Latest IFI epidemiology & unmet needs in Asia

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Disclosures

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DBT, Department of Biotechnology; DST, Defence Science and Technology Group; ICRM, Indian Council of Medical Research; MSD, Merck Sharp & Dohme; WHO, World Health Organization

Concern about invasive fungal infections

- **Concern of fungal infections is of recent origin, since 1980s with emergence of AIDS, transplantation, immunosuppression & medical device use**
- **Within short period provided a formidable challenge due to high number of cases & mortality**

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editorial

Stop neglecting fungi

Nature Microbiol 2017; 2: 17120

Fungal pathogens are virtually ignored by the press, the public and funding bodies, despite posing a significant threat to public health, food biosecurity and biodiversity.

mouth-watering mushrooms. However, few realize that over 300 million people suffer from serious fungal-related diseases, or that fungi collectively kill over 1.6 million people annually[1], which is more than malaria and similar to the tuberculosis death toll. Fungi

NATIONAL GEOGRAPHIC

SCIENCE

Changes in the environm
agriculture, have driven a
evading the few drugs d

BY CONNIE CHANG
PUBLISHED 5 AUG 2022, 14:39

SCIENCE

Humans are not prepared for a pandemic caused by fungi

Brown GD, *et al.* Sci Transl Med 2012; 4: 165rv; Rddrigues & Nosanchuk PLoS Negl Trop Dis 2020; 14: e0007964

'Black fungus' is creating a whole other health emergency for Covid-stricken India | Ian Schwartz and Arunaloke Chakrabarti

Rates of mucormycosis were high even before the pandemic, and now the country is running out of antifungal drugs, say global expert Prof Arunaloke Chakrabarti and infectious diseases doctor Ilan Schwartz

- **Mucormycosis is declared as notifiable disease in India**
- **Till August 3, Government of India portal mentioned 47,508 cases**
- **'It is very likely that the actual figures are considerably higher than this'**

Printed from THE TIMES OF INDIA

Gujarat: Tsunami of mucormycosis among Covid-19 recovered

https://governmentstats.com/mucormycosis/index.html

C. auris pandemic across the world

- **Developing antifungal resistant very fast**
- **Easily transmitted – spread to 43 countries within 1 decade**
- **Multiple outbreak reported**
- **Severe infections & mortality (30-day mortality 23-67%)**
- **Resilient pathogen – survives many disinfectants, desiccation & high salt**
- **Contaminates environment fast**
- **Not easily identified**

Chakrabarti & Sood. J Med Microb 2021; 70: 001318

C. auris in Asia

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae (S. pneumoniae)*
- Drug-resistant Tuberculosis (TB)

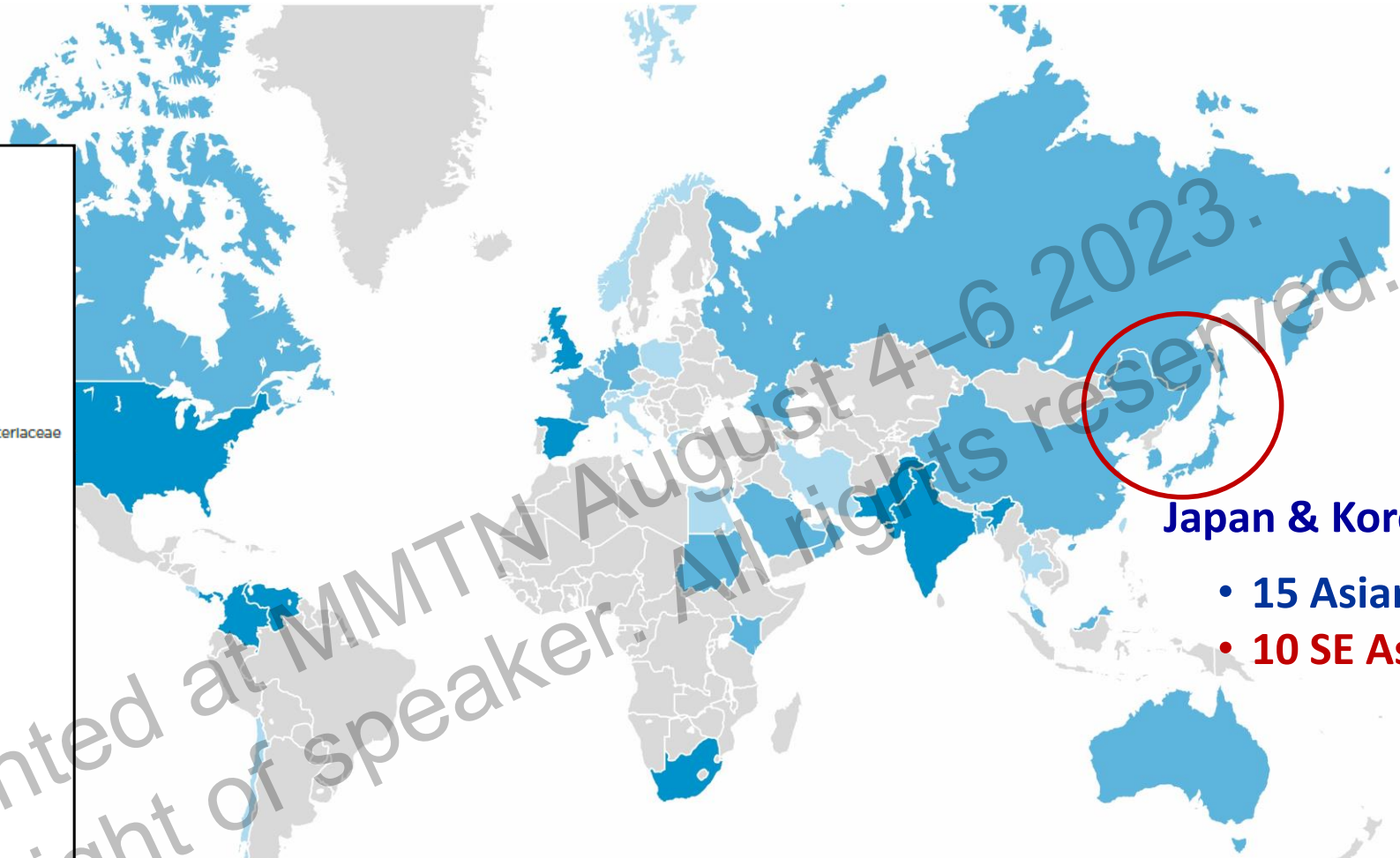
Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Watch List

- Azole-resistant *Aspergillus fumigatus (A. fumigatus)*
- Drug-resistant *Mycoplasma genitalium (M. genitalium)*
- Drug-resistant *Bordetella pertussis (B. pertussis)*

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf



Japan & Korea in 2008

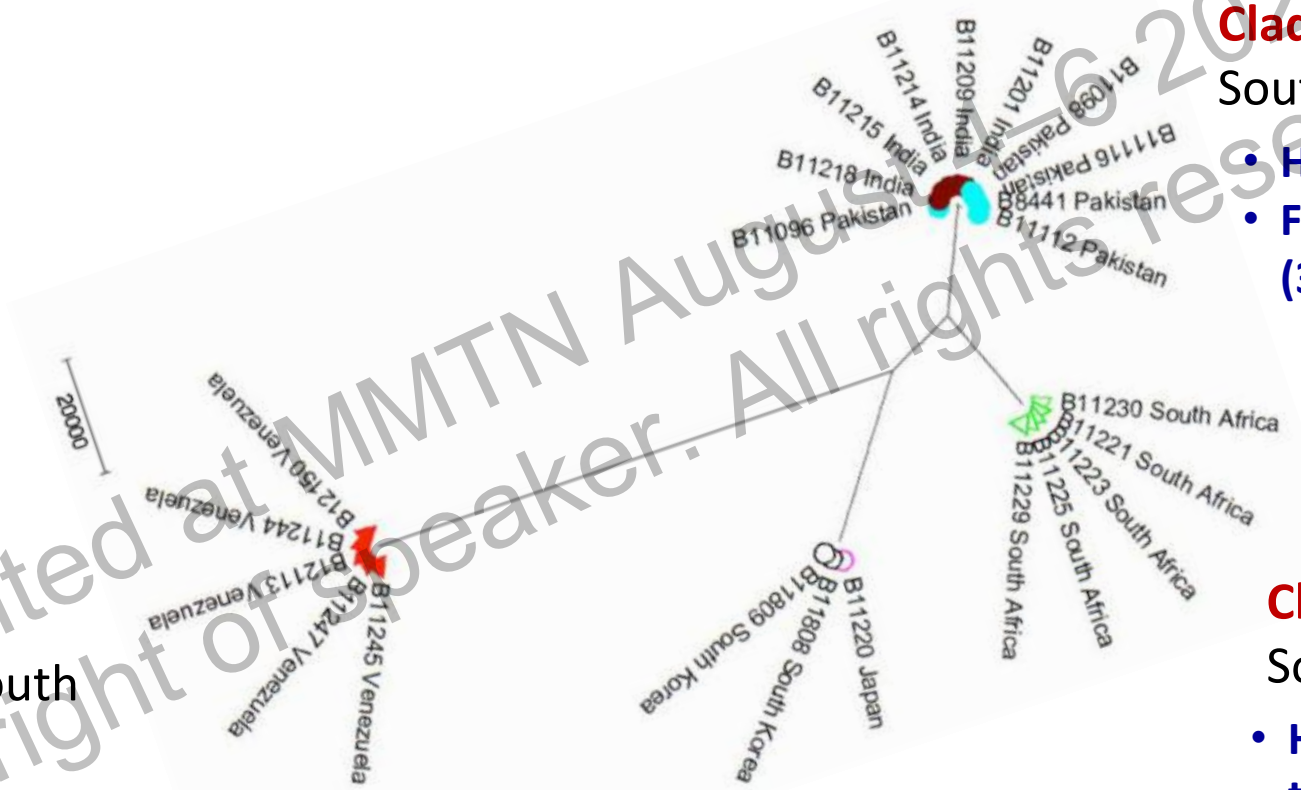
- **15 Asian countries**
- **10 SE Asian countries**

1996	1997	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
South Korea	Japan	Pakistan	South Africa, India	Kenya	China	Venezuela, Singapore	Colombia, USA, UK	Israel, Kuwait	Australia, Germany	Belgium, Norway, Spain, Russia, Oman, Panama	France, Switzerland, Canada, Taiwan, UAE, Egypt, Saudi Arabia	Austria, Greece, Netherlands, Poland, Chile, Bangladesh, Malaysia, Thailand, Iran	Italy, Costa Rica, Sudan

Chakrabarti & Sood. J Med Microbiol, 2021; 70: 001318

Clades in *C. auris* – by WGS

- **Possible Clade V in Iran** (Chow NA, *et al*. Emerg Infect Dis 2019; 25: 1780)



Clade I, South Asia

- **High drug resistance**
- **Flu (97%), Vori (54%), AmB (30%), 49% multi-drug**

Clade III, South Africa

- **High drug resistance to flu, vori, not AmB**

Clade IV, South America

- **Variable drug resistance**
- **50% AmB in Venezuela, but 11% Flu in Columbia**

Clade II, East Asia

- **Low drug resistance**
- **11-14% to flu only**

Chakrabarti & Sood. J Med Microbiol, 2021; 70: 001318

Lockhart SR, *et al*. Clin Infect Dis 2017; 64: 134

Invasive fungal infections – change in epidemiology

Fungi adapt warmer temperature & develop resistance to drugs, we need to bolster our defenses

Host

- New risk groups (**ICU stay, COPD, liver & renal diseases**, etc.)
- **More immunosuppression**, unrelated transplantation
- Immune modifying drugs
- More device use
- **Advanced age living longer in ICU**

All these trends challenge our ability to rapidly recognize, diagnose, & treat invasive fungal infections in Asian countries

Fungus

- New species – ***C. auris*, *C. vulturna*, *C. blankii*, *C. africana*, *C. viswanathii*. *Emergomyces*, *Blastomyces helicus*, *Rhizopus homothallicus* etc.**
- Azole resistance in *Candida* & *Aspergillus*; Echinocandins resistance evolving

Environment

- **Construction & demolition**
- Global warming
- Natural disasters
- Tropical environment
- **High spore count in air of LMIC**

Casadevall A. J Clin Invest 2020; 130: 553

Parsons & Diekema. Mod Pathol 2023; 36: 100187; Enoch DA, *et al*. Methods Mol Biol 2017; 1508: 17-65

Opportunist fungal infections classical risk groups

Malignancy	Incidence IFI	Incidence Molds	Incidence Yeasts
AML	**12 %**	7.9 %	4.4 %
ALL	**6.5 %**	4.3 %	2.2 %
Allogeneic HSCT	**7.8 %**	6.7 %	1.1 %

Invasive aspergillosis in haematological malignancies - meta-analysis

- Overall, IA **reported in 6.3%** of 16,815 patients
- IA risk ranged from **4% (during remission-induction, with prophylaxis) to 11% (during remission-induction, without prophylaxis)**
- **Pooled case fatality rate within 100 days was 29%** (95% CI: 20–38%)

Cadena J, *et al*. Infect Dis Clin N Am 2021; 35: 415-434: Korula A, *et al.* Mycoses 2017; 60: 686-691; Yanamandra U, *et al.* Indian J hematol Blood Transfusion 2018; 34: 466-468; Pagano L, *et al.* Br J Haematol 2015; 170: 434-439; Pagano L, et al. Clin Infect Dis 2007;45:1161-70; van de Peppel RJ, *et al*. J Infect 2018; 76: 550-562

