Epidemiology of Invasive Fungal Infections in Asia Pacific

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Disclosures

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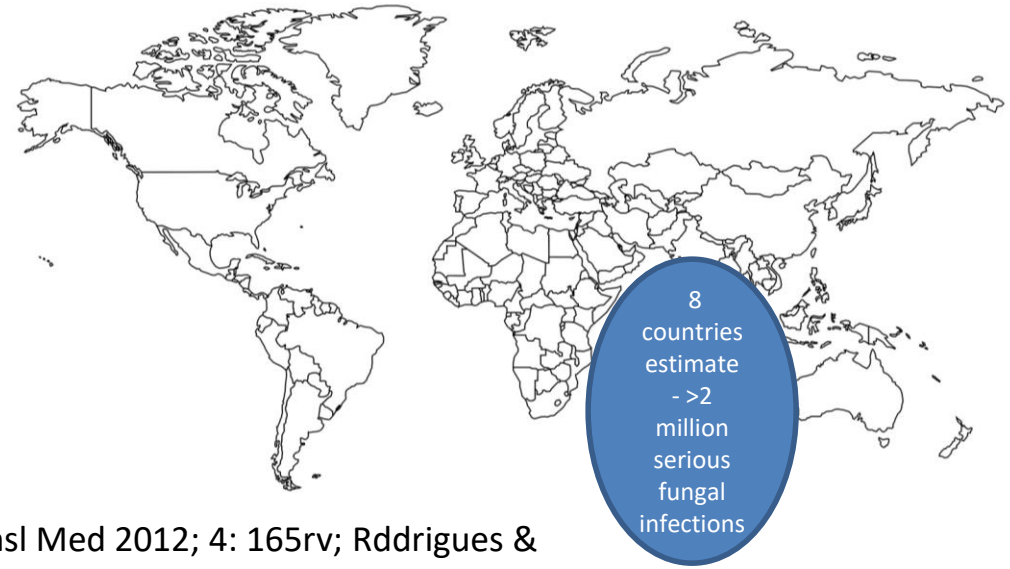
DBT, Department of Biotechnology; DST, Defence Science and Technology Group; ICRM, Indian Council of Medical Research; MSD, Merck Sharp & Dohme; WHO, World Health Organization

How is the region different from other continents?

- 30% world's land area & 60% of the world population – **largest & most populous continent**
- **Economy – most countries are within LMIC** categories except Singapore, Taiwan, Korea, Australia
- **Health infra-structures are sub-optimal**; large population cannot afford modern treatment
- Large population live in **Southeast Asia with similar climate** (between tropics)
- Generally **warm & moist weather** where fungi thrive easily

- **Challenge we face in this region due to IFI**
  - High magnitude
  - Shortage of everything – awareness, laboratory, manpower, antifungal drugs, affordability of antifungal drugs



https://en.wikipedia.org/wiki/Asia:
https://asiasociety.org/education/introduction-southeast-asia

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

Whatever happens in SE Asia, happens in large number

(in an outbreak 379 babies had *Wickerhamomyces anomalus* fungemia)

China & India are Capitals of diabetes

Over-capacity patient load

Compromise in healthcare

Candidiasis

Mucormycosis

Compliance to therapy poor

Construction without protective covering from the patient care area; AC duct not cleaned

IFI is looming large

Aspergillosis

Spore count = 100cfu/m^3

Hyalohyphomycosis
Phaeohyphomycosis

Tropical climate

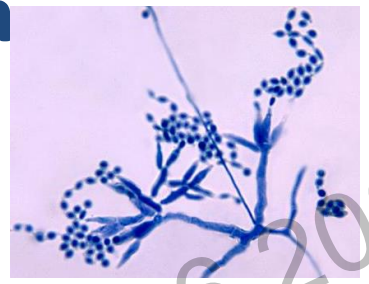
Fungi thrive easily

Chakrabarti A, *et al.* J Clin Microbiol 2001; 39: 1702-6; Rudramurthy SM, *et al*. Indian J Med Microbiol 2016; 34: 529-32; Chakrabarti A. Clinical Practice of Medical Mycology in Asia, Springer Nature, Singapore 2020; 1-6

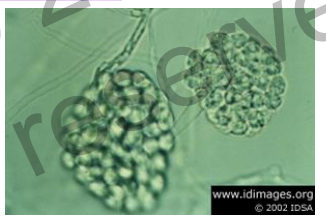
Unique fungal species in Asia-pacific region

Agent

Talaromyces marneffei
(South-east Asia)

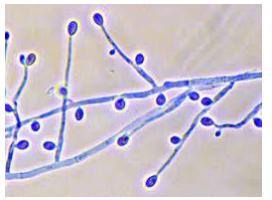


Pythium insidiosum
(Thailand, India)

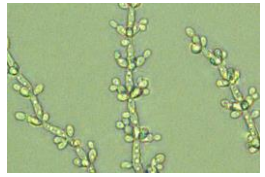


Black mycelial fungi
Cladophialophora bantiana (India)

Scedosporium, Lementospora
(Australia)



Candida tropicalis
(tropical region of Asia)



Trichosporon species
(Japan, Thailand, Taiwan)

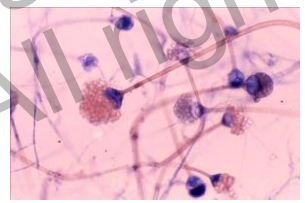
Unique fungal species in Asia-Pacific region

Agent

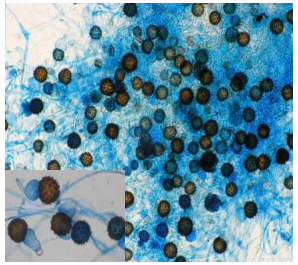
Many rare mucoromycetes agent prevalent in Asia

Mucor irregularis
(China, India)

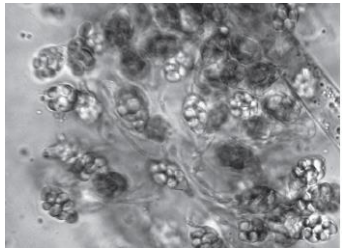
Apophysomyces elegans, Saksenaea vasiformis
(India, Australia)



Rhizopus homothalliculs
(India)



Thamnostylum lucknowense
(India)



Prakash & chakrkabarti. J Fungi 2019; 5: 26

Xess I et al. J Clin Microbiol 2012; 50: 1491

Dimorphic mycoses in Asia

- Histoplasmosis
- Talaromycosis
- Blastomycosis (rare)
- Emergomycosis

The incidence has markedly increased with rise in number of patients with AIDS

Imported dimorphic mycoses in Asia

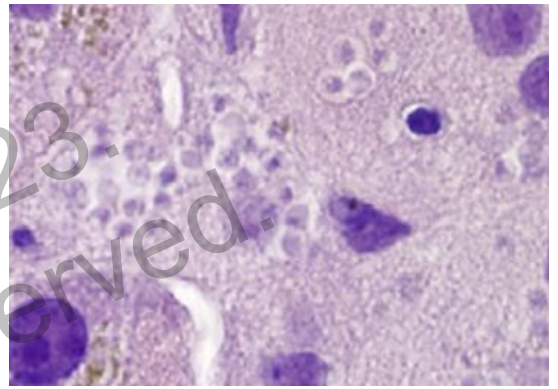
- Coccidiodomycosis
- Paracoccidiodomycosis

Histoplasmosis

Large number of cases in China, India, Thailand, Malaysia, Japan

Endemic area with large number of cases

Isolated cases



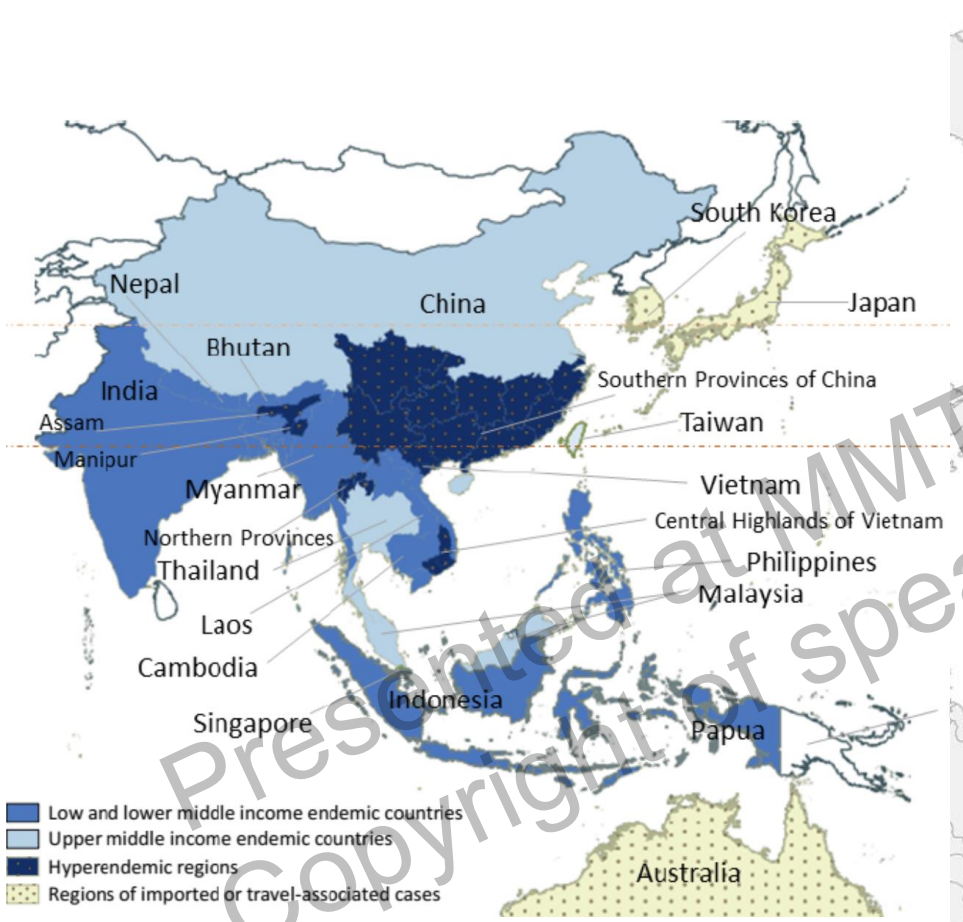
In Immunocompetent hosts, adrenal tumour, mucosal ulcers, & cutaneous lesions are common presentations

