ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

REGIONAL MMTN CONFERENCE 2023

Asia Pacific Medical Mycology Training Network (MMTN) Conference

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The Asia Fungal Working Group is an official working group of the International Society for Human and Animal Mycology (ISHAM).

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THE UNIVERSITY OF SYDNEY

WHO Fungal Pathogens: priority list, focus on research

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www.wslhd.health.nsw.gov.au/CIDM-PH

DISCLOSURES

- Untied educational grants from MSD Australia, F2G Ltd. Manchester, UK
- Antifungal Advisory Board of MSD Australia, Gilead Sciences Inc., F2G Ltd.
- Speakers Fees, Gilead Sciences, Inc.

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Agenda

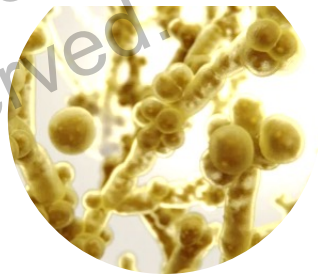
- **Key findings** from the WHO Fungal Pathogens Priority List (FPPL) developed using predefined criteria:
  - Mortality, hospitalised care
  - Complications and sequelae
  - ***In vitro* susceptibility**, risk factors, preventability,
  - annual incidence, global distribution

- **Broad perspective (my own!): mould pathogens**
- Focus on clinical needs and research

Emerging AMR

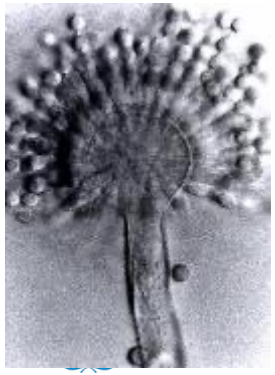
Candida auris

- Often multidrug resistant
- Resistant to standard infection control procedures
- *C. auris* 1st reported in Japan in 2009, since then in >55 countries
- Where did it come from?



Azole resistant *Aspergillus fumigatus*

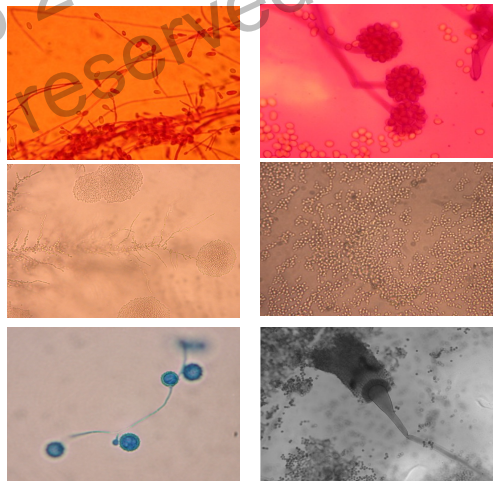
- Emerged over the last decade
- Worse clinical outcomes
- Driven by environmental agricultural contamination
- Rates seem very high in areas of China and SE Asia (90%!)



WHO response

Commissioned a FFPL to:

- direct R&D efforts towards pathogens with greatest gaps in knowledge;
- define R&D priorities to align investments and funding with unmet needs;
- enable international co-ordination in R&D to innovate new, and optimize existing therapeutics and diagnostics
- facilitate regular review of antifungal development pipeline for trends and gaps



Photos credit: Ana Alastruey-Izquierdo, **Instituto de Salud Carlos III , Spain**

Slide: Dr. J. Beardsley, with thanks

Ranking process

Slide: Dr. J. Beardsley, with thanks

Pathogens to be prioritized

1. *A. fumigatus*
2. *C. albicans*
3. *C. auris*
4. *C. glabrata*
5. *C. krusei*
6. *C. parapsilosis*
7. *C. tropicalis*
8. *Coccidioides*
9. *C. gattii*
10. *C. neoformans*
11. *Fusarium*
12. *Histoplasma*
13. *L. prolificans*
14. *Mucorales*
15. *Mycetoma (invasive)*
16. *Paracoccidioides*
17. *P. jirovecii*
18. *Scedosporium*
19. *T. marneffei*

Assessment criteria

Deaths	Average case fatality, guideline recommended treatment
Inpatient care	Average length hospital stays for treatment, following initial diagnosis
Complications and sequelae	Proportion of patients suffering long-term complications from disease
Antifungal resistance	Rate (or level) acquired or intrinsic resistance
Preventability	Transmission/acquisition dynamics evidence based effective, preventive measures
Incidence (p.a.)	No. new cases/10^6 population/year
Access to Dx	Availability of diagnostics
Evidence-based treatment	Treatment options are evidence based and accessible
Current global distribution	Extent global geographic distribution
Trends 10 years	Change in incidence/prevalence