- Prospective multi-centre study in AML patients
- 200 patients (118 male), during Nov2014 – Feb2016
- 93% newly diagnosed, 7% relapsed
- **IFI – proven (26.5%), probable (8.5%)**

George B, *et al*. Indian J Hematol Blood Tranfus 2020; 36; 97-103

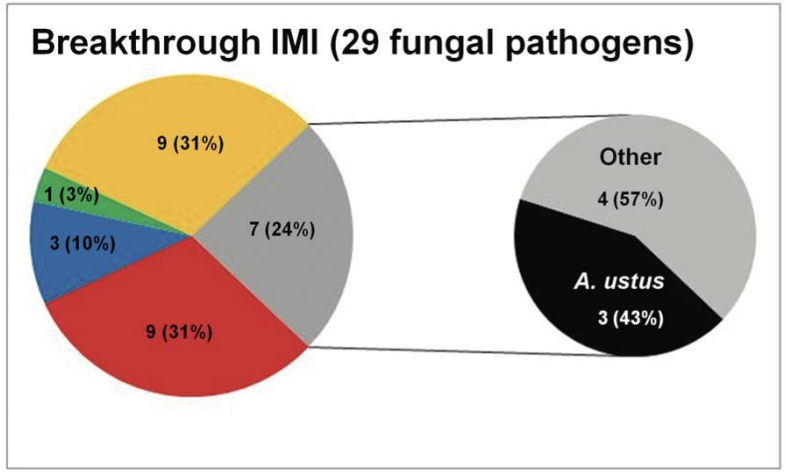
	Our study	Pagano et al, 2015
Study population (Acute promyelocytic leukaemia)	98	103
IFI	**18.3%**	**7.0%**

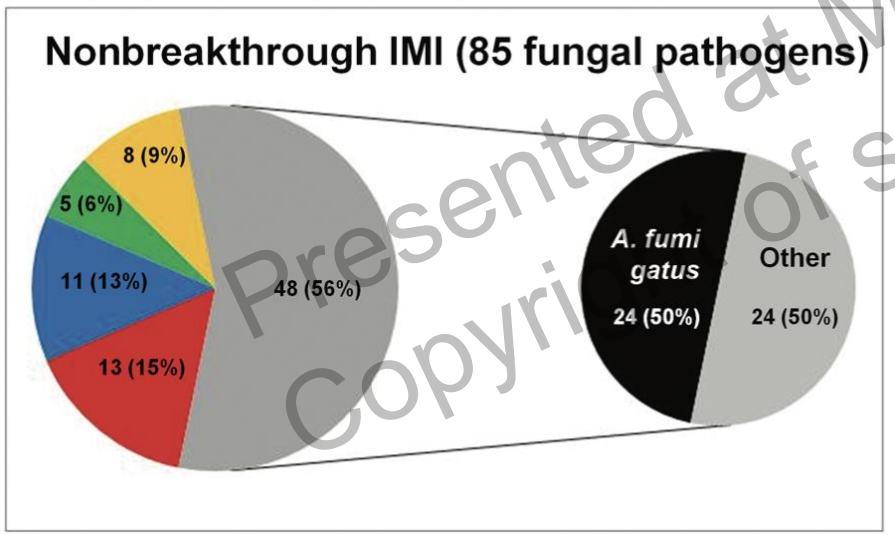
Yanamandra U, *et al*. Indian J Hematol Blood Tranfus 2018; 34: 466-468

Higher IFI in India

- Delayed diagnosis (median 30d)
- **Continued care of AML patients in non-HEPA filtered room**

Mould active prophylaxis - breakthrough mould infections





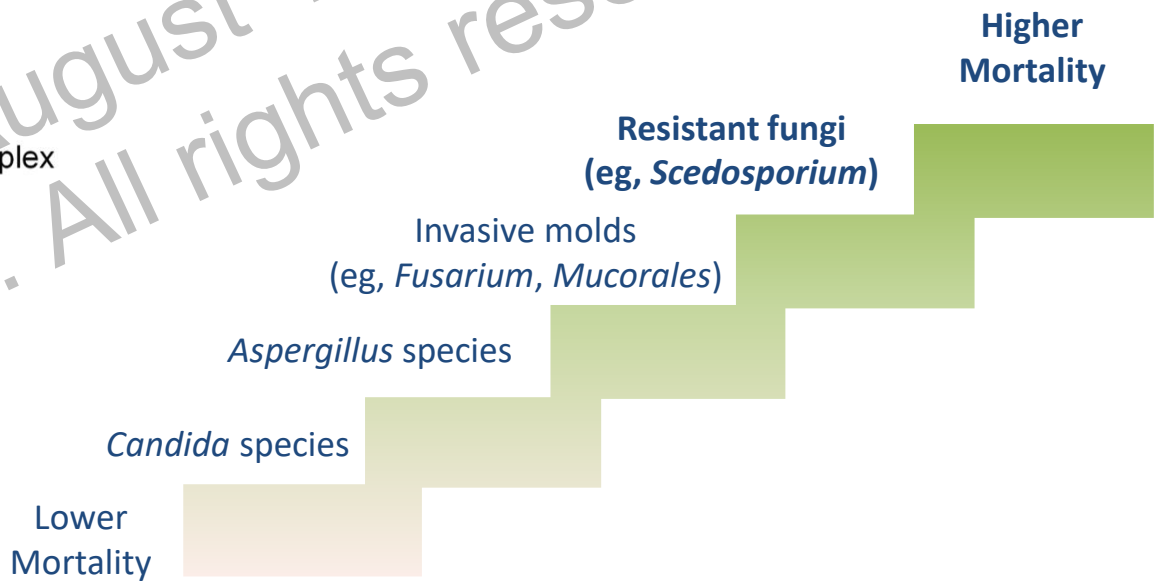
Aspergillus spp.

Mucorales

Fusarium spp.

Scedosporium apiospermum complex

Other molds

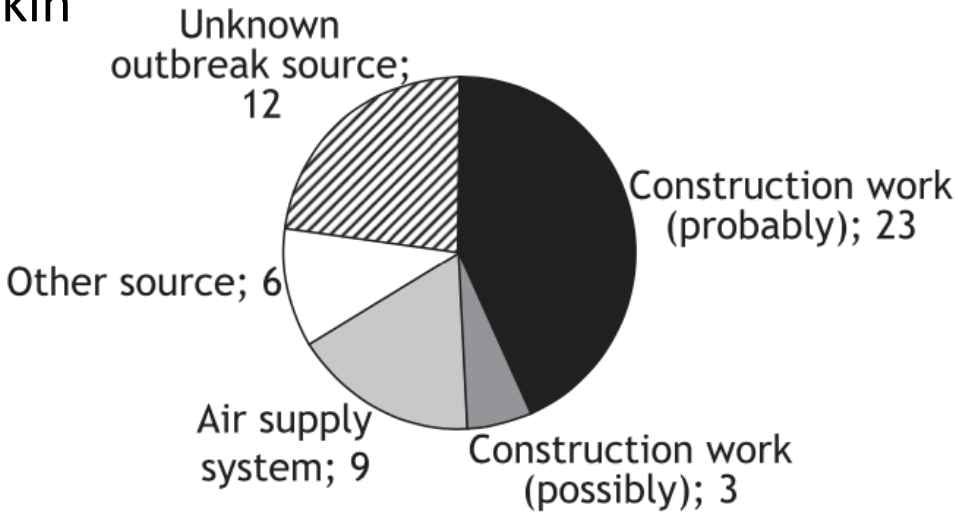


Lamoth F, *et al*. Clin Infect Dis 2017; 64: 1619-21; Andes. Clin Infect Dis. 2012;54:1110. Nivoix. Clin Infect Dis. 2008;47:1176. Park. Emerg Infect Dis. 2011;17:1855. Cortez. Clin Microbiol Rev. 2008;21:157.

Nosocomial *Aspergillus* outbreaks

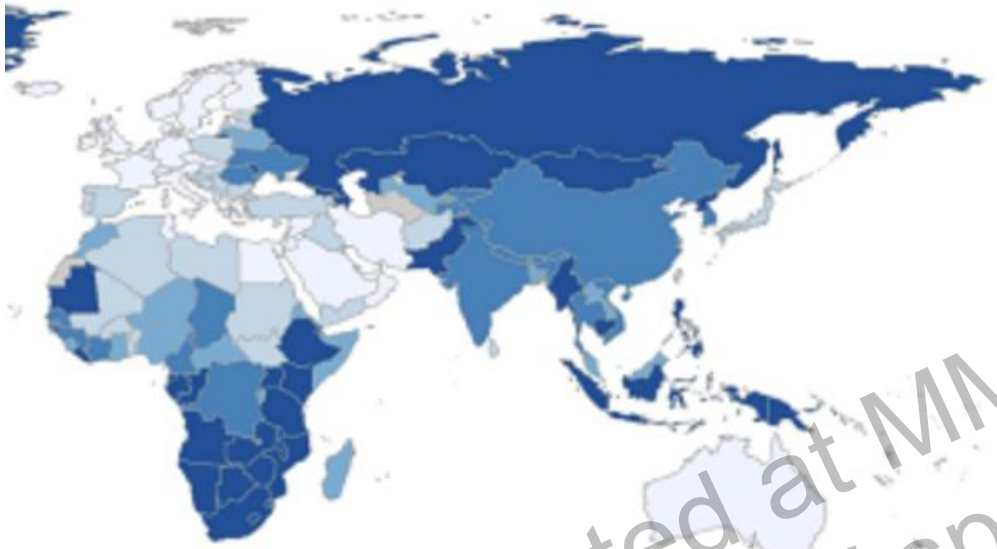
- **Review of 53 outbreaks involving 458 patients**
  - 33 outbreaks involving 299 patients **(65%) occurred in HSCT recipients/haematological malignancies**
  - SOT (10%) – predominantly renal transplant recipients
  - Patients without severe immunodeficiency (8%)
  - Patients on high-dose steroids (3%)
- **Lung was common site of infection;** 5% at surgical site or skin
- ***A. fumigatus* & *A. flavus*** common pathogen
- **Mortality – 57.6%**

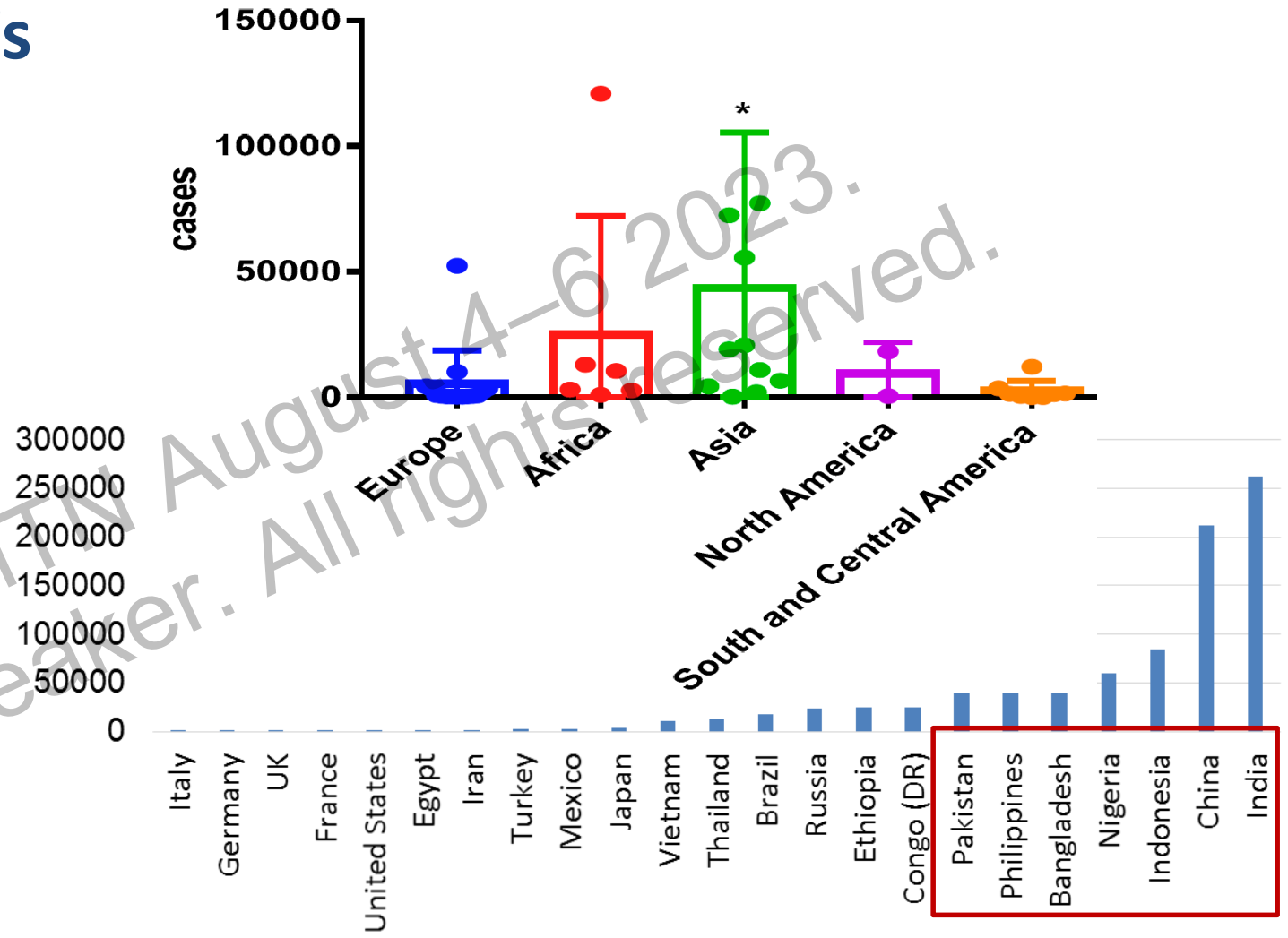
Aspergillus spp. below 1 CFU/m³ were sufficient to cause infection in high-risk patients



Vonberg & Gastmeier. J Hosp Infect 2006; 63: 246-54; Suleyman & Alangaden. Infect Dis Clin N Am 2021; 35: 1027-53.