Gupta A, *et al*. Mycopathologia 2017; 182: 1077-93
Ray A, *et al.* Open Forum Infect Dis 2022; 9: ofac603

Patel AK, *et* al. Indian J Med Microbiol 2018; 36: 61-4; Deodhar D, *et al.* N Med J India 2013; 26: 214

Talaromycosis

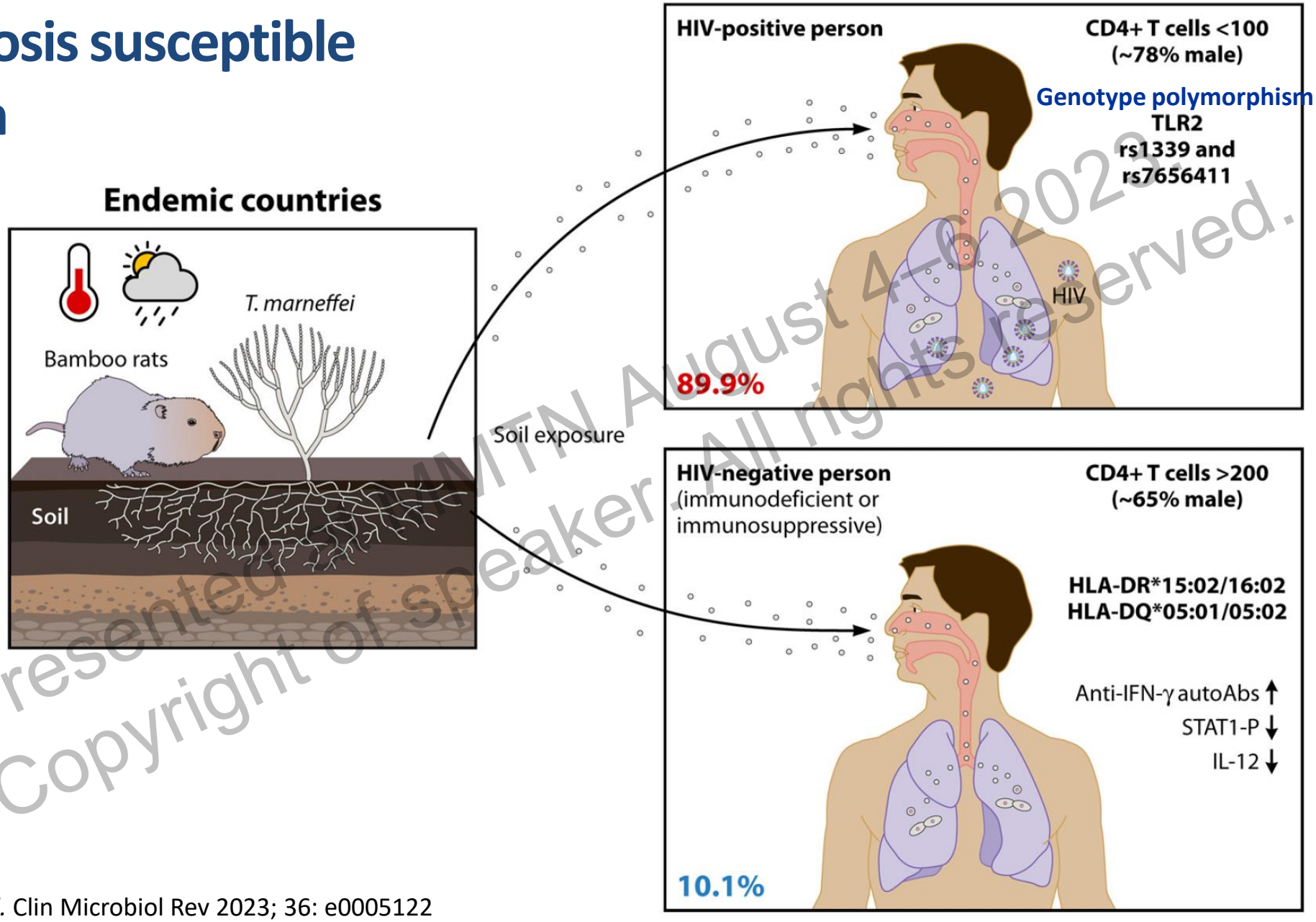
Reported cases during 1960s to 2020s



Narayanasamy S, *et al.* Lancet Glob Health 2021; 9: e1618-22

Wang F, *et al.* Clin Microbiol Rev 2023; 36: e0005122

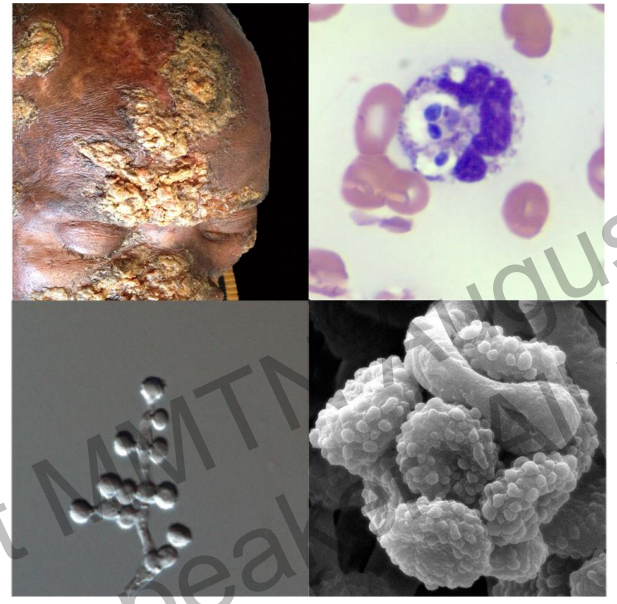
Talaromycosis susceptible population



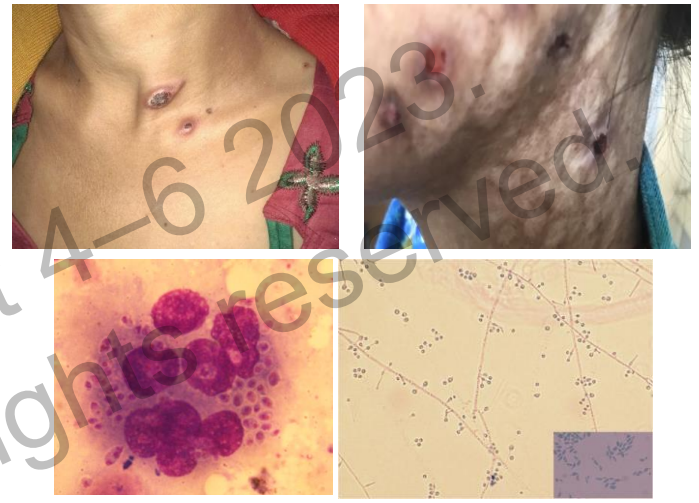
Wang F, *et al.* Clin Microbiol Rev 2023; 36: e0005122

Emergomycosis – a new disease in HIV

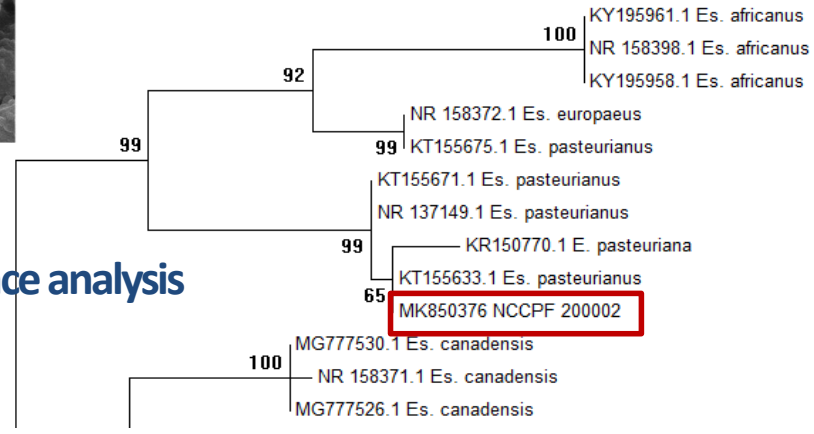
- Prevalent in South Africa
- CD4 count <50, poly-morphic skin lesion in majority of patients
- Skin biopsy helps in diagnosis; 24% blood culture positive
- *E. africanus* is present in soil & air of south Africa