FPPL ranking process

Describe pathogens in terms of pre-selected criteria

Assign pathogens to pre-specified levels for all criteria

- Systematic review
- Blinded allocations
- Expert opinion where needed

Determine importance of the criteria

Discrete choice experiment (DCE) among large international cohort of mycology experts

- Informs the multi-criteria decision analysis

R&D Rank

Each pathogen is scored according to

- allocated levels for each criteria
- multiplied by the importance weight from DCE

PH Rank

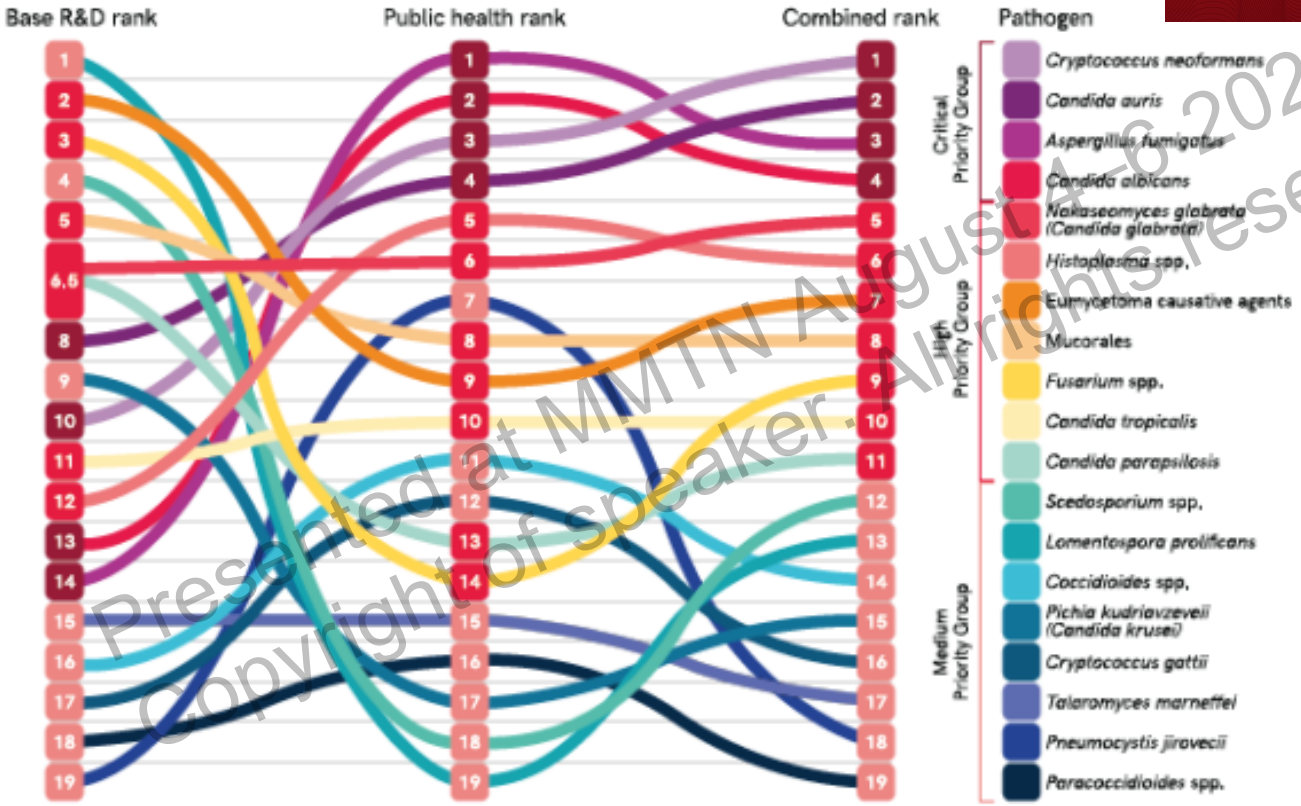
Each pathogen ranked indirectly via DCE

- Experts determine relative importance of R&D need and PH importance

Slide: Dr. J. Beardsley, with thanks

WHO FUNGAL PRIORITY PATHOGENS LIST TO GUIDE RESEARCH, DEVELOPMENT AND PUBLIC HEALTH ACTION

Fig. 3. Overall pathogen rankings



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

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FPPL findings

Public health importance strong determinant of priority: survey respondents favored public health importance over unmet R&D

Antifungal resistance top priority: respondents gave highest weighting to antifungal resistance when prioritising R&D need

Disease-burden-related criteria ranked highly: amongst the highest weightings for relative importance in the R&D survey.