Chronic pulmonary aspergillosis





Estimation of CPA at 2019 ~3 million: 1.2 million patients post-tuberculosis, >410,000 patients as a complication of ABPA, & ~72,000 patients as a complication of pulmonary sarcoidosis

Bongomin F, *et al.* J Fungi 2020; 6: 75; Bongomin F, *et* al. J Fungi 2017; 3: 57; van der Torre MH, *et al.* J Fungi 2021; 7: 152; Denning DW, *et al*. Eur Respir J 2016; 47: 45-68

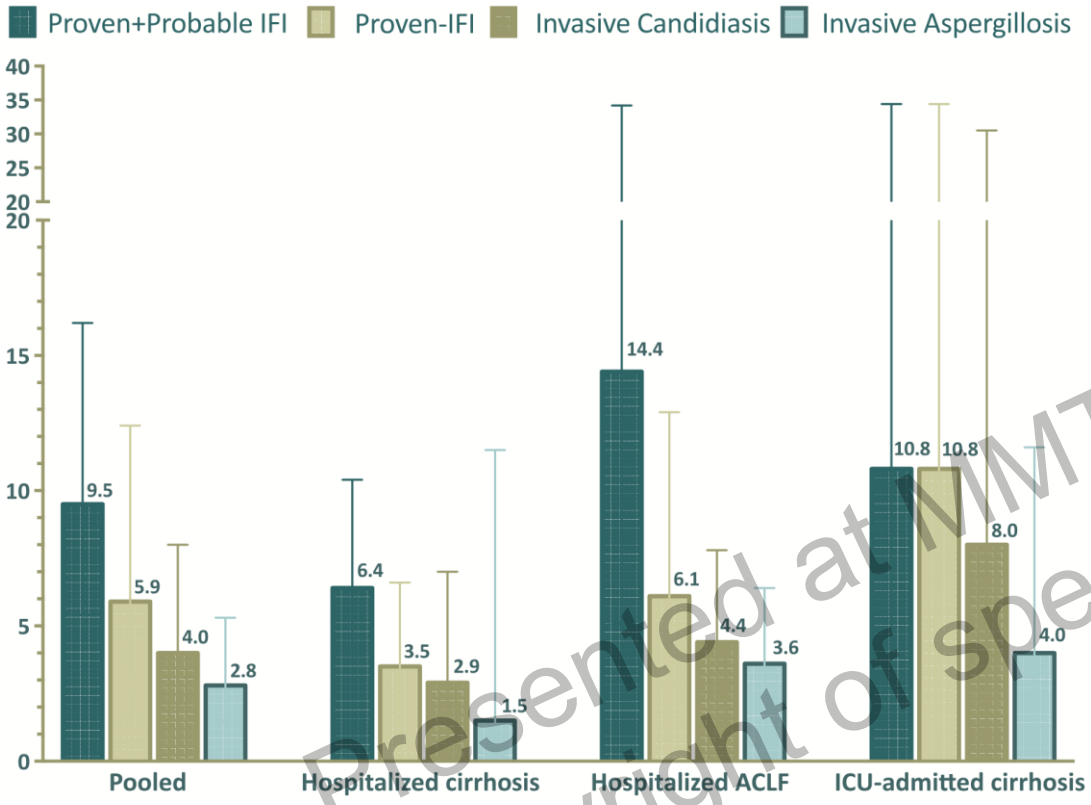
New risk factors/patient groups

- **Prolonged ICU stay, COPD, structural lung defect, chronic liver & kidney disease, ARDS**
- **Influenza & COVID-19 association**
- **TNFα blockers (infliximab, adalimumab, etanercept, golimumab, certolizumab pegol) – 6-9 IA cases/100,000 persons**
- **Tyrosine kinase inhibitor (ibrutinib), anti-B cell inhibitors (CD 20, CD 22, CD 30), anti-rejection (CD 52, CD 25) antibody, check-point inhibitors**

Molecule	Target	Disease indications	Fungal infections
Dasatinib	BCR-ABL	Phc +ve CML/ALL(imatinib-resistant)	PCP
Ibrutinib	Btk, Irk, Bmx, Blk	CLL; MCL; Waldenström macroglobulinaemia; steroid-refractory GvHD	CNS aspergillosis, cryptococcosis, PCP, histo, mucormycosis, fusariosis
Ruxolitinib	JAKs 1/2	Myeloproliferative disease (including mycelo-fibrosis, polycythaemia rubra vera)	Cryptococcosis, PCP
Tofacitinib	JAKs 1/3	Rheumatoid arthritis, psoriasis arthritis	Candidiasis, PCP, cryptococcosis
Idelalisib	PI3Kδ	CLL, follicular lymphoma (treatment refractory)	PCP, aspergillosis

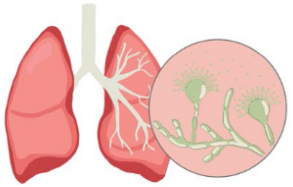
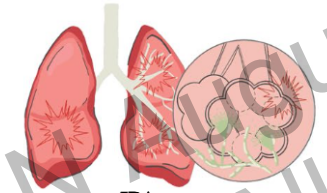
Bassetti & Bouza. J Antimicrob Chemother 2017; 72 (Suppl 1): i39-i47; Bernardes & Hohl. Curr Clin Microbiol Rep 2020; 7: 142-149; Cadena J, *et al*. Infect Dis Clin N Am 2021; 35: 415-434; Chamiols G, *et al.* Clin Infect Dis 2018; 66: 140-148; Edes CP & Armstrong-James DPH. Med Mycol 2019; 57: S307-317

IFI in cirrhosis patients
(meta-analysis of 38 studies)



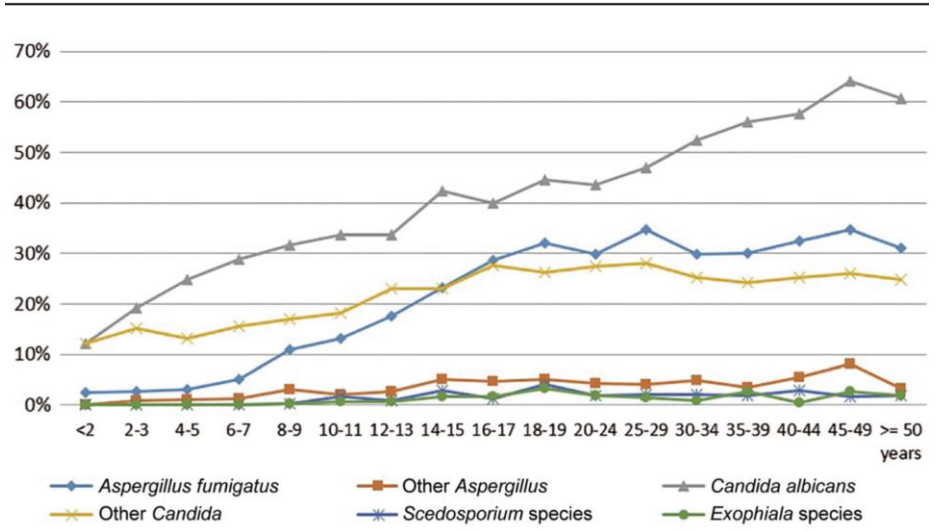
Verma N, *et al*. Mycoses 2022; 65: 266-284; Tiew PY, *et al*. Mycopathologia 2021; 186; 623-638; Schwarz C, *et al.* Mycopathologia 2021; 186; 639-653

IFI in COPD & bronchiectasis

Conditions	COPD	Bronchiectasis
 Aspergillus Colonisation	• 13-29% of sputum in COPD patients [13-15] • Risk factors: Exacerbations in the previous year, concomitant *Pseudomonas* isolation and inhaled corticosteroid use & dosage [13-14, 17]	• Associated with frequent exacerbations in South-East Asia [59] • Geographic variability in conidial burden where Asian and non-Asian patients assessed [59]
 IPA	• ↑ Risk in hospitalized COPD patients [22] • Risk factors: ICU admission, chronic heart failure, prior antibiotic and steroid treatment [12, 19, 41-45] • ↑ Mortality [12, 42-43, 46-47]	• Described largely in the context of existing bronchiectasis [75, 81] • Lack of data on direct association, but may manifest in certain aetiologies of bronchiectasis such as primary immuno-deficiency syndromes [75, 81, 88-89]

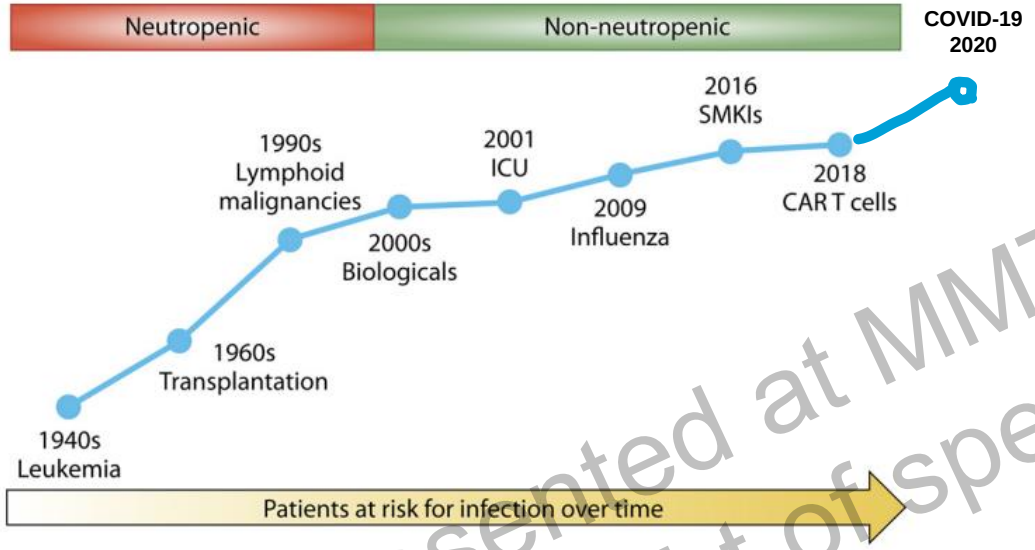
Annual rate of IPA in hospitalized COPD - between 1.3 & 3.9%

Prevalence of fungi in German cystic fibrosis (CF) registry



Risk factors for IFIs in ICU

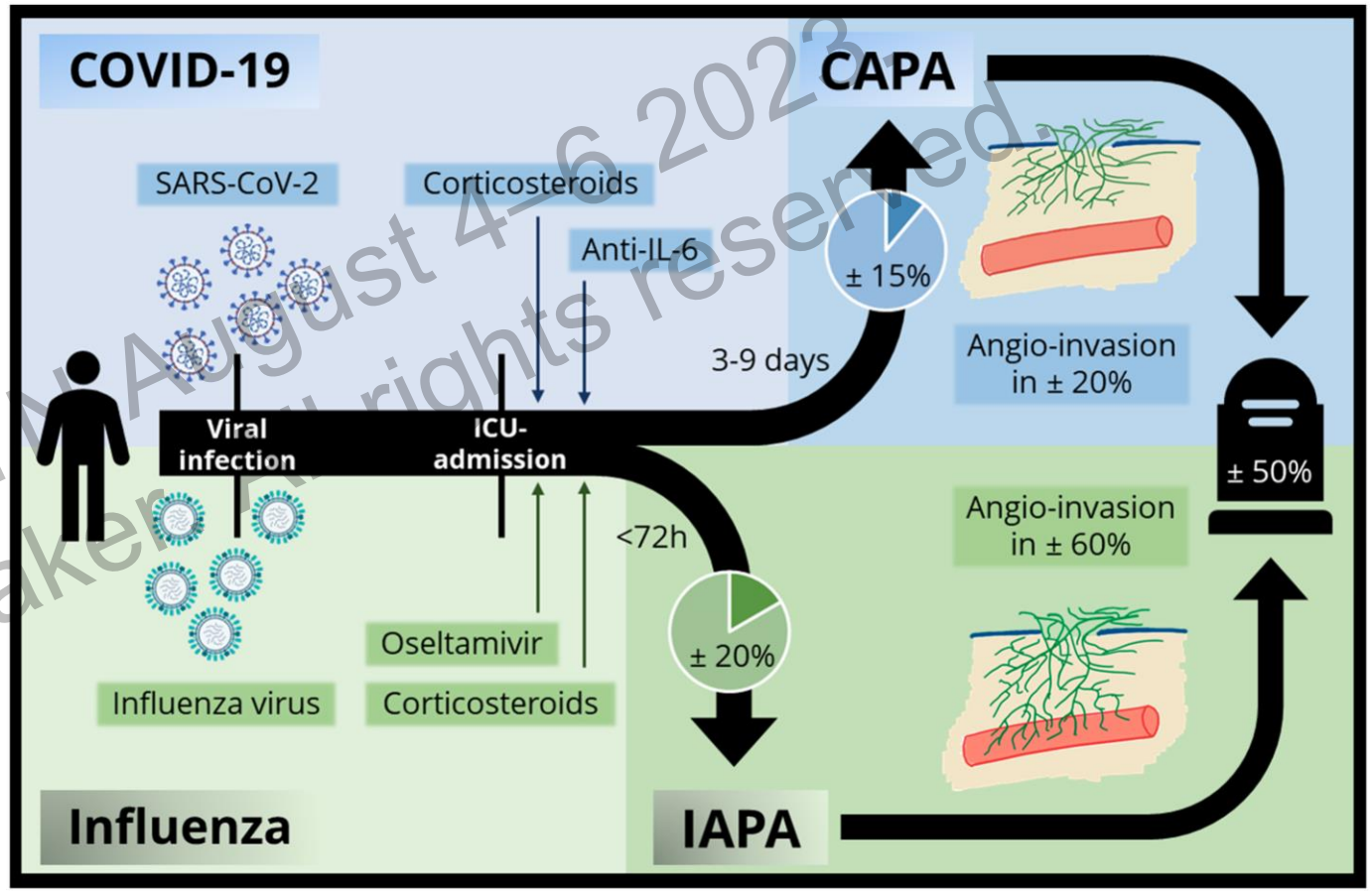
Epidemiological trends of IA



SMKI, small-molecule kinase inhibitor; CAR T cells, chimeric antigen receptor T cells.