We have two cases of *Emergomyces pasteurianus* infection



ITS sequence analysis

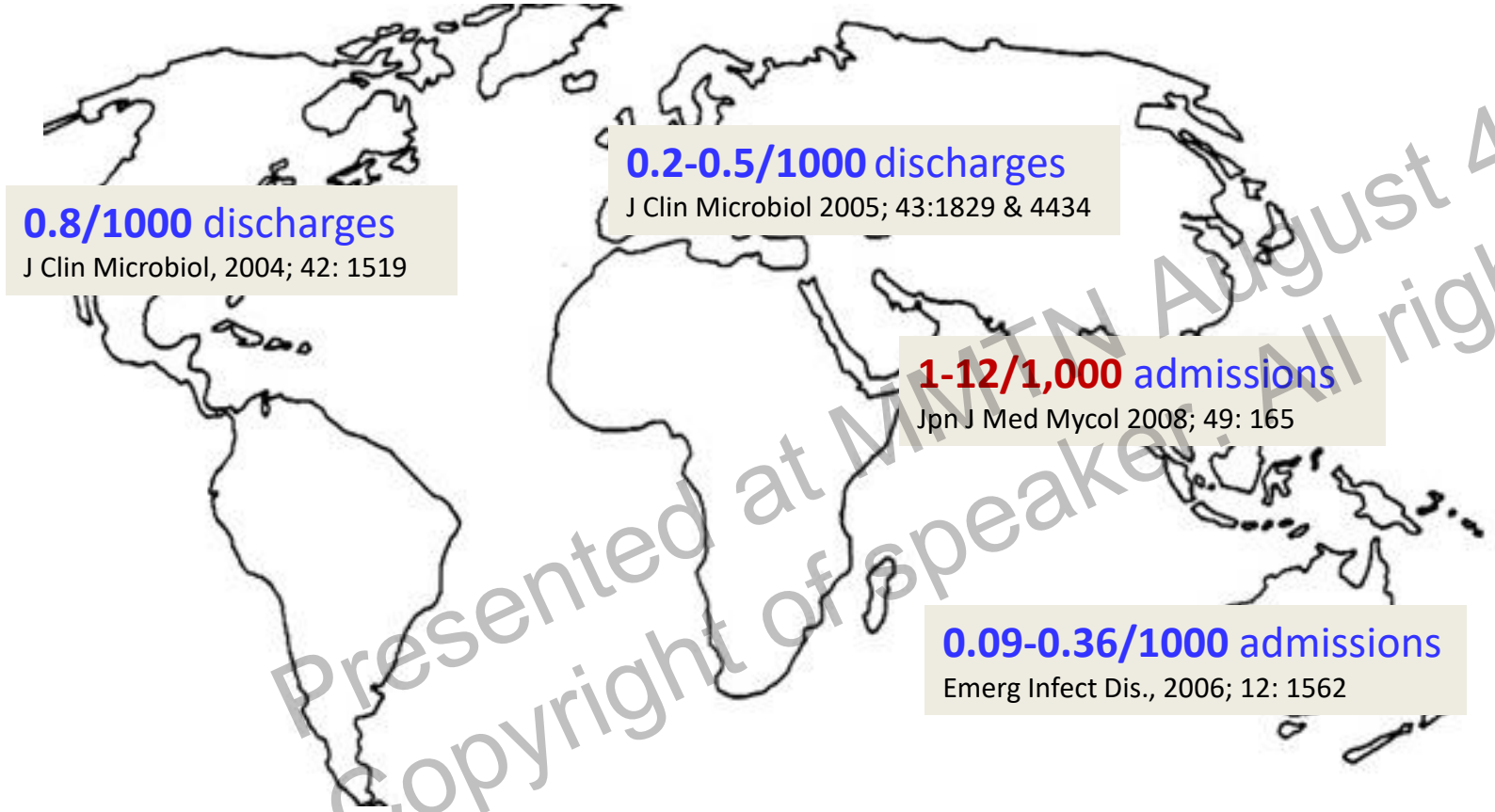


Malik R, *et al.* Mycoses 2016; 59: 127; Capoor MR, *et al.* Mycopathologia 2020; 185: 193

Schwartz IS, *et al.* PLoS Negl Trop Dis. 2018; 12: e0006174; Schwartz IS, *et al* Emerg Infect Dis. 2018; 24: 377–380; Schwartz IS, *et al* . Open Forum Infect Dis. 2017; 4: ofx186.

Candida

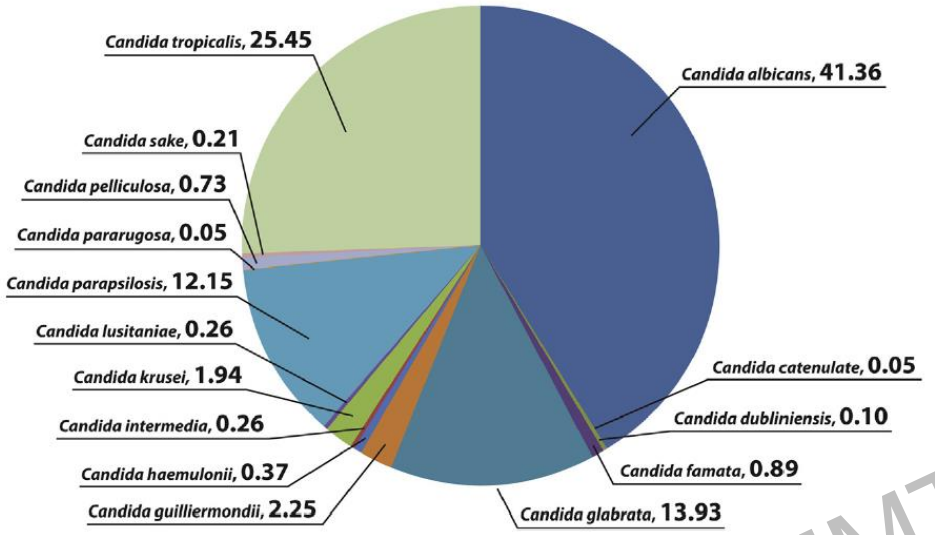
Candidemia – comparing to global scenario

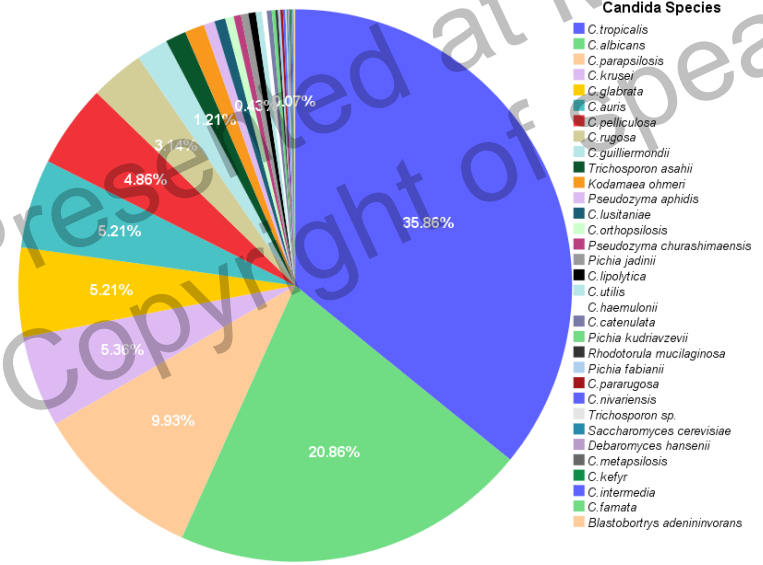


India – candidemia rate 7-20 times more common

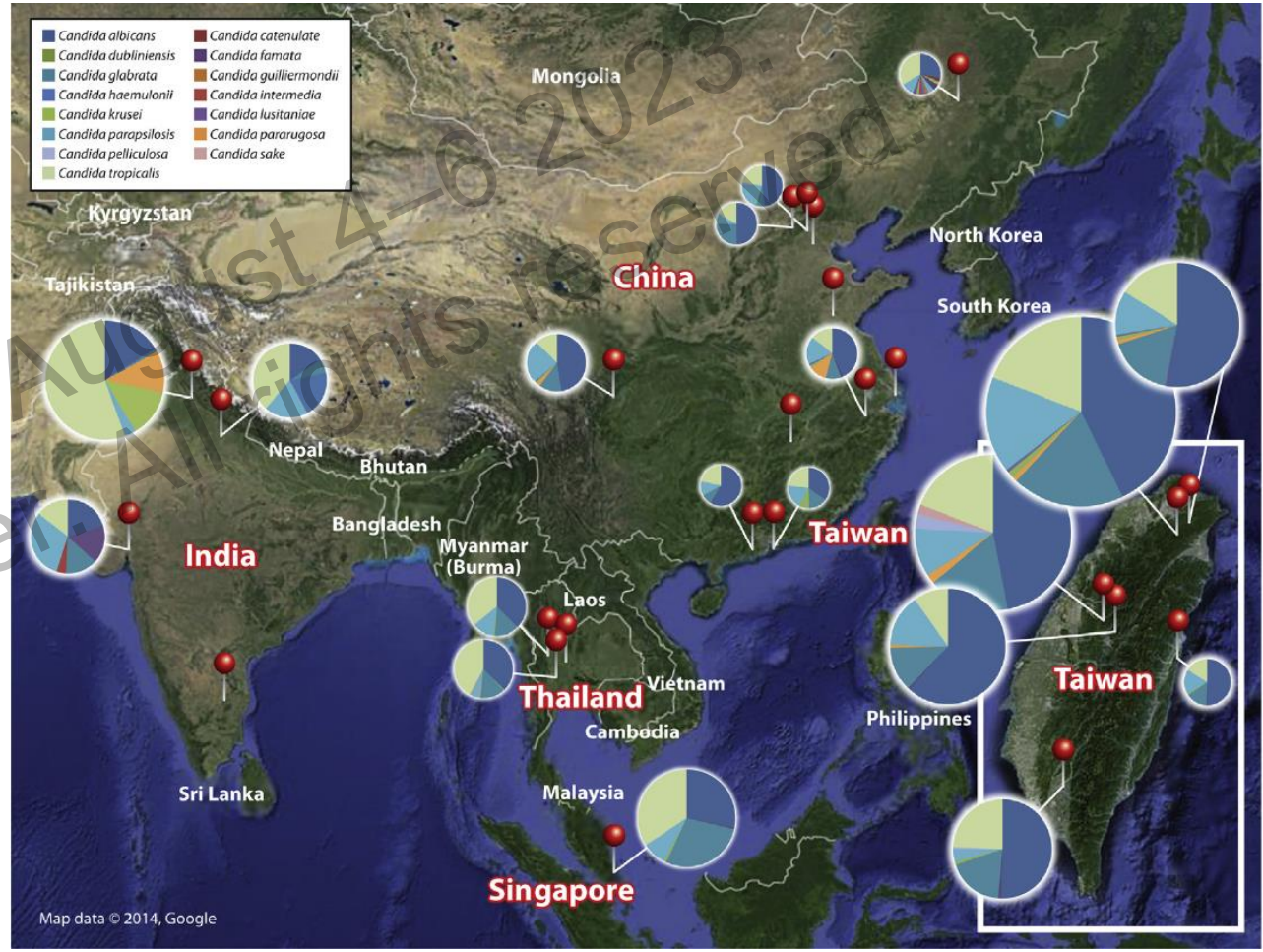
https://gaffi.org/why/burden-of-disease-maps/