Systematic reviews: major knowledge gaps on global IFD burden and disability outcomes. Drug resistance data extensive but inconsistent.

Global Vs. Endemic: invasive fungal pathogens vary significantly by region.

WHO FPPL: final

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

Aspergillus sections (human infection, n>14)

Section	~~SERIES~~ Species complex	Species	Comment
Fumigati	***A. fumigatus***	*A. fumigatus sensu stricto*	Grows at 50°C
63 pathogenic species	Sibling species	*A. lentulus*	Drug-resistant
		A. fischerianus	More drug resistant
		A. fumigatiaffinis	More drug resistant
	A. viridinutans	*A. viridinutans sensu stricto*	Aussie discovery (1954)
		A. udagawae	Chronic lung aspergillosis (CLA)
Jos Houbraken publications		*A. felis*	CLA

Manual of Clinical Microbiology 12th Ed, ASM, Chapter 122, 13th Edition

Invasive aspergillosis: Key WHO findings

- Relevance: ‘One Health’, *Aspergillus* in environment (49 articles, final analysis)
- Mortality: 30, 42, 100-d, 12-wk, azole-resistance, CAPA vs. non-CAPA (13-50%)
- Length of hospital stay (LOS): 2 studies; no data on excess LOS related to IA or LOS variation in subgroups e.g. cancer patients
- No data on IA complications or sequelae
- **Azole susceptibility rates varied ++ with study and geography (9.6-100%),** cross resistance, increase rate within time fame of review in 1 study
- Newer host risks: viral infections (CAPA, ‘flu), confounders: diabetes, COPD, ESKD
- Annual inc.: wide range, varied denominators, CAPA (5-35%), acute leukemia 5.84/100 patients
- Globally distributed

Morrissey O… Beardsely J. Systematic review (to be submitted) 1 Jan 2016- 10 Jun 2021

Azole resistance: clinical *A. fumigatus* isolates

Continent	Country, years	Prevalence	Characteristics	Reference
Europe	Denmark 2018-2020	**6.1%**	National TR_{34} - 39/66	Risum 2020
	Belgium, 2016-2020	**7.1%**	Single centre TR_{34} - 74/78	Resendiz-Sharpe, 2021
	Netherlands; 2019-2020	**9.2%**	Multicentre TR_{34} - 392/660 TR_{46} -132/660	www.swab.nl/nl/nethmap
	Spain; 2019	**4.7%**	Multicenter TR_{34} -19/34, TR_{46} 1	Escribano 2021
	Turkey; 2018-2019	**3.3%**	Multicenter TR_{34} - 9/19	Ener 2022
Americas	USA; 2015-2020	**3.5%**	Multicenter TR_{34}, TR_{46} 1 each	Badali 2022

Azole resistance rates: clinical *A. fumigatus* isolates

Continent	Country, years	Prevalence	Characteristics	Reference
Asia-Pacific	China; 2019-2020	4.1% (3/73)	Single center,. TR_{46} (2)	Wang, 2022
	China; 2016-2018	4.3% (19/445)	Two hospitals TR_{46} (1)	Xu, 2020
	Taiwan; 2015-2020	1.8% (2/113)	Single center TR_{34}/L98H (2/2)	Hsu, 2022
	Australia, 2009-2017	2.6% (3/117) 0% envir.	Single jurisdiction TR_{34}/L98H (1) G54R (2)	Talbot, 2018

Agricultural countries: highest prevalence

- Is every use of pesticide equally harmful ?
- What do to about the tulips and the azole composting ?
- What with the newer “ipflufenoquin” – Dihyro-orotate dehydrogenase (DHODH) inhibitor (similar to olorofim)
- One Health collaboration needed

Keukenhof, the Netherlands

Verweij *et al*., pers comm.