Bassetti M, *et al.* Intensive Care Med 2017; 43: 1225; Latge & Chamilos Clin Microbiol Rev 2020; 33: e00140-18; Meersseman W, *et al*. Clin Infect Dis 2007; 45: 205-16; Rudramurthy SM, *et al*. Indian J Med Microbiol 2016; 34: 529-32

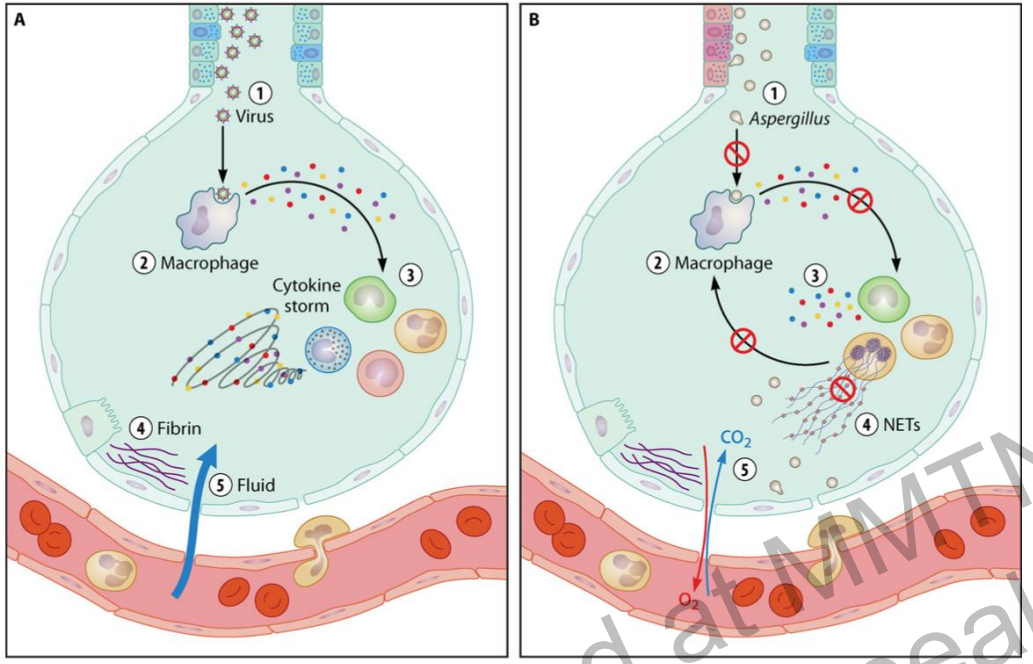
Virus associated pulmonary aspergillosis



Feys S, *et al*. J Fungi 2021; 7: 1067

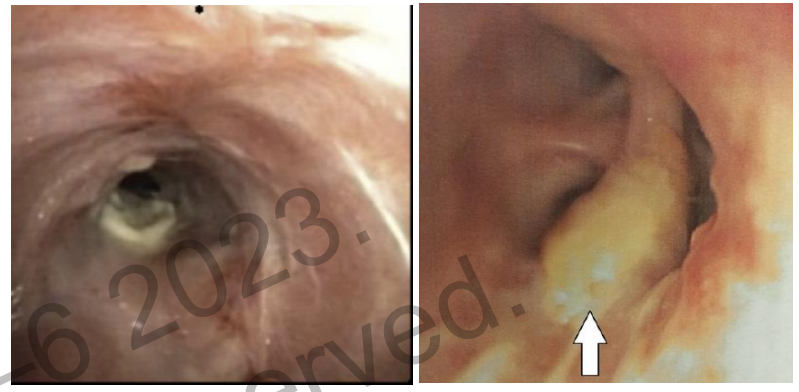
Influenza-*Aspergillus* co-infections

Salazar F, *et al.* Clin Microbiol Rev 2022; 35: e00094-21



(A) Entry of virus into alveolar space. (1) Virus infects airway epithelium. (2) Alveolar macrophages produce cytokines. (3) Cytokines attract more immune cells (neutrophils & monocytes). (4) Damage further through the formation of fibrin & scar tissue. (5) Weakened blood vessels allow fluid to seep in & fill the lung cavities, leading to respiratory failure.

(B) Entry of fungi into the alveolar space. (1) damaged epithelium facilitates invasion. (2) alveolar macrophages impaired. (3) Recruitment of neutrophils also affected. (4) Loss of neutrophil mediated fungal killing. (5) Fibrinous material can cause the obstruction of small airways, decreasing oxygen & carbon dioxide diffusion, leading to hypoxia

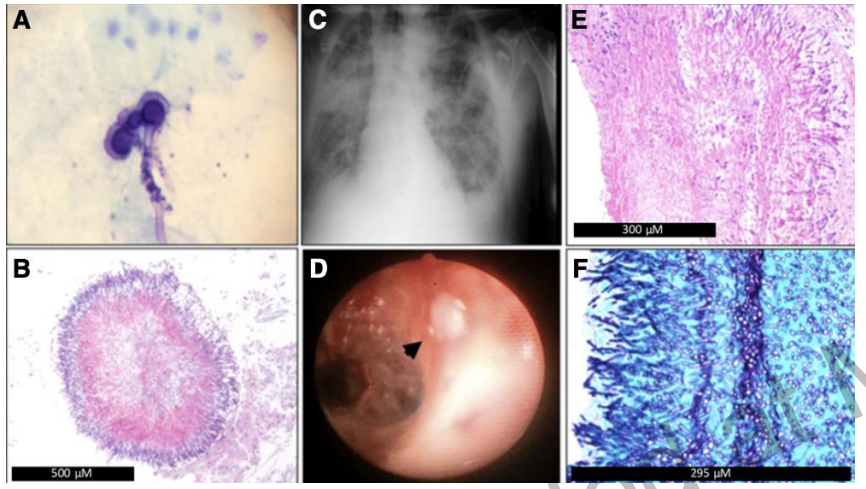


Factor	Influenza associated pulmonary aspergillosis
Incidence	**10% of ICU patients**
Risk factors	male sex, smoking, chronic lung disease, corticosteroid (within 28d) , SOT & haematological malignancy
Tracheobronchitis	**Up to 55% patients**
Aspergillus diagnostic	**BAL GM positive in > 88%**
	Serum GM positive in 65%
Mortality	51%

Shi C, *et* al. Mycoses 2022; 65: 152-163; Salmanton-García J, *et al.* Emerg Infect Dis. 2021; 27: 1077–86

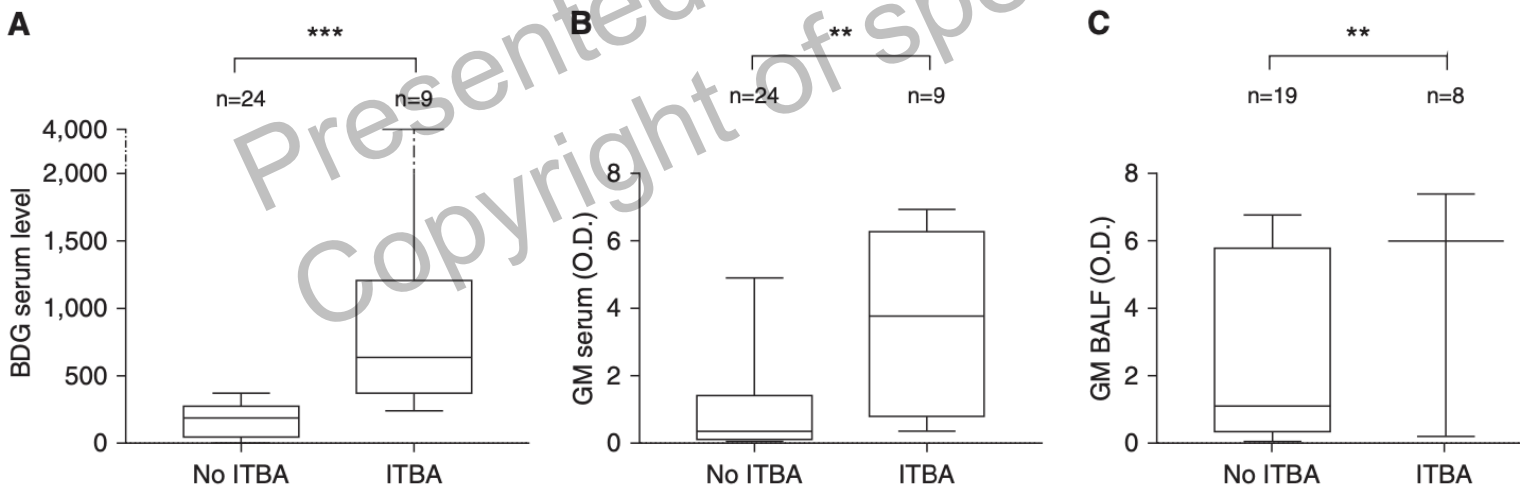
Invasive tracheobronchial aspergillosis (ITBA) in ICU patients with severe influenza

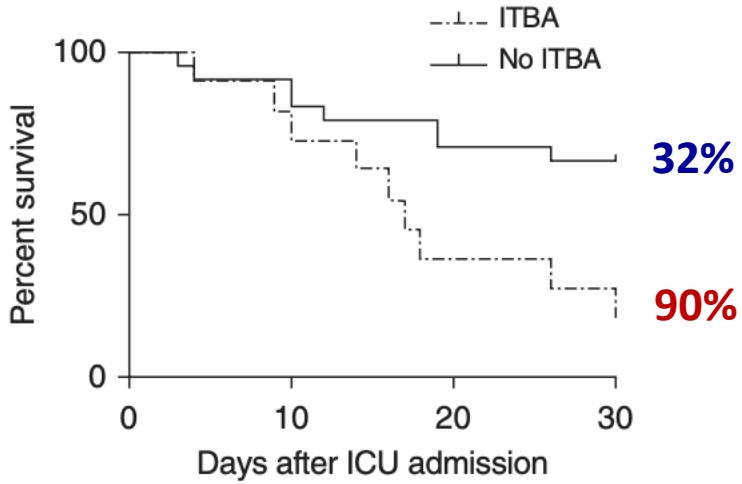
- Multi-centre, retrospective (2010-2019) observation study; 3 ICUs in France
- Eligible: admitted in ICU with respiratory failure, diagnosis of influenza & IPA + bronchoscopy



ITBA represented 27% of all IAPA cases

- **No diagnostic delay: screening upon admission in ICU**
- **Higher severity score in ITBA**
- **Shorter delay between diagnosis of influenza & IPA in ITBA**
- **Future study needed for combination of antifungal**





Nyga R, *et al*. AJRCCM 2020; 202; 708-16

Rare yeasts: outbreaks

Strongly recommended | Marginally recommended | Moderately recommended | Recommended against

Pathogen/fungal group	First line	First line alternative	Second line	Avoid	Central venous line removal
Geotrichum spp.	LAMB ± 5FC	VCZ	Drug class not used as first line	Echinocandins	No specific data Moderately recommended
Saprochaete/Magnusiomyces spp.	LAMB ± 5FC	VCZ	-	Echinocandins	Yes
Trichosporon spp.	VRZ	FLU	LAMB/DAMB	Echinocandins	Yes
Kodamanea ohmeri	LAMB/DAMB	Echinocandins	-VCZ/FLU/Azole	-	Yes
Malassezia spp.	LAMB	DAMB	-	-	Yes
Pseudazyma spp	LAMB	VCZ	ABLC	FLU, Echinocandin	Yes
Rhodotorula spp.	LAMB ± 5FC	DLAB ± 5FC	-	Itraconazole/ Echinocandin	Yes
Saccharomyces spp.	LAMB/DAMB	FLU/Echinocandins (CASPO or MICA)	Drug class not used in first line	-	Yes
Sporobolomyces spp,	LAMB	VCZ	No data	FLU/Echinocandins	Yes

