing
- Need test to diagnose *C. albicans*, *Aspergillus* and rare yeast
- There is a large gap in abilities to detect resistance in Africa

## Surveillance

- Lack of resistance surveillance programs
- Need to monitor trends (new patient groups, new pathogens, new resistance variants, intervention)
- Future antifungal surveillance activities should include species identification and in vitro susceptibility testing
- Increase lab expertise and capabilities
- Implement a one health surveillance approach
- International recognition of the importance of surveillance to give accessible and available tools
- Find ways to gather solid data and include LMIC in clinical trials

## Therapeutics

- Development of New targeted therapeutic strategies and treatments for Antifungal resistance against:
  - Same target – new drug
  - New targets
  - Other modes of delivery: inhaled drugs, which can reach high concentration in lungs
  - Novel formulations: oral
  - Drug Combination to increase efficacy and reduce resistance

## Transmission and the environment

- Broad-spectrum usage in humans and plants increased resistance to Azoles.
- Wide use of fungicides is causing an increase in resistance.
- More research is needed to understand how fungal resistance is transmitted from the environment to patients
- One health approach is absolutely needed to better understand the spread of antifungal resistance from the environment to patients
- Collaboration between agriculture and public health should be reinforced

- Collaboration between different disciplines is needed to develop new tools

### **Stakeholders and the public**

- Need to increase awareness on the danger of fungal resistance to public health
- Need to incorporate fungal resistance in AMR programs and develop expertise
- Joint calls and events between antibacterial resistance and antifungal resistance research communities

### **Lessons learned from antibacterial resistance**

- It's important to use a one health approach while considering antifungal resistance
- Mistakes done while treating bacterial infections should not be reproduced by the antifungal community
- Try to avoid serial monotherapies to protect new drugs
- Use combination therapy to extend the spectrum

# Acronyms and references

## Acronyms

AMR: Antimicrobial Resistance

AFR: Antifungal resistance

ERA-NET: European Research Area Network

JPIAMR: Joint Programming Initiative on Antimicrobial Resistance

LMIC: Low and Middle Income Countries

MD: Medical Doctor

No.: Number

PhD: Doctor of Philosophy or Doctorate degree

R&D: Research and Development

SAB: Scientific Advisory Board

UK: United Kingdom

USA: United States of America

WHO: World Health Organization

## References

Fisher, M.C., Alastruey-Izquierdo, A., Berman, J. *et al.* Tackling the emerging threat of antifungal resistance to human health. *Nat Rev Microbiol* (2022).

<https://doi.org/10.1038/s41579-022-00720-1>

## Annex I. Webinar Agenda

Thursday 23 <sup>th</sup> June 2022, Chair: Prof. Micha Fridman, Tel Aviv University, Israel		
14:00 C.E.T	<b>Welcome Remarks:</b> Prof. Avi Israeli, Chief Scientist, Israel Ministry of Health	
14:05-14:15	<b>Introduction:</b> JPIAMR and fungal resistance consultation	<b>Laura Plant</b> , PhD, JPIAMR Secretariat
Short lectures: <b>Tackling the emerging threat of fungal drug resistance</b>		
14:15-14:30	Fungal Priority Pathogen List by WHO: Call for action	<b>Ana Alastruey-Izquierdo</b> , PhD, National Centre for Microbiology, Madrid, Spain
14:30-14:45	Diagnostics and surveillance of fungal resistance - current and future directions	<b>Paul E. Verweij</b> , MD/PhD Radboud University Medical Centre, Nijmegen, the Netherlands
14:45-15:00	Current and anticipated antifungal drugs	<b>Tihana Bicanic</b> , MD/PhD, St George's University of London, UK
15:00-15:15	Environment–One Health links and emerging fungal resistance	<b>Matthew Fisher</b> , PhD, Imperial College London, UK
<b>Expert panel – Consultation and discussion</b>		
15:15-16:00	<ul style="list-style-type: none"> <li>- Raising awareness of the danger of fungal disease amongst public, clinical, government and industry stakeholders</li> <li>- Identifying critical needs, gaps and opportunities for fungal research.</li> <li>- Developing new diagnostic and treatment approaches.</li> <li>- Building on experiences (successes and failures) with antibacterials.</li> <li>- Connecting between diverse communities dealing with pathogens: fungal &amp; bacterial; clinical &amp; agricultural.</li> </ul>	<p><b>Micha Fridman</b>, PhD, Tel Aviv University, Israel</p> <p><b>Neil Stone</b>, MD/PhD Hospital for Tropical Disease/ University College London Hospitals, UK</p> <p><b>Ronen Ben Ami</b>, MD/PhD Tel Aviv Sourasky Medical Centre, ICHILOV Israel</p> <p><b>Patrick Van Dijck</b>, PhD, KU Leuven, Belgium</p> <p><b>Tom Harrison</b>, MD/PhD, St George's University of London, UK and JPIAMR Scientific Advisory Board</p>

## **Annex II. Experts, speakers and panellists**

### **Prof. Micha Fridman**

Full Professor in the School of Chemistry; Faculty of Exact Sciences, Tel Aviv University, Israel. Vice President of the Medicinal Chemistry Section of the Israel Chemical Society. His research concentrates on Development of Novel Drugs and Drug Combinations to Treat Persistent and Drug-Resistant Fungal Infections

### **Dr. Ana Alastruey**

Ana is a research scientist in the Mycology Reference Laboratory at the Spanish National Centre for Microbiology, Madrid, Spain, she chairs the WHO Technical advisory Fungal disease expert group and is a member of the JPIAMR scientific advisory board.