Candidemia data in six Asian countries





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



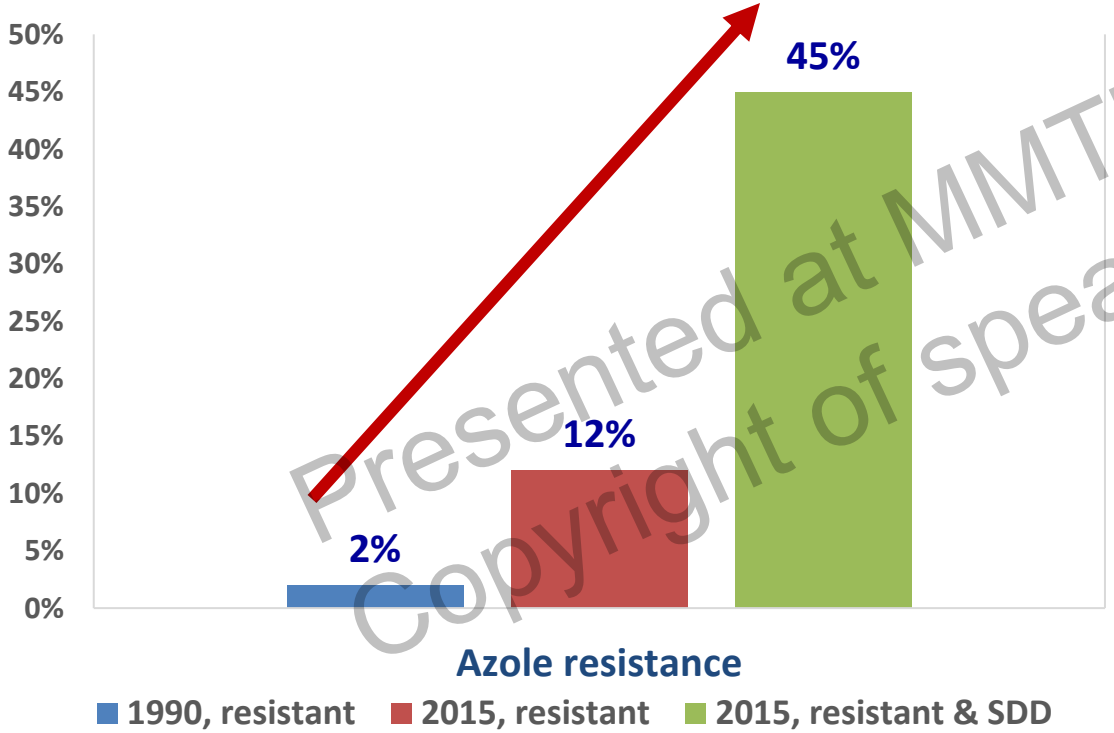
Tan *et al.* Clin Microbiol Infect 2015; 21: 946-953

Azole susceptibility profile of *Candida*

India data

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

(Including resistant & SDD)

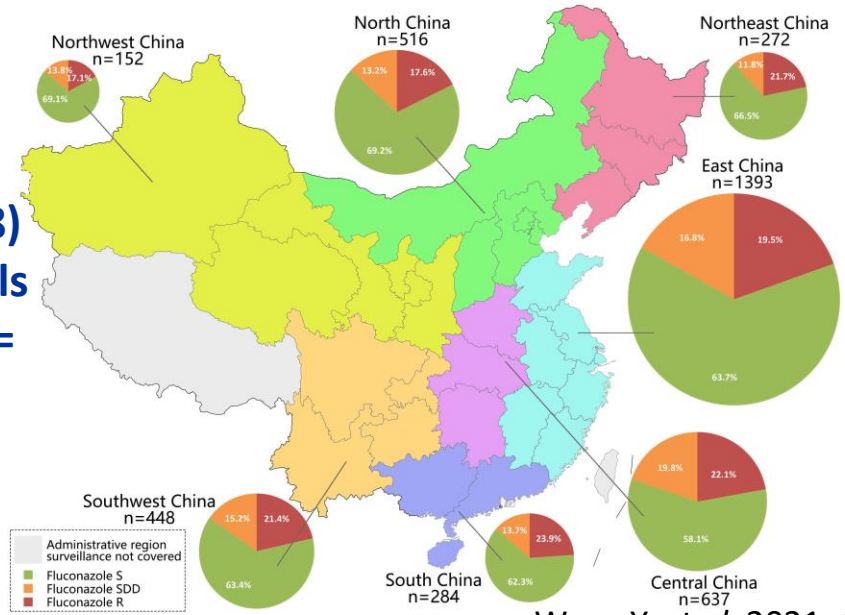


Chakrabarti A, *et al.* Intensive Care Med 2015; 41: 285

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

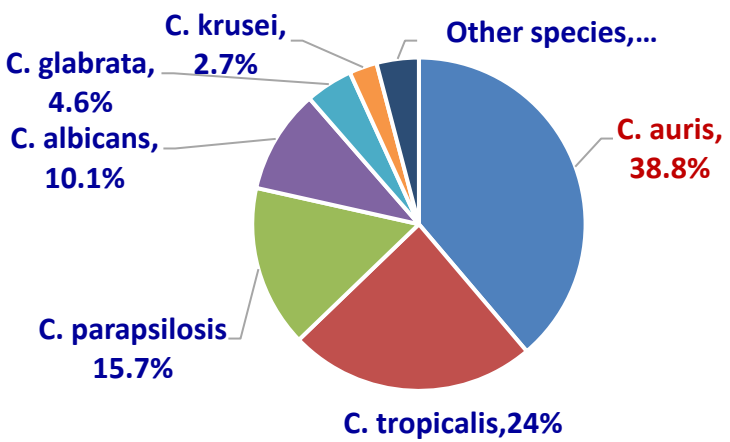
China: 9 year data (2009-2018) from 87 hospitals - *C. tropicalis* (n= 3702)

R & SDD ~42%

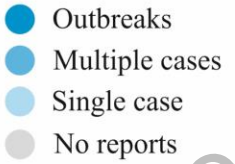


Wang Y, *et al.* 2021; 12: 702839

C. auris in Asia



Shastri P, *et al.* J Crit Care 2020; 57: 42-48



Japan & Korea in 2008

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

- **South Asian isolates are Clade I**
- **97% to flu, 54% Vori, 30% AmB, 49% multi-drug**

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

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

Fungal outbreaks in ICUs – many rare yeast caused the outbreaks in ICUs

› Mycoses. 2021 May 3. doi: 10.1111/myc.13297. Online ahead of print.

Fungaemia due to rare yeasts in paediatric intensive care units: A prospective study

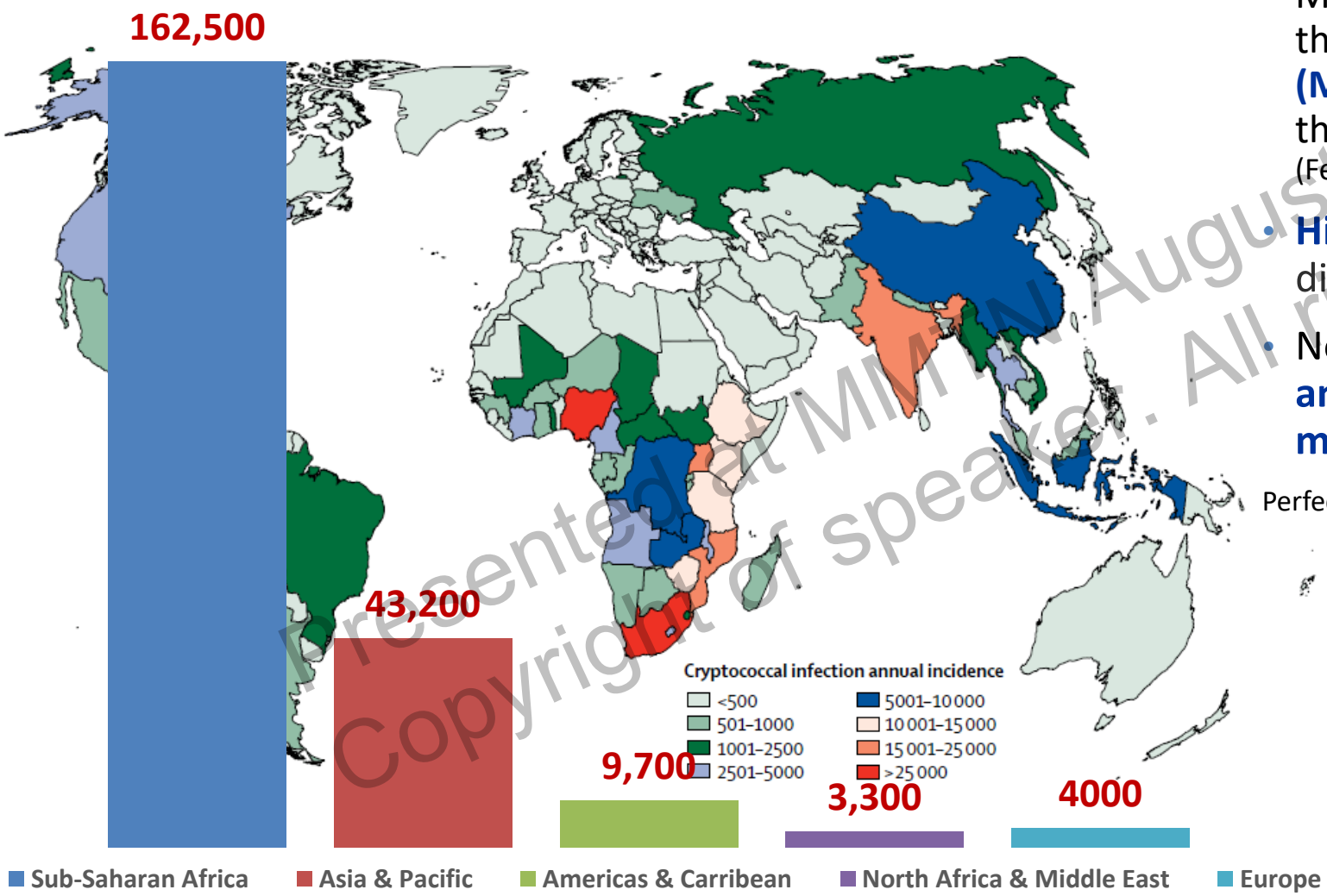
Harsimran Kaur [1], Shreya Singh [1], Shivaprakash Mandya Rudramurthy [1], Muralidharan Jayashree [2], Nitin James Peters [3], Pallab Ray [1], Ram Samujh [3], Anup Ghosh [1], Arunaloke Chakrabarti [1]