Chen SCA, *et al.* Lancet Infect Dis 2021; 21: E375-E386

Emergence of rare moulds

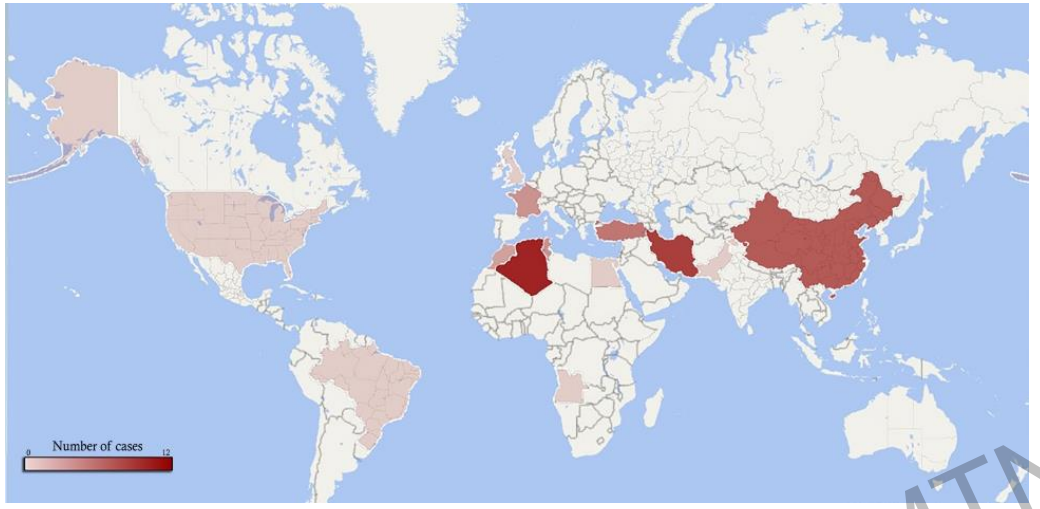
Strongly recommended | Moderately recommended | Marginally recommended | Recommended against

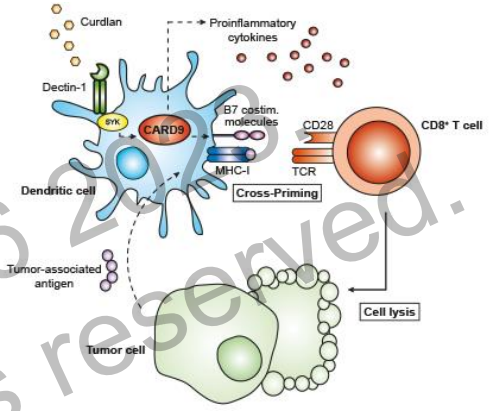
	First-line	First-line alternative	Second-line	Treatments to avoid	Salvage treatments
Fusariosis	Voriconazole, or voriconazole plus L-AmB, or voriconazole plus ABLC	L-AmB, or ABLC	Isavuconazole, or posaconazole	D-AmB	Posaconazole
Lomentosporosis	Voriconazole plus terbinafine	Voriconazole	Isavuconazole, or posaconazole	L-AmB	Voriconazole
Scedosporiosis	Voriconazole	Voriconazole in combination with L-AmB, ABLC, echinocandins, or terbinafine	Isavuconazole, or posaconazole, or itraconazole	L-AmB	Voriconazole echinocandins, or posaconazole
Phaeohyphomycosis: localised infection	Voriconazole	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: cutaneous or subcutaneous infection	Itraconazole or voriconazole	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: disseminated infection	Posaconazole, or voriconazole plus echinocandins, or voriconazole plus terbinafine	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: *Exserohilium rostratum*	Voriconazole with or without L-AmB	..	L-AmB plus triazoles other than voriconazole	D-AmB	..
Rasamsonia spp	Caspofungin, or micafungin	Caspofungin plus L-AmB or posaconazole, or micafungin plus L-AmB or posaconazole	..	Azole monotherapy	..

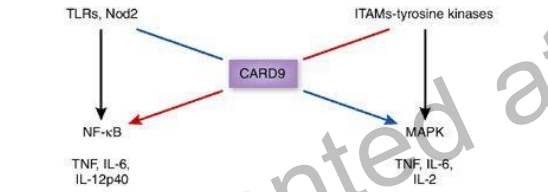
ABLC, amphotericin B lipid complex; (L-/D-) AmB, (liposomal/deoxycholate) amphotericin B.
Hoenigl M et al. *Lancet Infect Dis* 2021;21:e246–e257.

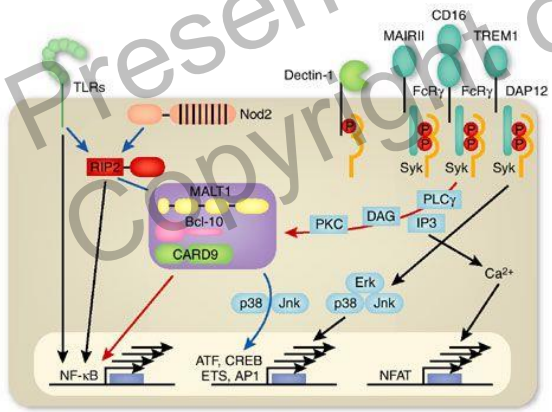
Slide from Martin Hoenigl

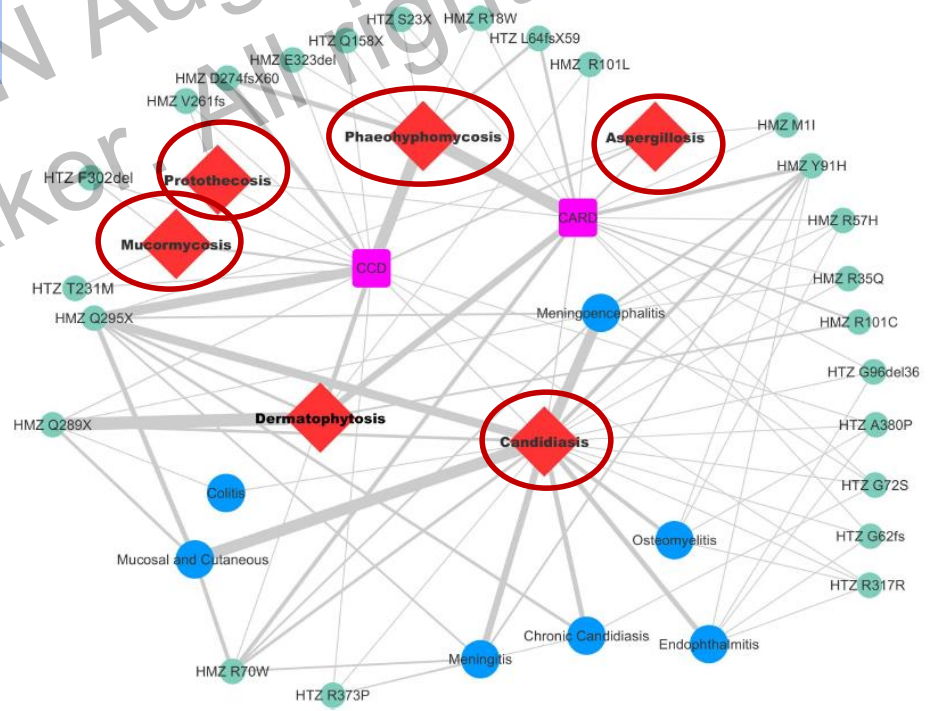
CARD 9 deficiency linked many fungal infections











Vaezi A*, et al*. Front Microbiol 2018; 9: 2434

Mycobiome in gut

- Human mycobiome (the fungi and their genome) in healthy individuals **GI tract contains 66 fungal genera and 184 fungal species**, with *Candida* as the dominant fungal genera
- **Diet is major factor** influencing colonization of fungi in the GIT. ***Candida* is positively associated with dietary carbohydrates**, but are negatively correlated with dietary amino acids, proteins, & fatty acids
- Although fungi are associated with a number of GI diseases, **mycobiome has mainly been focused on IBD and graft-versus-host disease**
- **Dysbiosis of intestinal fungi** can cause **invasive infections & inflammatory bowel diseases (IBD)**
- **However, it is not clear whether dysbiosis of the mycobiome is a cause, or a result of IBD**
- Compared to non-inflamed intestinal mucosa, the abundance and diversity of **fungi is significantly increased in the inflamed mucosa**
- **Most common fungal infections in patients with IBD were caused by *Candida* species**

Li J, *et al.* Microb Ecol 2018; 75: 821-829; Stamatiades GA, *et al*. Mycoses 2018; 61; 366-76

IBD - Interaction of intestinal fungi & immune cells

IBD	Sample	Intestinal fungi	Histopathologic characteristics	Potential association with immune cells and/or cytokines
Crohn's disease (CD) [37]	Feces	*Candida albicans* (14.2%), *Saccharomyces cerevisiae* (14.0%), *Cryptococcus neoformans* (8.6%), *saccharomyces castellii* (6.6%), *Gibberella moniliformis* (6.1%), *Aspergillus clavatus* (5.0%), *others* (40.5%)	Crypt dilation, goblet cell depletion, mixed cell infiltration, involving mainly mononuclear cells and lymphocytes, and injury with ulceration	Fungi→ PRRs(CLRs/TLRs)→ NF-κB→T helper cells activated→production of IL-17/TNF-α/ IFN-γ
Ulcerative colitis(UC) [65]	Sample from pouch endoscopic biopsies	*Candida* (6%), *Penicillium* (61.5%), *Saccharomyces* (24.1%) uncultured *Ascomycetes*, *Basidiomyeetes* (7.7%).	Crypt destruction, mucosal erosion and inflammatory cell infiltration	CARD9,IL-17,IL-22, NF-κB, nuclear factor of activated T cells(NFAT)
Dextran sulfate sodium (DSS)-induced colitis [16]	Colonic samples	*Aspergillus*, *Penicillium*, *Cladosporium*, *Wickerhamomyces*, *Alternaria*, *Wallemia*, *Emericella*, *Cryptococcus*, *Phialemonium*, *Fusarium*, *Candida*, unidentifed *Saccharomycetales*	Mucosal and submucosal inflammation, bowel wall thickening, a moderate level of lymphocyte infltration and regeneration with crypt depletion	Two key tight-junction proteins (occludin and ZO-1) were decreased, IL-17A, IL-23, and TNF-α were strikingly increased in colonic mucosa samples

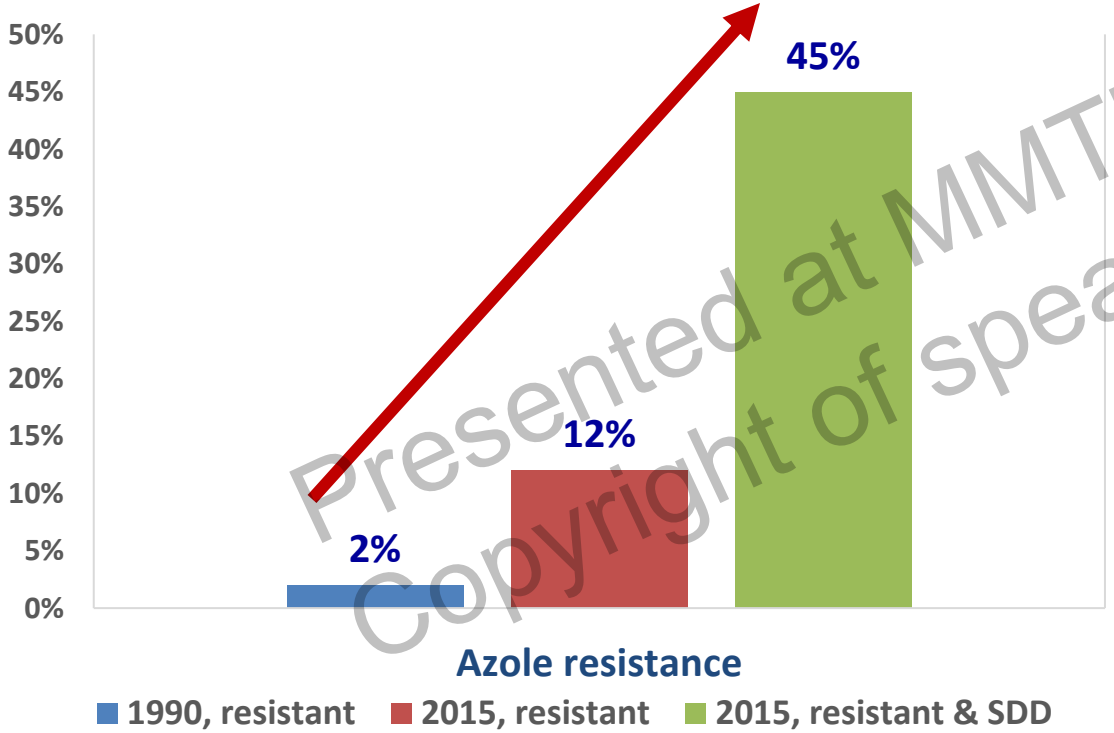
Li J, *et al.* Microb Ecol 2018; 75: 821-829

Azole susceptibility profile of *Candida*

India data

- ***C. tropicalis* – 5-41.6%**
- ***C. albicans* - 9.4-40%**

(Including resistant & SDD)