Clinical and Research Needs I

- *Mortality measure*: WHO review identified substantial variation, type of mortality, time-point, patient population, uncertainty of trends over time
  - RCTS; identify all cause mortality at 6 wk, 12 wk - standardise?
  - Attributable mortality (2 studies identified by WHO) but how to define ? Important in determining relative efficacy of different antifungal regimens
- *Excess costs due to IA* (economic studies),
- *Longer term outcomes*; 6 month mortality, complications of IA, sequelae,
- *Resistance:* need more studies outside of Europe, and USA, identify barriers and link to outcomes

Clinical and Research Needs II

- New risks: Bruton kinase inhibitor, influenza, COVID-19
- Surveillance – local, regional to be encouraged; denominators need standardising
- **Prophylaxis and treatment guidelines well established for IPA in classic high risk patients**
  - CNS aspergillosis
  - Bone and joint infection
  - SOTs, ICU, other risk groups
- Breakthrough disease vs. primary disease

Chen and Miceli, MSG ERC meeting, New Mexico, 2022

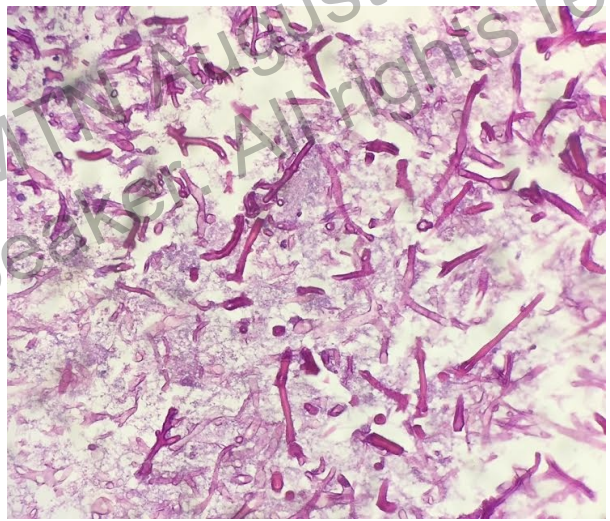
Clinical and Research Needs III

- Oral treatments that are fungicidal needed
- What is the best time to assess treatment response? Would shortening time to response assessment be useful ?
- What do we mean by response vs. stable disease vs. failure for different forms of invasive aspergillosis
  - Does one size fit all?
    Can we apply this response definitions to all hosts?
    -SOT vs HCT/HM vs ICU vs others
-

Miceli M and Chen S, MSG ERC meeting, 2022

Other moulds: similar needs as aspergillosis but burden is less; data are fewer

- Mucorales
- *Fusarium*
- *Scedosporium*
- *Lomentospora prolificans*



Mucorales: H&E in lung

Host risks: move beyond the “classic”

- Diabetic patients (Mucorales)
- Burn/trauma (Mucorales, *Scedosporium, Lomentospora)*
- **Cystic Fibrosis Patients (many molds)**
- **Lung transplants (many molds)**

Mucormycosis: additional needs (therapeutics)

- No randomized controlled clinical trials
- Currently: amphotericin B formulation (lipid) IV → step down isavuconazole or posaconazole
- Do we need new trials or open label studies
    - Optimum timing of step down
    - Hematology/oncology vs diabetes mellitus
    - ROCM vs. other
    - Case-control prospective studies
    - Combination therapy: typically late in the game

Other uncommon moulds

Likelihood of RCTs are even smaller for non-Mucorales uncommon mold pathogens

- Open label studies, salvage therapy trials

Timing of enrollment is problematic…….

→ why do patients need to fail before being able to enroll if we have better/promising drug to offer?

→what's the purpose?

→Adaptive trial design with its pros and cons

Messages

- **Focus on unmet needs**
  - Surveillance and burden
  - Broaden trial eligibility criteria to include:
    - Specific populations at risk (e.g. lung transplants and prophylaxis)
    - Non-pulmonary and sanctuary sites
    - Children
    - Breakthrough infections
- **AFWG and other professional societies**
  - Promote discussions and laboratory capacity
  - Update the response definition criteria for mold infections to be more realistic and to achieve endpoints based on specific pathogen or host group

THANK YOU!

Host – beyond the "Classic"

Cystic Fibrosis patients

- 28-49% have fungi in sputum (variation ++)
- most likely colonized with *non-fumigatus Aspergillus*, *Fusarium* and *Alternaria, Scedosporium and Lomentospora*
- Performance of biomarkers?
- Definition criteria differ from EORTC/MSG Criteria
- Exposure to antifungals → azole resistance
- Pharmacokinetic issues

- Why is this important??
  - most patients will be listed and receive bilateral lung transplant

Denning DW et al, Lancet, 2017;; Schwarz C et al, Mycopathologia 2018 and 2021; DiPaolo M, JAC 2021