- Outbreaks – **affects large number of people**
- *Pichia anomala* – 379 babies suffered
- *Kodamaea ohmeri* - 38 cases
- *Candida viswanathii* – 23 cases
- *Pichia fabianii*

- **Epidemiology not well understood** with regard to environmental reservoirs, modes of transmission, & ways to detect them
- Because of rarity, **laboratory diagnosis is challenging;** Specific identification **requires expertise**
- Antifungal susceptibility testing challenging because **antifungal breakpoints not available**

Chakrabarti A, *et al.* J Clin Microbiol 2001; 39: 1702; Chakrabarti A, *et al.* Clin Microbiol Infect. 2014; 20: O83;Shankarnarayan SA, *et al.* Emerg Infect Dis. 2018; 24: 1956

Cryptococcosis

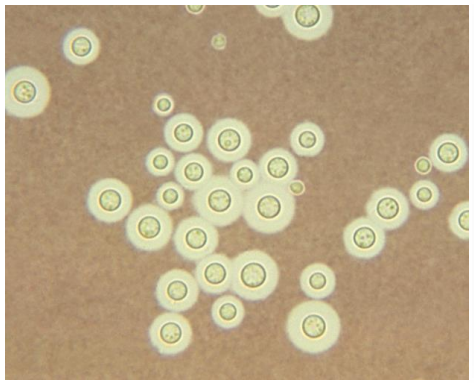


Rajasingham R, *et al*. Lancet Infect Dis 2017; 17: 873

Immunocompetent hosts

- **Majority in China in non-HIV group**
- May be attributed to **multiple polymorphisms** in the genes encoding **mannose-binding lectin (MBL) and Fc-gamma receptor 2B (FCGR2B)** in the **Han population, major ethnic group in China** (Feng W, *et al.* Fungal Genet Biol 2015; 78: 7-15)
- **High mortality (>30%)** due to delay in diagnosis (Bratton et al., 2013)
- No treatment guideline - **requires prolonged antifungal therapy in combination with the management of intra-cranial pressure**

Perfect & Bicanic. Fungal Genetics Biol 2015; 78: 49-54



Invasive mould infections

Invasive mould infections in Asia-pacific

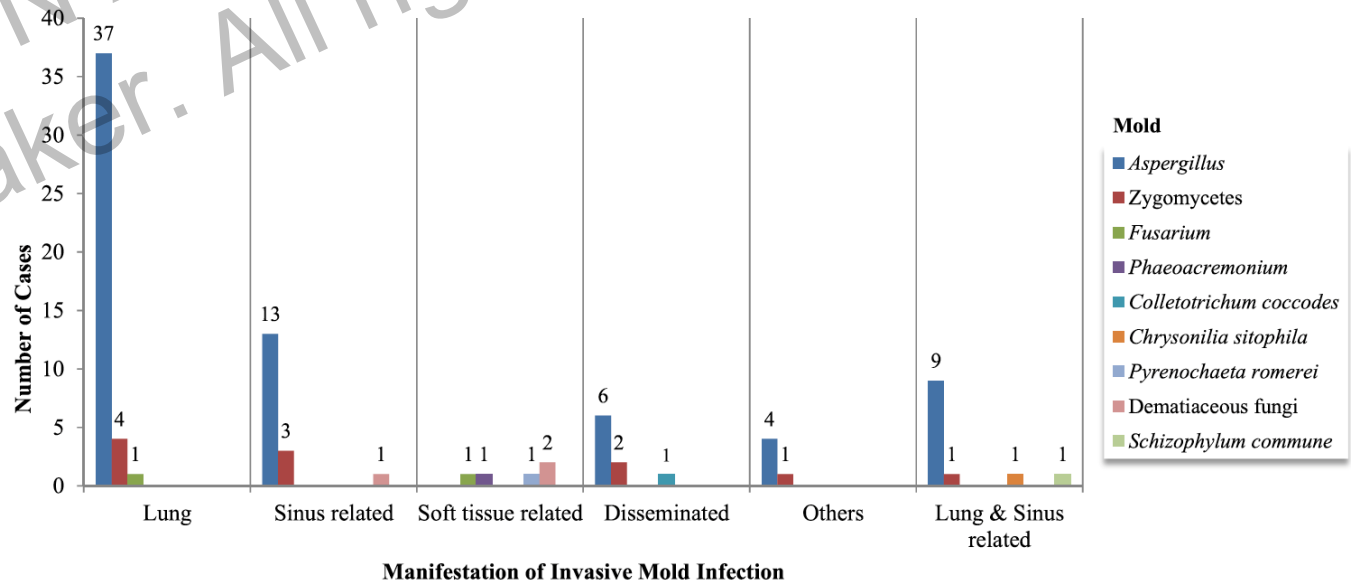
- Studied in 5 countries (Thailand, Taiwan, Singapore, China & India)
- Underlying disease – DM (30.9%), AML (19.4%), Rheumatogenic condition (11.6%)
- Other factors – Steroid (39.4%), neutropenia (38.7%)
- *Aspergillus* most common – *A. fumigatus* & *A. flavus* primarily

Indian multi-centre study in ICU

- 9.5 IMI cases/1000 ICU admission
- *Aspergillus* – 82.1% (*A. flavus* more common than *A. fumigatus*); Mucorales – 24%