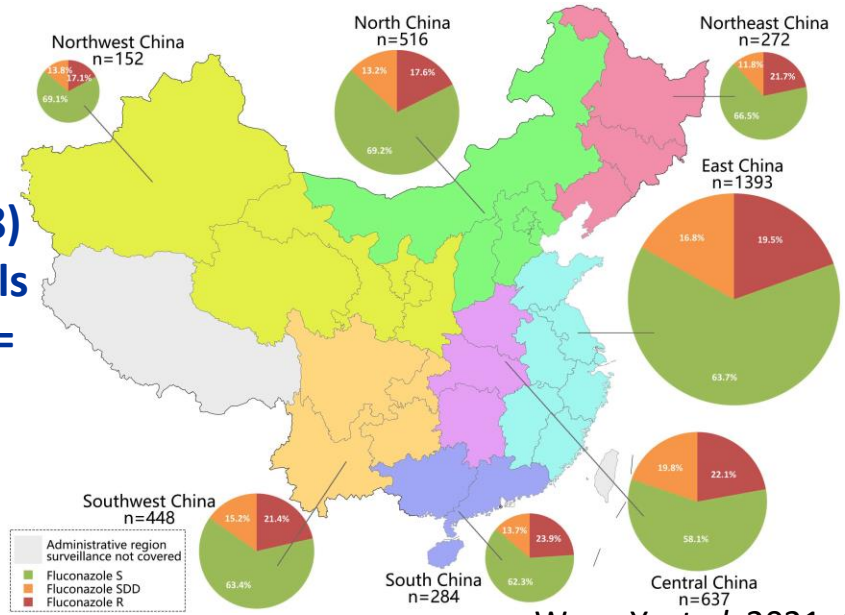


Chakrabarti A, *et al.* Intensive Care Med 2015; 41: 285

Organism	Fluconazole (R + SDD)	Voriconazole (R + SDD)	Itraconazole (R + SDD)	reference
Malaysia				
C. albicans	**5.6%**	**1.4%**	**2.8%**	J Med Microbiol 2011; 60: 1312
C. tropicalis	**7.4%**	**0.0%**	**3.7%**	
China				
C. tropicalis	**14.1%**	**7.1%**	**96.1%**	JAC 2013: 68: 778
C. albicans	**34.6%**	**7.7%**	**40.4%**	JAC 2014; 69: 162

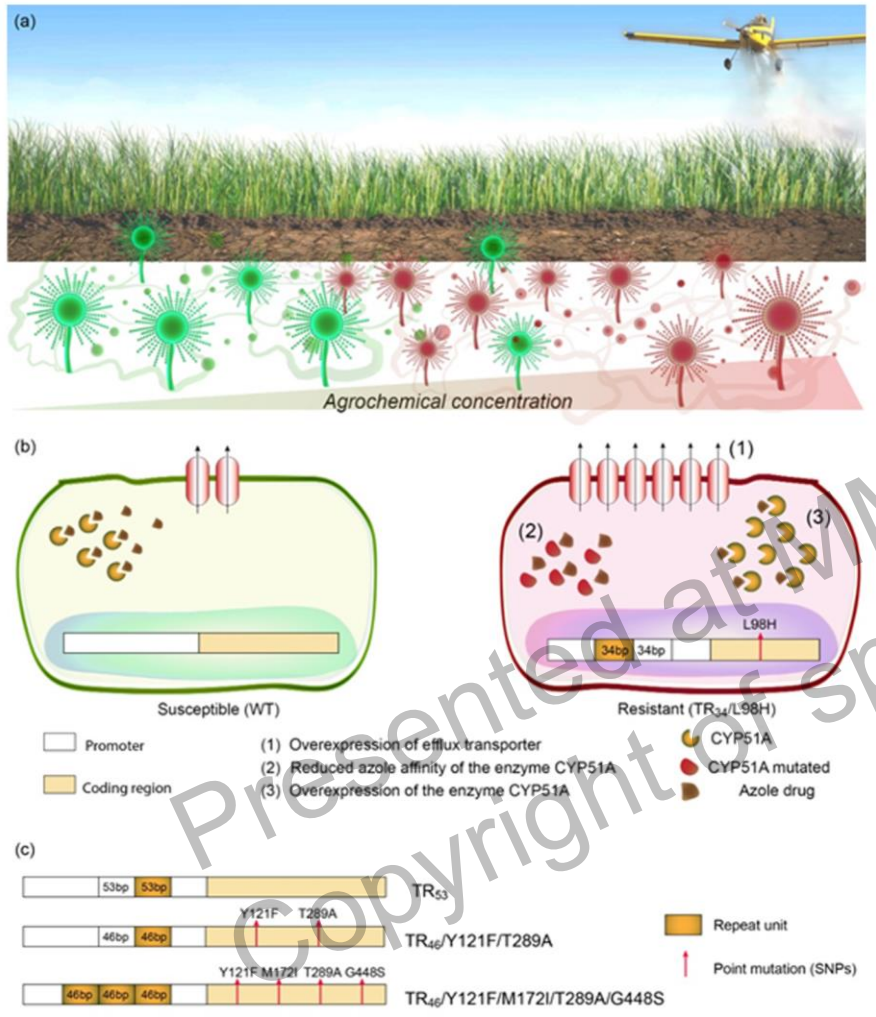
China: 9 year data (2009-2018) from 87 hospitals - *C. tropicalis* (n= 3702)

R & SDD ~42%

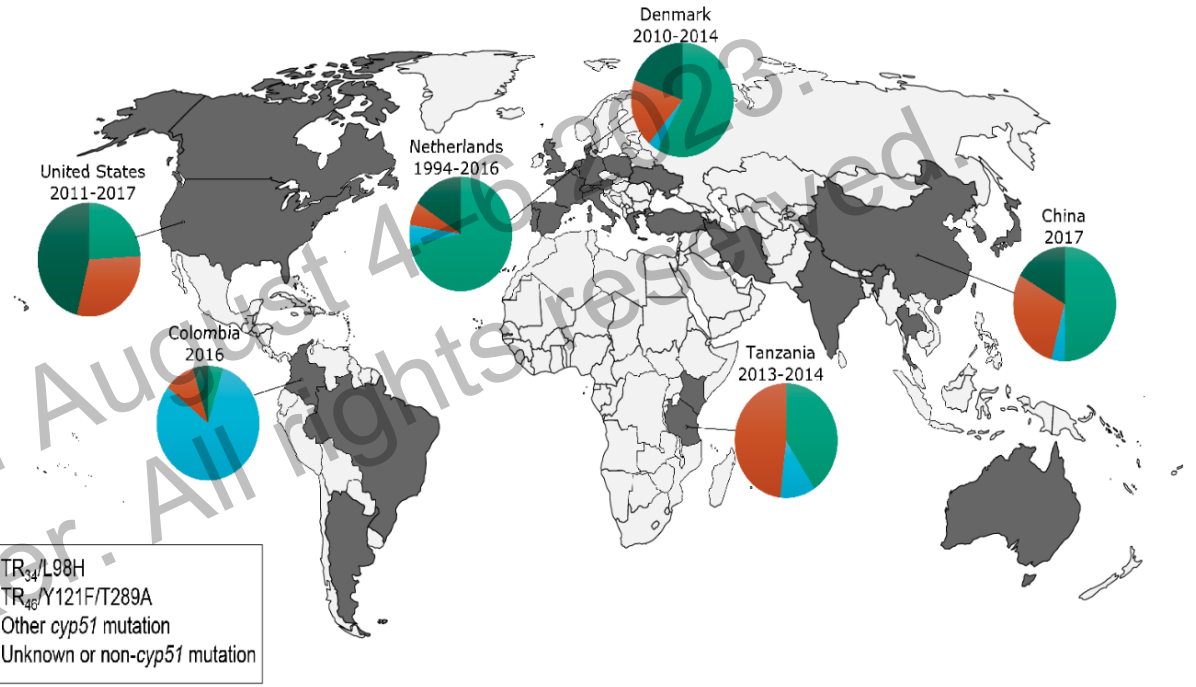


Wang Y, *et al.* 2021; 12: 702839

Aspergillus azole resistance



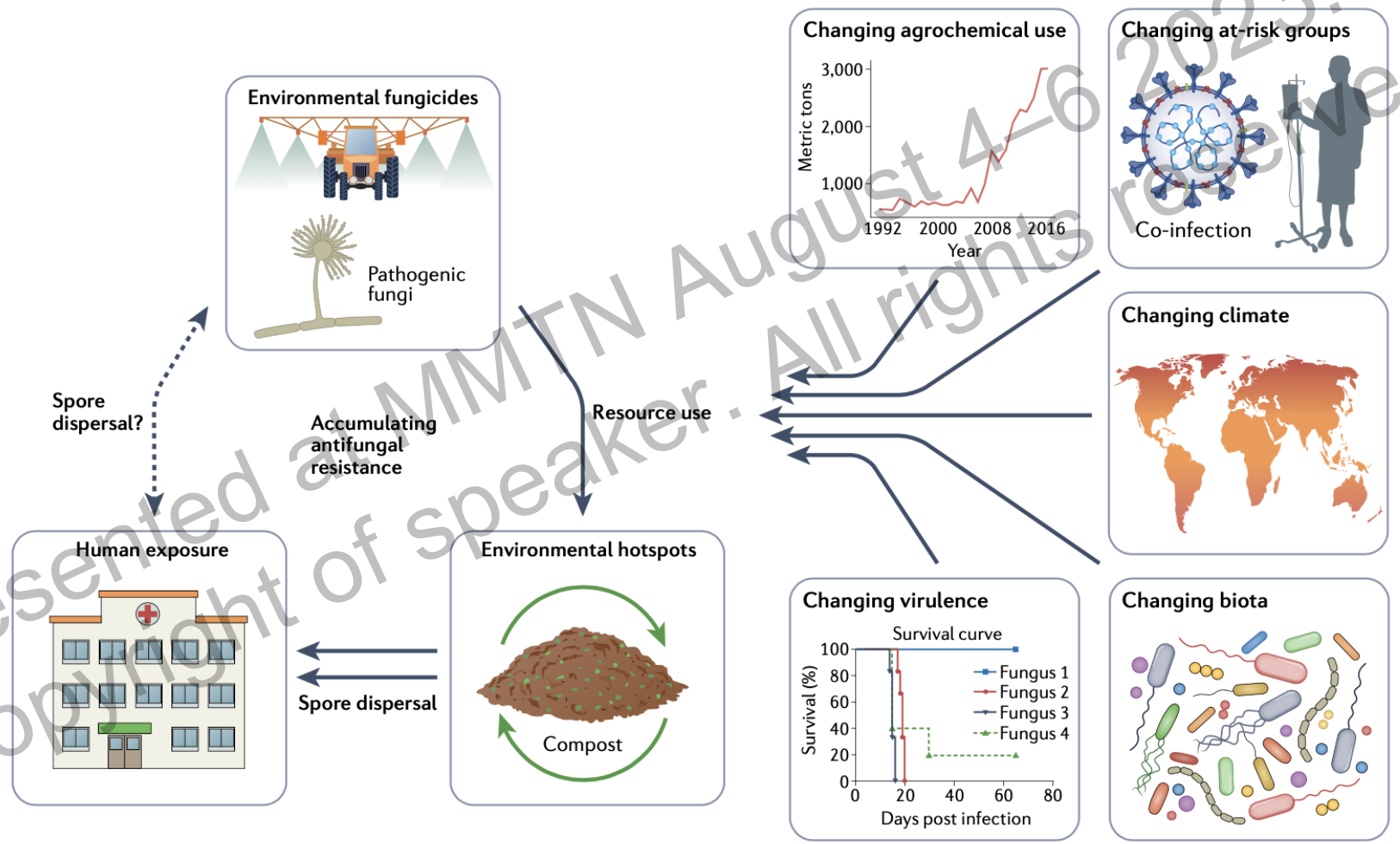
Countries reporting resistance & mechanism of resistance



- **Increasingly recognized** : clinical, environmental isolates
- **In European countries - 0.6% to 30%, having reached the highest rate (>20%) in the Netherlands, UK, & Germany**
- **China (5.5%), India (1.7%), Iran (3.5%), Japan (12.7%), Thailand (3.2%), Australia (2.6%), and the United States (0.6% to 11.8%)**

Bastos RW, *et al.* PLoS Pathogen 2021; 17: e1010073; Friedman & Schwartz. J Fungi 2019; 5: 67; Verweij PE, *et al.* Clin Infect Dis 2016; 62: 362-368

Emerging antifungal resistance & environment – one health drivers



Fischer MC, *et al*. Nature Rev Microbiol 2022; 20: 557-571

Azole susceptibility (UK National Mycology Reference Laboratory)

		MIC (mg/L)									
	Voriconazole	0.03	0.06	0.125	0.25	0.5	1	2	4	8	≥16	%R
2006–2016 *	*Aspergillus fumigatus* (2384)	1	13	309	**1631**	299	66	45	13	-	7	2.7
2019–2020 *	*Aspergillus fumigatus* (209)	1	2	4	31	**96**	20	29	17	4	5	26.3

		MIC (mg/L)										
	Itraconazole	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**≥16**	**%R ****
2006–2016 *	*Aspergillus fumigatus* (2268)	22	453	629	**632**	370	53	24	21	9	55	4.8
2019–2020 *	*Aspergillus fumigatus* (135)	–	4	27	**39**	34	4	7	8	7	5	20

		MIC (mg/L)										
	Posaconazole	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**≥16**	**%R ****
2006–2016 *	*Aspergillus fumigatus* (396)	111	**150**	65	37	21	8	2	–	1	1	8.3
2019–2020 *	*Aspergillus fumigatus* (187)	2	**65**	33	18	37	24	7	1	–	–	**36.9**