### **Prof. Paul E. Verweij**

Paul is a Clinical Mycology expert. He is chairperson of the Department of Medical Microbiology at Radboud University Medical Centre. He is also member of the board of the Nijmegen Center for Infection, Inflammation and Immunity, the Netherlands.

### **Dr. Tihana Bicanic**

Tihana is a Reader and Honorary medical Consultant in Infectious Diseases at St. George's University of London, UK. She is a leading medical expert on cryptococcal meningitis in HIV.

### **Prof. Matthew Fisher**

Mat is a Professor of Fungal Disease Epidemiology in the School of Public Health at the Imperial College London since 2013 and a Theme lead in the MRC Center for Global Infectious Disease Analysis since 2018. Mat works on emerging pathogenic fungi.

### **Prof. Ronen Ben Ami**

Ronen is a medical expert on infectious diseases and internal medicine, he is Head of the infectious Diseases Department and Director of the National Mycology Reference Laboratory at the Tel Aviv Sourasky Medical Center, Israel. His research focuses on mechanisms of resistance in pathogenic fungi.

### **Dr. Neil Stone**

Neil is a medical expert in Infectious Diseases and Microbiology at the Hospital for Tropical Disease/University College London Hospitals. His research interests include Diagnosis and treatment of invasive fungal disease, cryptococcal meningitis, antifungal drug resistance, fungal Infections in the immunosuppressed.

### **Prof. Tom Harrison**

Tom is Lead for the Centre for Global Health, and Deputy Director of the Institute for Infection and Immunity, at St Georges University of London. He is an Infectious Diseases

Consultant at St Georges Hospital, London, and Professor in Medical Mycology at the MRC Centre for Medical Mycology, University of Exeter. Tom is a member of the JPIAMR scientific advisory board.

**Prof. Patrick Van Dijck**

Patrick is head of the Molecular cell biology lab in the unit for Molecular Biotechnology of Plants and Microorganisms at the KU Leuven University, Belgium. His research interest includes human fungal pathogens and antifungal compounds.

## **Annex III. Organising committee**

### **Prof. Judith Berman (Tel Aviv University, Israel)**

Full Professor, Dept. Molecular Microbiology & Biotechnology, Tel Aviv University, Israel. She studies pathogenic yeasts, and their responses to antifungal drug stress. Her current work focuses on antifungal drug tolerance, a mechanism involving phenotypic heterogeneity, with the aim of understanding how genetically identical cells grow differently in response to drug stress.

### **Dr. Ronit Meyuhas, MBA (CSO-MOH, Israel)**

Holds a PhD from the Hebrew university Jerusalem. She is the Scientific Advisor on the regulation of Biological Disease Agents in the Israeli Ministry of Health since 2014. Prior to her work in the Ministry, she held the position of Team leader in Teva pharmaceutical Industries Ltd. Ronit is involved in JPIAMR, for which she has the responsibility of running the ethics reviews and the early career research group.

### **Dr. Caroline Johnson (MRC, UK)**

Program Manager for the Infections and Immunity Board at the MRC, covering bacterial disease, fungal disease and antimicrobial resistance. After a PhD in Immunology from King' College London, Carolyn moved to Lincoln, then Oxford to pursue her research career. In the past, Carolyn has worked for several UK based Charities (Alopecia UK and The Daphne Jackson Trust). She joined the MRC in 2020.

### **Dr. Sophie Gay (ANR, France)**

Scientific officer for transnational collaborations in the Biology & Health department. After a PhD in molecular oncology (Sorbonne Université, Paris), she moved to Milan (Italy) to pursue her research activity at the IFOM Cancer Research Center. She joined ANR in 2018 to manage national and multilateral programs. She is currently coordinating the drafting of the Scientific Research and Innovation Agenda of the candidate OH-AMR Partnership in the framework of the DESIGN CSA.

### **Dr. Laura Plant (JPIAMR secretariat)**

PhD in Microbiology from the University of New South Wales in Australia. She has a research background in the field of bacterial pathogenesis and immunity from the Nestlé Research Centre, University of Melbourne, and Karolinska Institute. Since 2013, Laura has worked as a Senior Research Officer at the secretariat of the Joint Programming Initiative on Antimicrobial Resistance at the Swedish Research Council. Laura is engaged in management of projects funded by the European Commission, and is the Swedish delegate in the Global AMR R&D Hub.