Australia – voluntarily reported

- *Aspergillus* – 47%, Mucorales - 21%, *Fusarium* -15%, *Scedosporium* – 15%

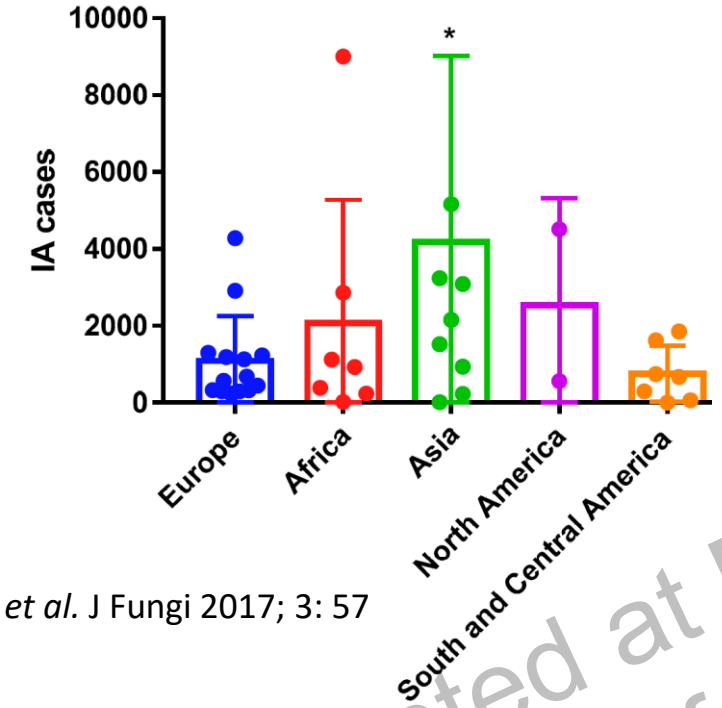


Chakrabarti A, *et al*. J Critical Care 2019; 51: 64-70

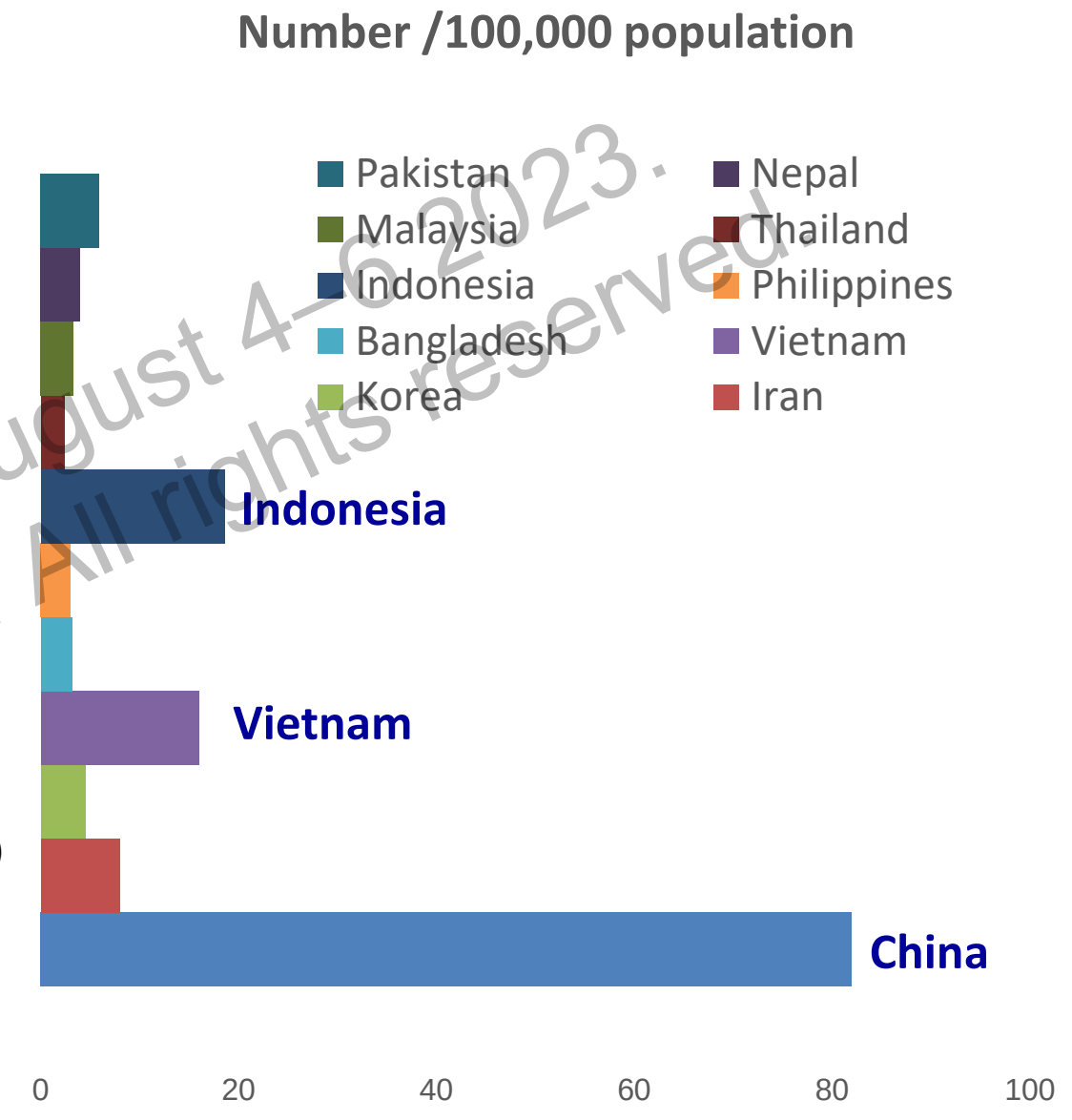
Slavin MA. J Antimicrob Chemother 2002; 49: 3-6

Rojanapan P, *et al*. Med Mycol 2018; 56: 186-196

Invasive aspergillosis - magnitude



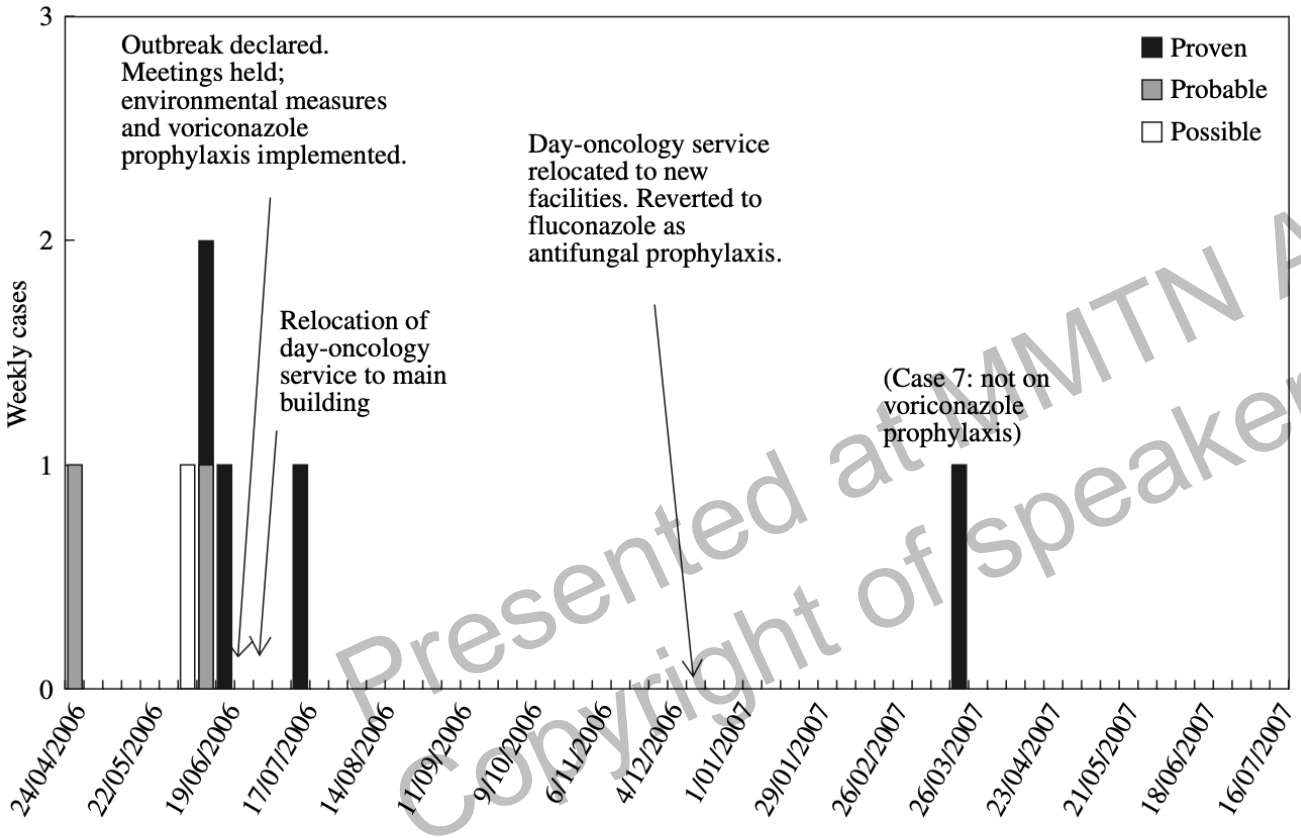
Bongomin F, *et al.* J Fungi 2017; 3: 57



https://gaffi.org/why/burden-of-disease-maps/

- Leading cause of IFI in Thailand (J Med Assoc Thai 2007; 90: 895), Japan (Pathol Int 2003; 53: 744), Korea (Transplant Infect Dis 2010; 12: 309)
- Also occurs in so called **immunocompetent host (6-14%)**
- ***A. fumigatus*** more common in temperate climate; ***A. flavus*** more prevalent in invasive infections in tropical climate

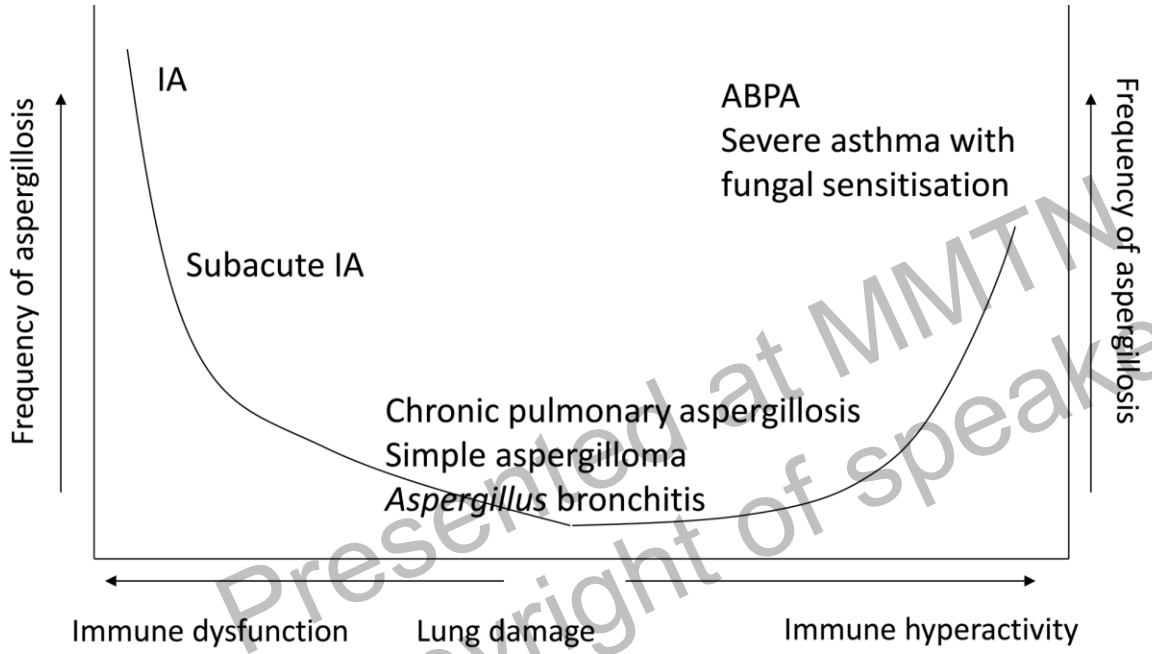
Aspergillosis outbreak during building works in Australia



- 6 cases of nosocomial outbreak of invasive aspergillosis (IA) in hematology unit
- **Coincided with major hospital construction**
- **Infection control changes – unit relocation, impermeable barriers at construction site, face masking, voriconazole prophylaxis**
- **No further breakthrough IA**
- Multi-faceted pre-emptive approach involving clinicians, hospital management, engineering & building department is essential to prevent nosocomial outbreaks