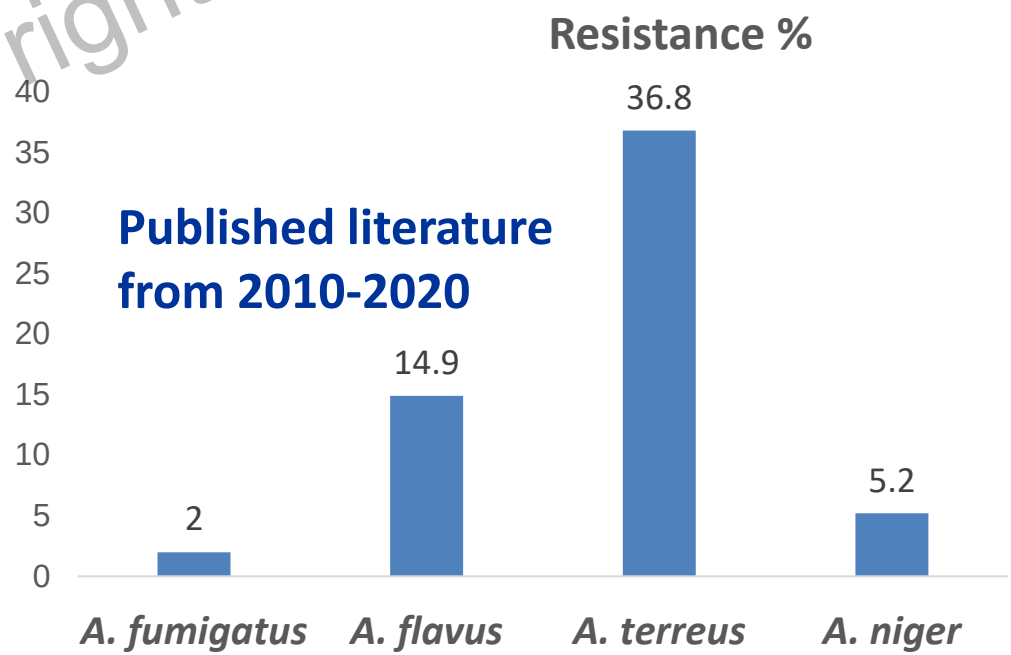
		MIC (mg/L)										
	Isavuconazole	**≤0.03**	0.06	0.125	0.25	0.5	1	2	4	8	≥16	%R *
2019–2020 *	*Aspergillus fumigatus* (339)	-	2	2	70	**92**	76	41	33	11	12	28.6

Borman AM, *et al*. J Fungi 2021; 7: 271

Amphotericin B

UK National Mycology Reference Laboratory

	MIC (mg/L)										
Amphotericin B	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**>16**	**%R ****
Aspergillus fumigatus (201) *	–	–	22	**99**	63	17	–	–	–	–	0



Borman AM, *et al*. J Fungi 2021; 7: 271

Fakhim H, *et al*. J Med Mycol 2022; 32: 101310

Changes in landscape of *Aspergillus* spp. infection (10-15% of all IFI)

Species	Disease	Resistance
Emericella nidulans	IA in CGD	AmpB
E. Quadrilineata	IA in CGD & IA	?caspofungin
A. calidoustus	IA	?caspofungin
A. terreus	IA	AmpB
A. tubingensis	IA, ear infection	Azoles
A. lentulus	IA	Azoles, echinocandins, AmpB
A. aliaceus	IA	? caspofungin & AmpB
A. novofumigatus	IA	Azoles
A. ustus	IA	Azoles, echinocandins, AmpB
A. felis	IA	Voriconazole & caspofungin

- **Change due to expanding use of *Aspergillus*-active antifungal in prophylaxis, empirical & targeted therapy**
- **Emergence of resistant cryptic *Aspergillus* spp (*A. lentulus, A. ellipticus* etc.) in ~10%**

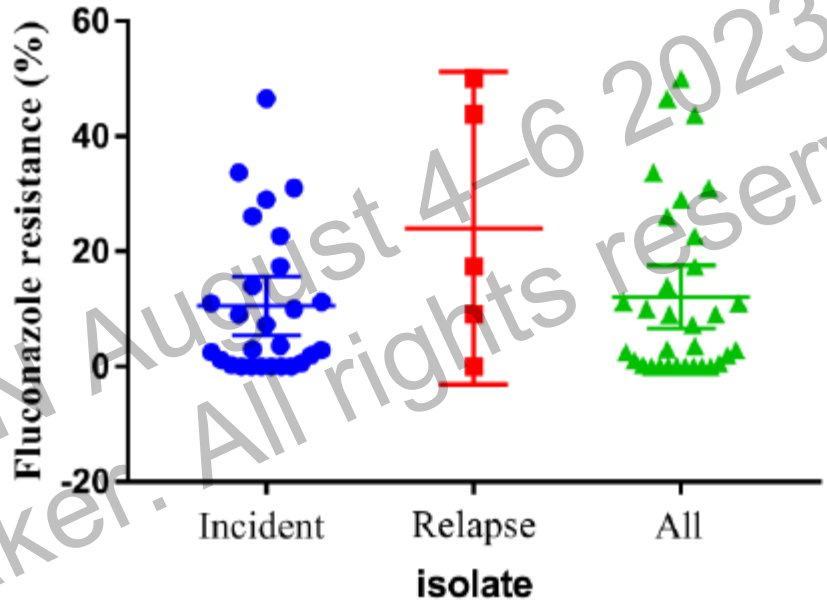
Cryptic species of *Aspergillus*

- 9.2% cryptic species in 109 clinically relevant aspergillosis
- *A. lentulus, A. ellipticus, A. alliaceus, A. nominus, A. tubingensis, A. montevidensis*
- Majority had immunosuppression & ICU admission
- Mortality – 40%
- High MIC to azoles & amphotericin B

Lass-Florl & Cuenca-Estrella. J Antimicrob Chemother 2017; 72 (Suppl 1): i5-i11; Fernandez-Pittol M, *et al*. Rev Iberoam Micol 2022; 39: 44-49

Fluconazole resistance in *Cryptococcus neoformans*

- A total of 4,995 *Cryptococcus* isolates from 3,210 patients were evaluated



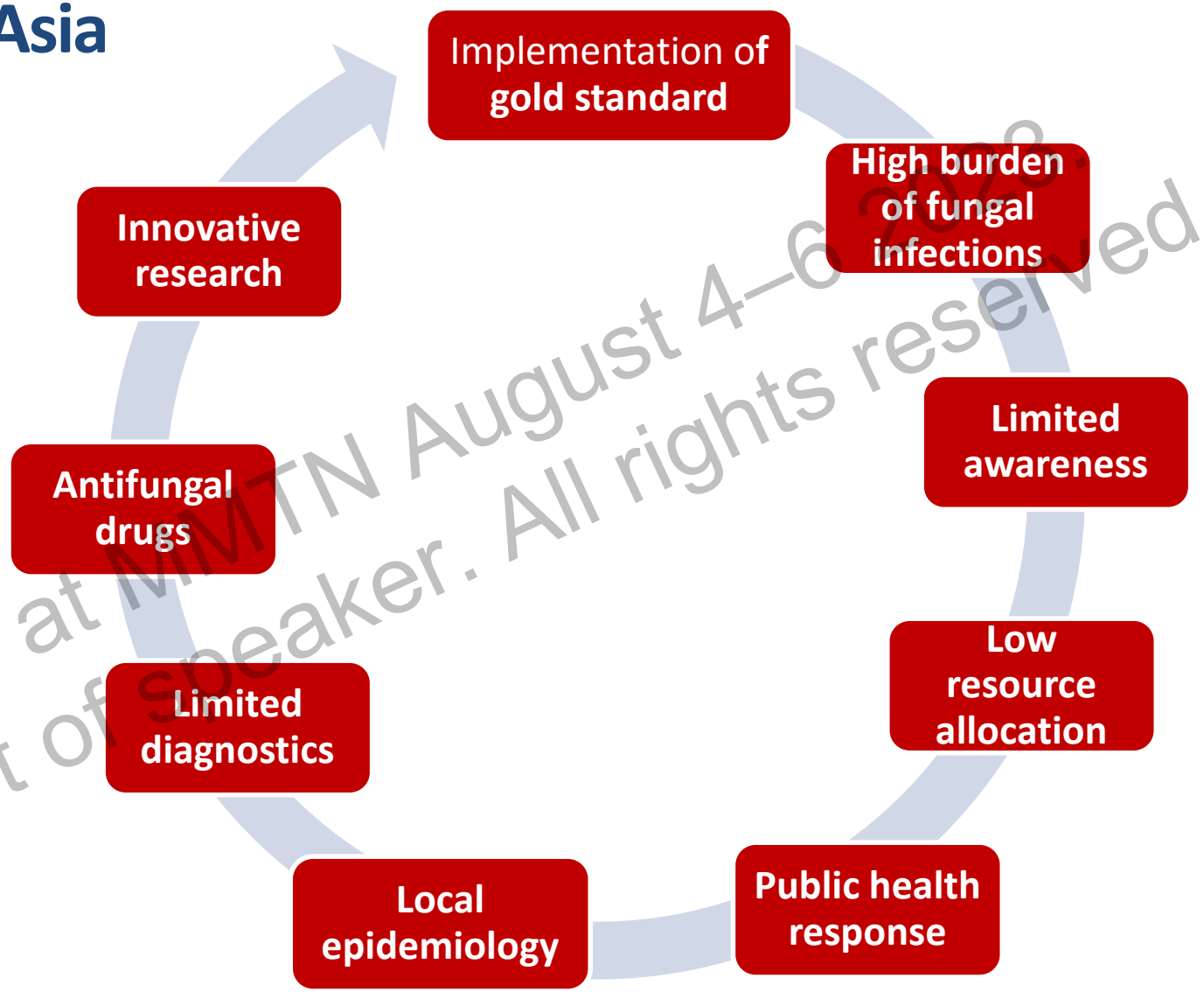
- **Mean prevalence of resistance is 12.1%**
- Mean fluconazole resistance was **10.6%** (95% CI: 5.5% - 15.6%) **for the incident isolates** (n=4,747), and **24.1%** (95% CI: -3.1% - 51.2%) **for the relapse isolates** (n=248).

Bongomin F, *et al*. Mycoses. 2018; 61: 290

Specific challenges in Asia

Challenges in diagnosis & management

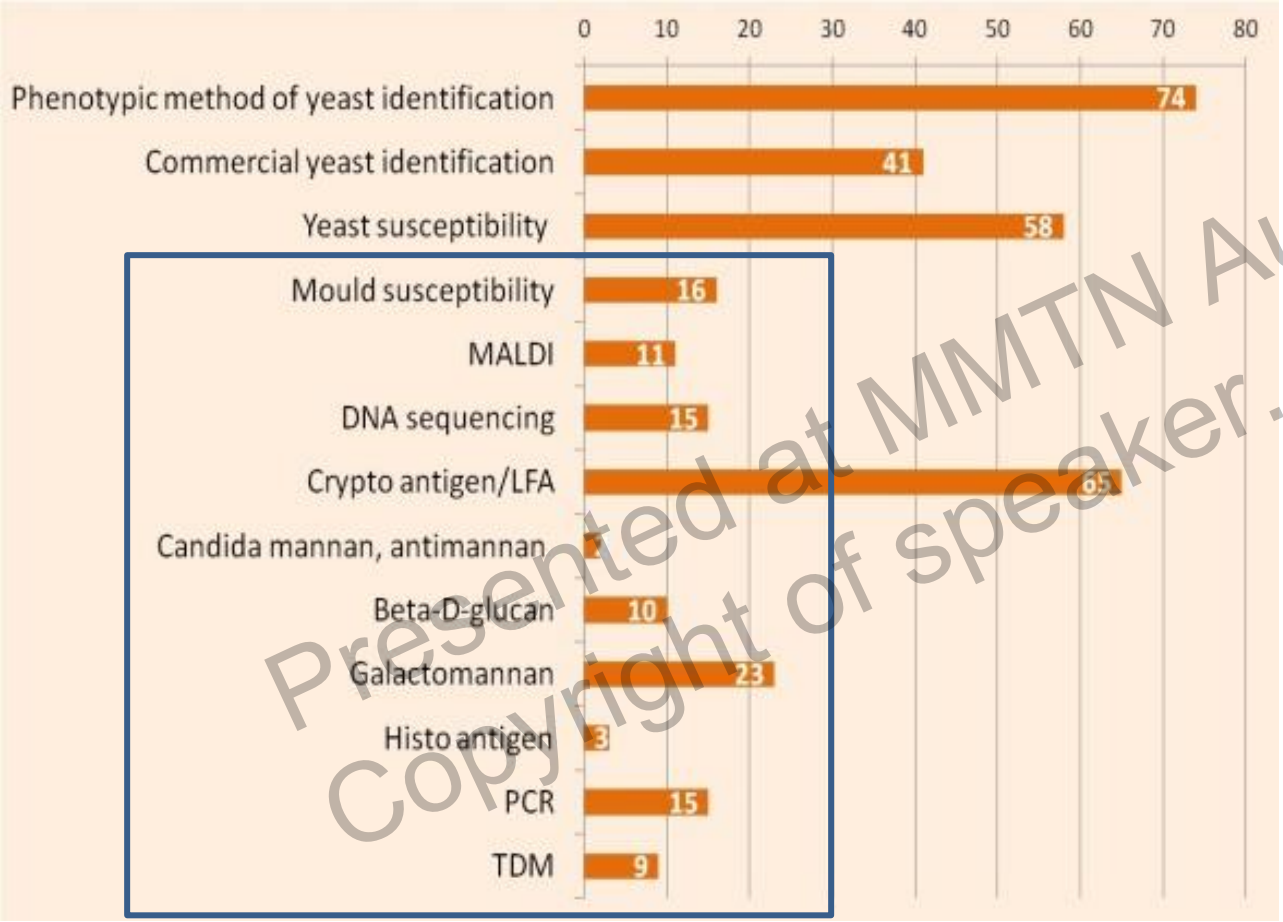
- **Few diagnostic mycology laboratories**
- **Therapy**
  - **Only three classes of antifungal**
  - **All drugs not available in LMIC**
  - **New antifungals take at least 5 years to reach LMIC**



Tan BH, *et al.* Int J Infect Dis 2020; 95: 471; Chindamporn A, *et al*. Med Mycol. 2018;56:416

Challenges – lack of laboratory facilities, awareness, availability & affordability of antifungals