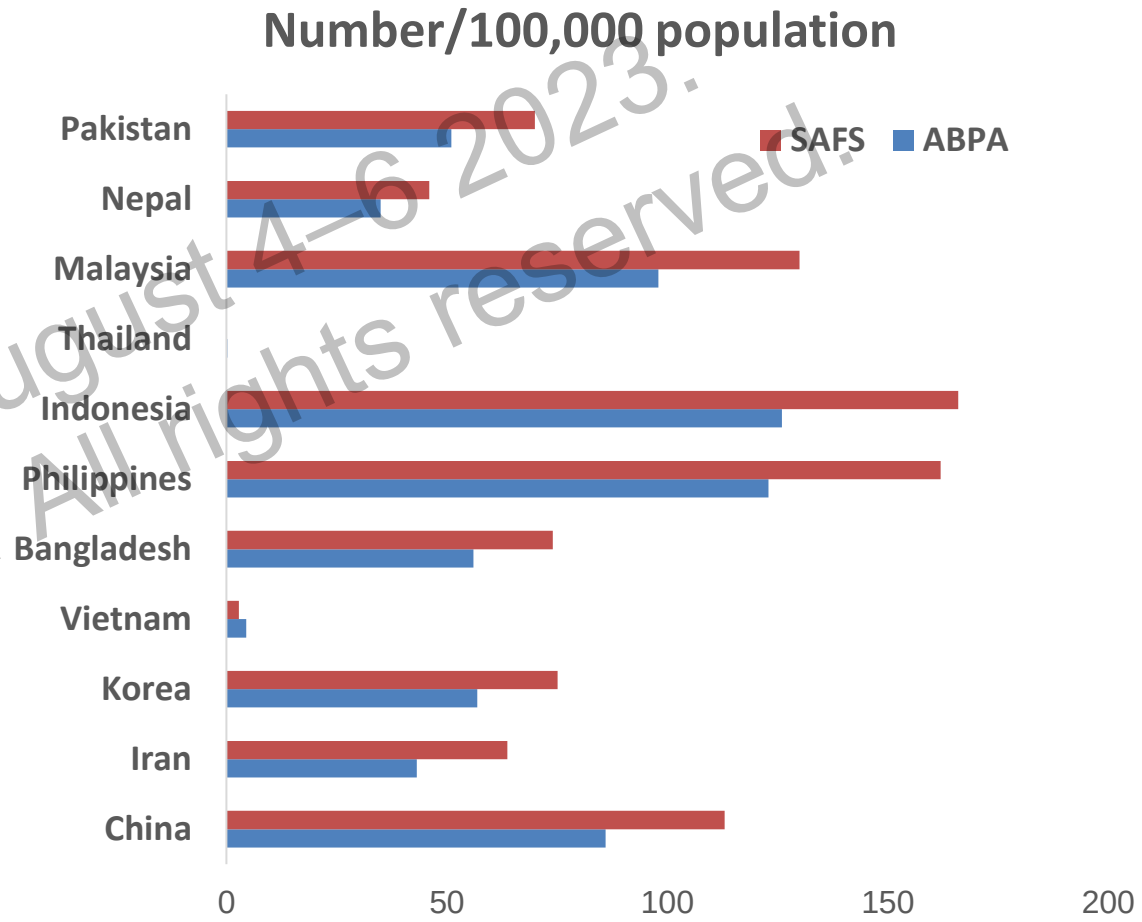
Chang CC, *et al.* J Hosp Infect 2008; 69: 33-38

Concern with aspergillosis – varied presentations



Kosmidis et al. Thorax 2015; 70: 270-277

ABPA & SAFS not rare in Asia

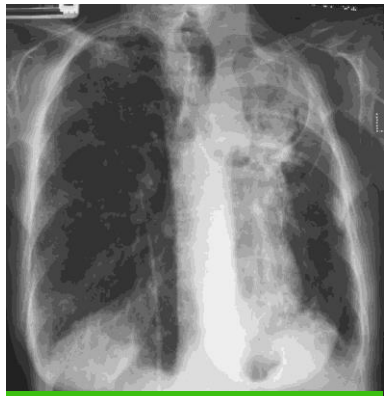


India

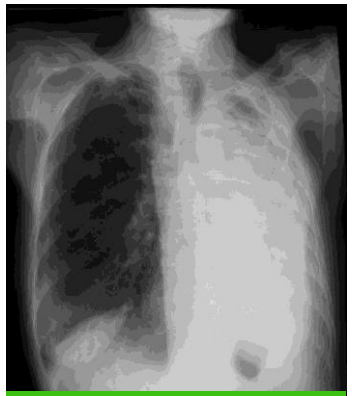
- In adult asthmatics **ABPA is estimated at 592,719**.

https://gaffi.org/why/burden-of-disease-maps/

Chronic pulmonary aspergillosis post-TB



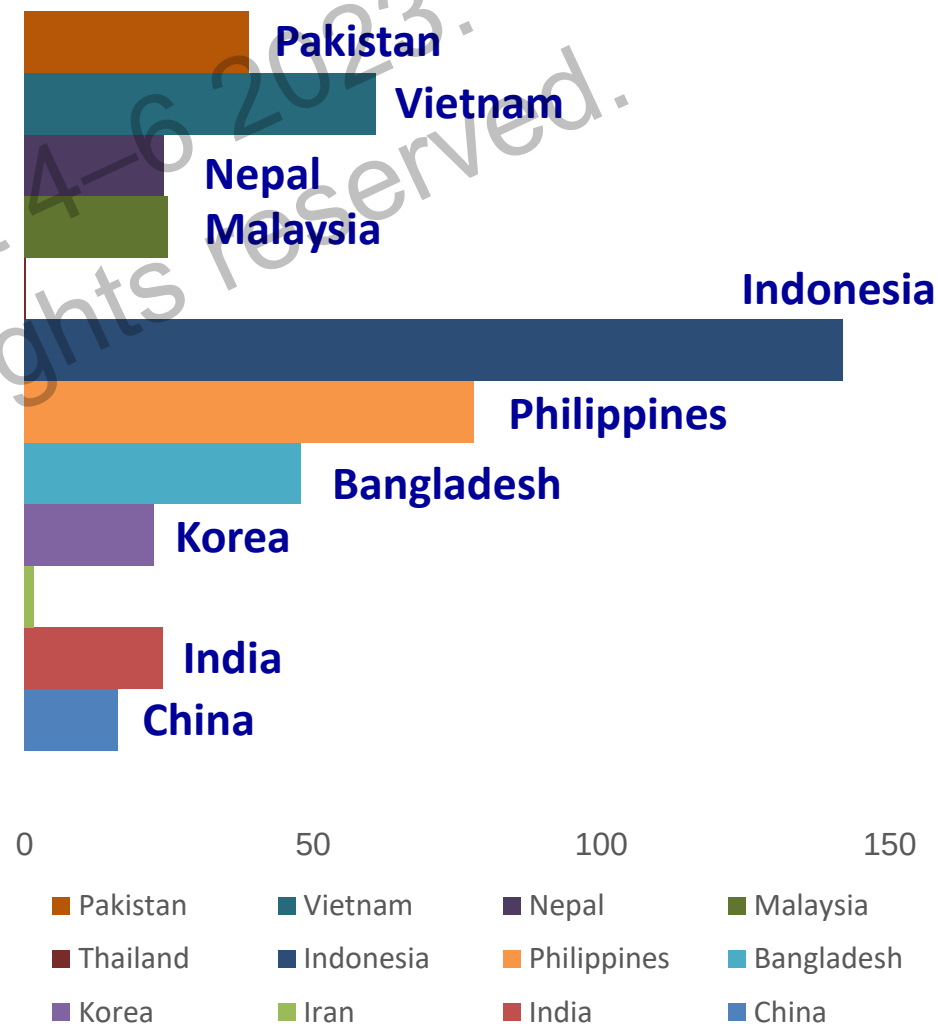
July 2001, untreated



April 2003, untreated

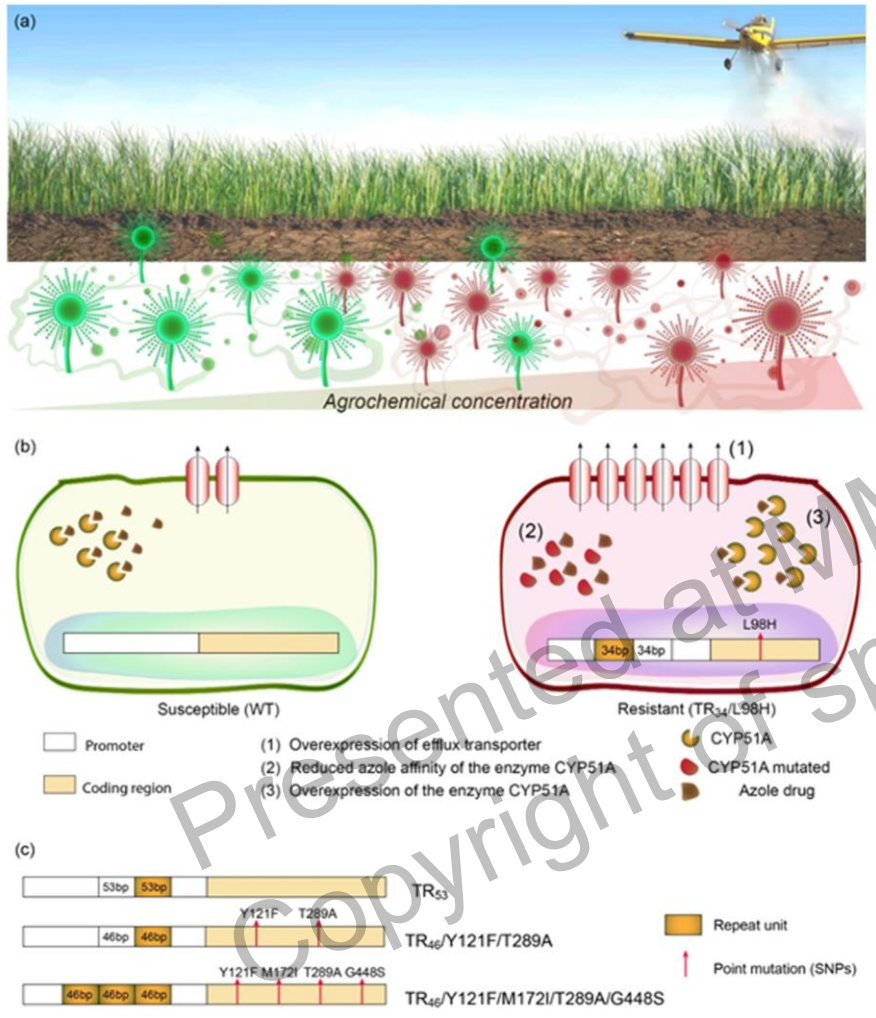
Fungal ball removed from lung

Country	Population (2005)	Annual pulmonary TB cases, alive at 1 year	Estimated annual CPA caseload from TB	5 year estimated CPA prevalence from TB
Global total	6,512,276,000	5,899,619	372,385	1,173,881
China	1,312,253,000	1,052,925	67,387	212,427
India	1,130,618,000	1,297,047	83,011	261,679
United States	302,741,000	8,907	588	1,853