7 Asian countries – China, India, Indonesia, Philippines, Singapore, Taiwan, Thailand



Chindamporn *et al*. Med Mycol 2018; 56: 416-425

China National Survey

- Most hospitals do not have separate laboratory space, manpower, or equipment dedicated for fungal testing.
- **Fungal serology testing at 81.1% laboratories**
- **MALDI-TOF MS & DNA sequencing in few centres**
- Antifungal susceptibility testing for **yeasts in 91.8%, but mould in 13% laboratories**
- **EQAS participation in 57.5% laboratories**

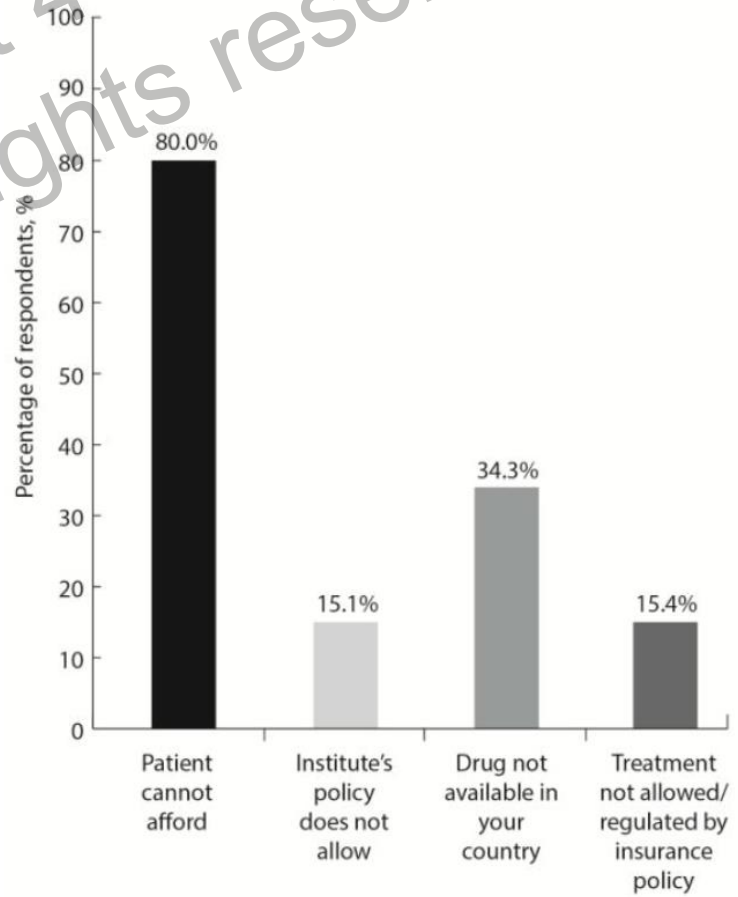
Wang H, *et al*. J Microbiol Immunol Infect. 2020; 53: 845

Clinicians' Challenges in Managing Patients with Invasive Fungal Diseases in Seven Asian Countries: An Asia Fungal Working Group (AFWG) Survey

Ban Hock Tan FRCP(UK)[1]*, Arunaloke Chakrabarti MD[2], Atul Patel MD[3], Mitzi Marie M Chua ....

- 292 respondents from 7 countries, 51.7% ID specialist
- **63% had no formal training** in Medical Mycology
- Handle **only 2-4 proven cases of IFI/month** due to lack in diagnosis
- **GM available in 60%, BDG in 21%, TDM in 25% centres**
- Only 30% had antifungal stewardship program

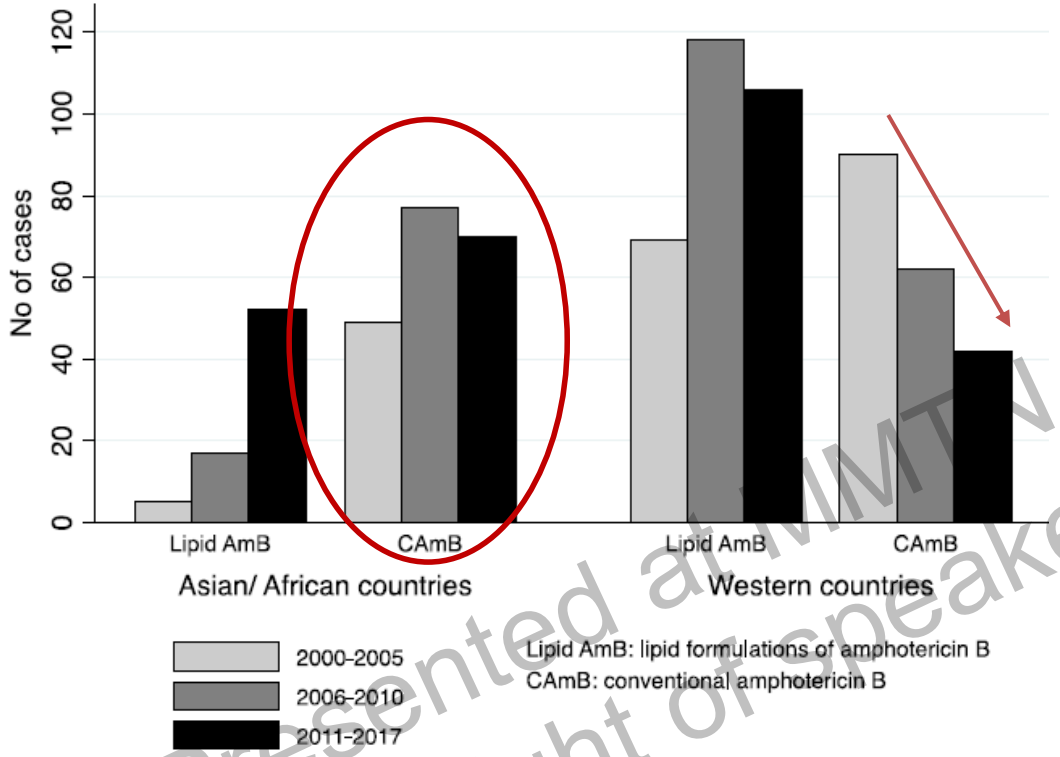
Factors preventing use of preferred antifungals



Int J Infect Dis 2020; 95: 471-480

Antifungal use in developed & developing countries

Jeong W, *et al.* Int J Antimicrob Agents 2019; 53: 589-597



- **A recent multi-centre study on mucormycosis – 25% patients could not afford complete therapy**

(Patel A, *et al*. Clin Microbiol Infect 2020; 26: 944.e9-e15)

Pathadka S, *et al.* Drugs 2022; 82: 1193-1205

To improve management: 75% want improvement of diagnostic tests, 71% training course, 70% development of institutional or national guideline

Tan BH, *et al.* Int J Infect Dis 2020; 95: 471-480

WHO Fungal Prioirty Pathogens List (FPPL)

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.

Accordingly, the 19 fungal pathogens were ranked in three priority groups:

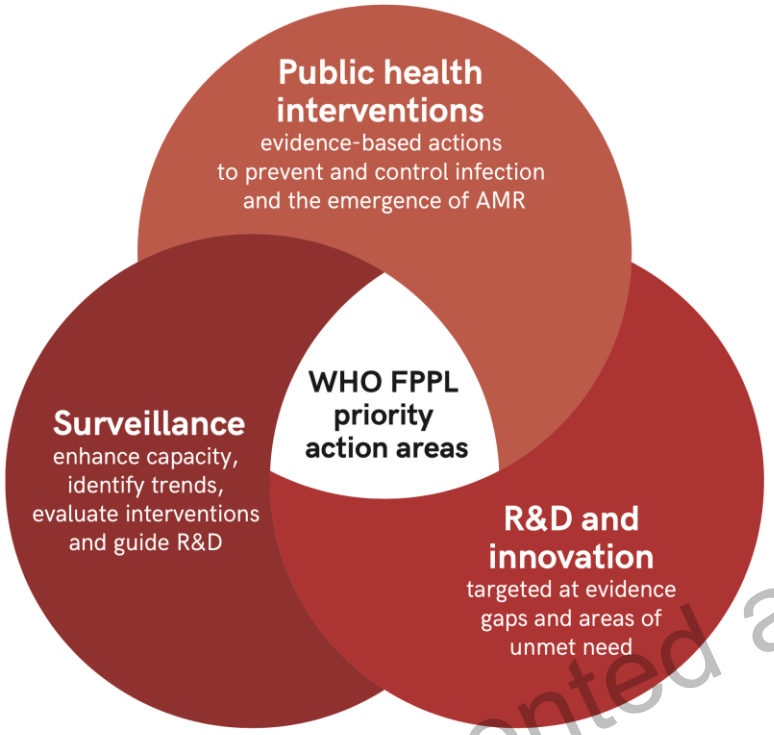
- **Where is *Aspergillus flavus*?**
- **Why Mucorales are not in critical group?**

➢ **Major knowledge gap in resistance**

➢ **More data required from LMIC**

https://www.who.int/publications/i/item/9789240060241

WHO recommends – three primary areas for action in fungal infections



Strengthening laboratory capacity & surveillance

Public health intervention

Investment in research, development, & innovation

https://www.who.int/publications/i/item/9789240060241

Implementation: priority areas for action for implementation

Highlights actions, interventions, and strategies:

1. **Enhance laboratory capacity**
2. **Where resources are limited, establish at least one central Mycology Reference Laboratory**
3. Integration of **WHO's Model List of Essential Diagnostics**.
4. Develop **disease registry & surveillance networks** at national and international levels (e.g. GLASS-FUNGI, ReLAVRA. EARS-Net).
5. **Utilize surveillance data** to understand the burden of invasive fungal diseases and drug resistance & **plan public health interventions**

Surveillance

Slide from Hatim Sati

Implementation: priority areas for action for implementation

Highlights actions, interventions, and strategies:

1. Focus R&D investments on **innovative antifungals** (new class, new chemical entity, new target, safety profile and no cross-resistance) effective against priority pathogens.
2. **Improve existing therapies**.
3. **Support research into novel, accurate, rapid diagnostic tests** for priority pathogens – especially **affordable point of care tests**, with the potential for rapid, wide-spread roll-out, including in LMICs.
4. Research to **improve efficacy, efficiency, & quality of fungal identification & susceptibility testing**.
5. **Public-private partnerships & multi-country collaborative research platforms** to support development of new antifungal therapies and diagnostics.

Research and development, and innovation

Slide from Hatim Sati

Use of new antifungal agents

Antifungal drug	*Candida* spp.		*Aspergillus* spp.		*Mucorales*	*Fusarium* spp.	*Scedosporium / Lomentospora* spp.
	Wild-type[1]	Echinocandin-resistant[2]	Wild-type[3]	Azole-resistant[4]			
Rezafungin	Except *C. parapsilosis* (higher MIC)						
Ibrexafungerp							
Olorofim						Activity against *F. oxysporum* >> *F. solani*	
Manogepix	Except *C. krusei* (higher MIC)					Some resistant isolates (*F. oxysporum*, *F. verticilloides*)	Few resistant isolates (*S. apiospermum*)

Activity against most isolates

Variable activity (species-specific or isolate-specific)

Marginal activity (few susceptible isolates or relatively high MIC

No significant activity

- **Rezafungin** – i.v. only, **once a week**, good bioavailability
- **Ibrexafungrep** – oral formulation, good safety profile, but drug interaction with anti-calcineurin inhibitors
- **Olorofim** – oral & i.v., no relevant drug interaction
- **Fosmanogepix** – oral & i.v., no relevant drug interaxtions

Lamoth F, *et al.* Clin Infect Dis 2022, online , January 5

Implementation: priority areas for action for implementation

Actions, interventions, and strategies:

1. **Incorporate fungal diseases and FPPL** in medical (clinical) and public health **training programs**, and curricula at the graduate and post-graduate levels.
2. **Improve global coordination** and efforts to strengthen and align **action on invasive fungal infections and antifungal resistance** prevention and control.
3. **Promote existing infection prevention & control measures** and develop new prevention measures at both healthcare facilities level and at the community.
4. Promote **rational use of antifungal agents** through the promotion of existing or development of evidence-based treatment guidelines.
5. Develop mechanisms and policies to ensure **equitable, affordable access to quality antifungal agents**. Utilize the WHO Model Lists of Essential Medicines as a procurement tool, tailoring to each country local disease epidemiology.

Public Health

Slide from Hatim Sati

Unmet needs in Asia – food for thought!

- Local epidemiology study
- Training of clinicians and laboratory personnel for diagnosis & management of fungal infections
- Association of fungal disease with existing communicable disease program
- Improving infection control program
- Advocacy to implement WHO essential diagnostic and antifungal drug list
- Integration with public health
- Developing & incorporating point of care test
- Partnering with industry for affordable diagnostics & antifungal drugs
- Management guideline suitable to Asian countries
- Antifungal stewardship
- Judicious use of antifungal & available expertise

SAVE THE DATES

5th International Conference
on Fungal Infections & Mycology Masterclass
by Fungal Infections Study Forum

MYCOCON - 2023

Pre-Con Workshop - 8th Sept 23 ✱ Conference - 9th &10th Sept 23

UNDER THE AEGIS OF

FISF
FUNGAL INFECTION STUDY FORUM

HIGHLIGHTS:

- Pre conference workshop highlighting Lab Diagnostics and Therapeutic Aspects
- Clinical Case Discussions
- Lectures, Debates, Panel Discussions by National & International Faculty
- Poster Presentations

TOPICS OF RELEVANCE TO:

Critical Care, Internal Medicine, Microbiology, Pediatrics, Transplantation, Pulmonology, Hematology, Oncology

Thank you!