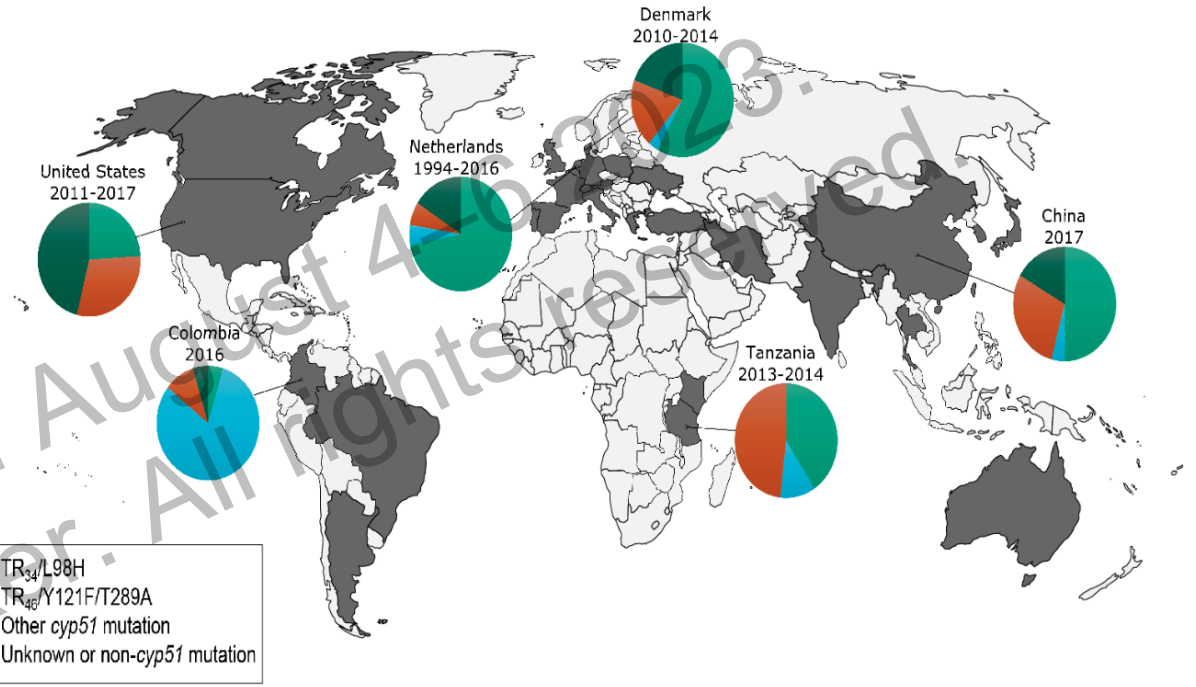


Barac A, *et al*. Med Mycol 2019; 57: S104

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

In vitro susceptibility of *Aspergillus flavus* (188 isolates)

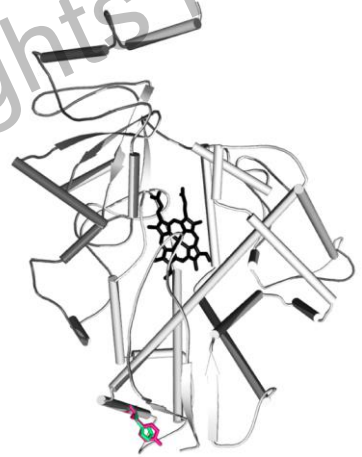
Antifungal agent	MIC/MEC (mg l^{-1})			
	Range	GM	50%	90%
Amphotericin B	0.25–2	0.592	0.5	1
Itraconazole	0.062–0.5	0.177	0.125	0.25
Voriconazole	0.5–4	1.167	1	2
Posaconazole	0.062–0.25	0.123	0.125	0.25
Isavuconazole	0.125–2	0.697	1	1
Caspofungin	0.25–1	0.506	0.5	0.5
Anidulafungin	≤0.008–0.016	0.004	≤0.008	≤0.008
Micafungin	≤0.008–0.125	0.025	0.016	0.062

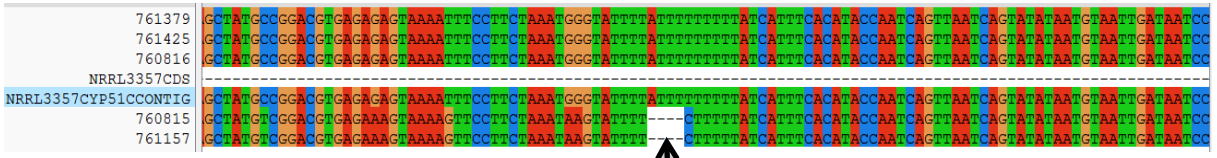
Shivaprakash MR, *et al.* Mycoses 2011; 54: e583-9

Antimicrob Agents Chemother. 2015 Oct;59(10):6615-9.

A Novel Y319H Substitution in CYP51C Associated with Azole Resistance in *Aspergillus flavus*

R. A. Paul,[a] S. M. Rudramurthy,[a] J. F. Meis,[b,c] J. W. Mouton,[b,c] A. Chakrabarti[a]





4 bp indel mutation at 2734bp In CYP51C

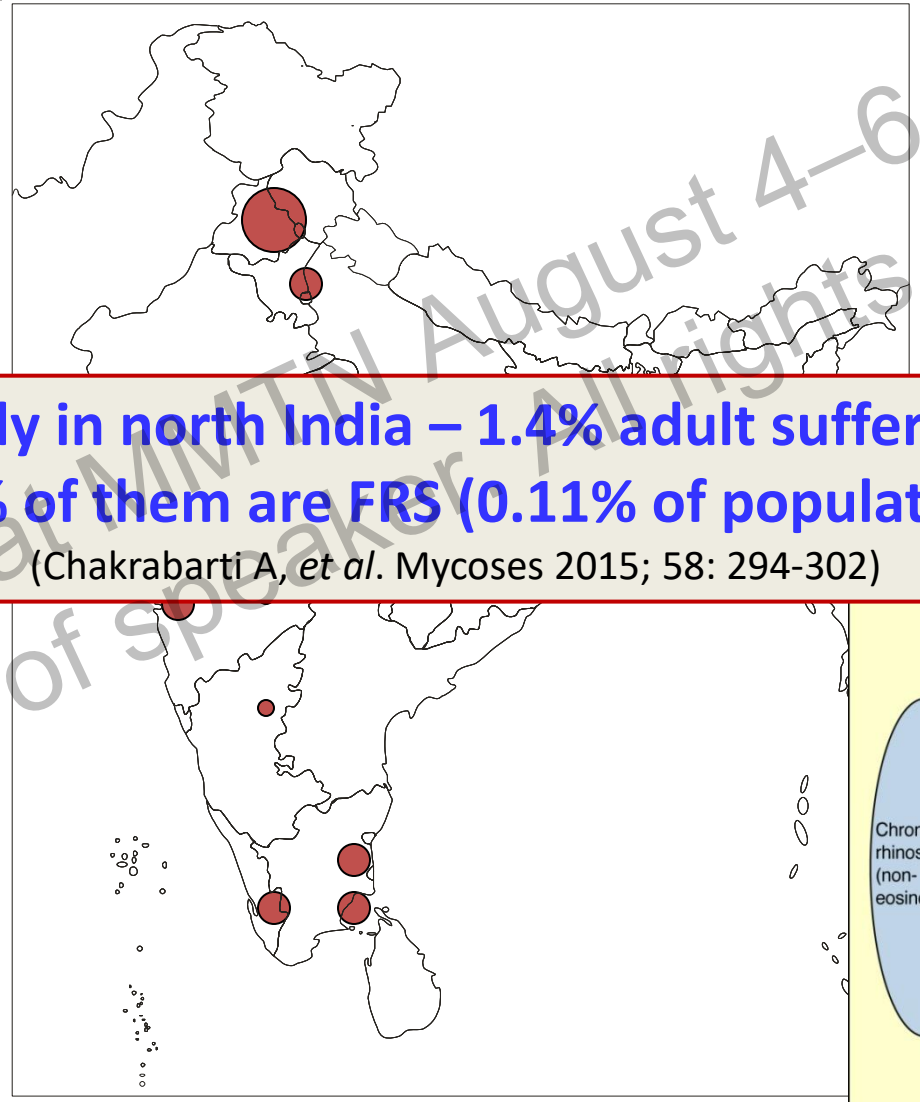
Fungal rhinosinusitis in India

The Laryngoscope

Contemporary Review

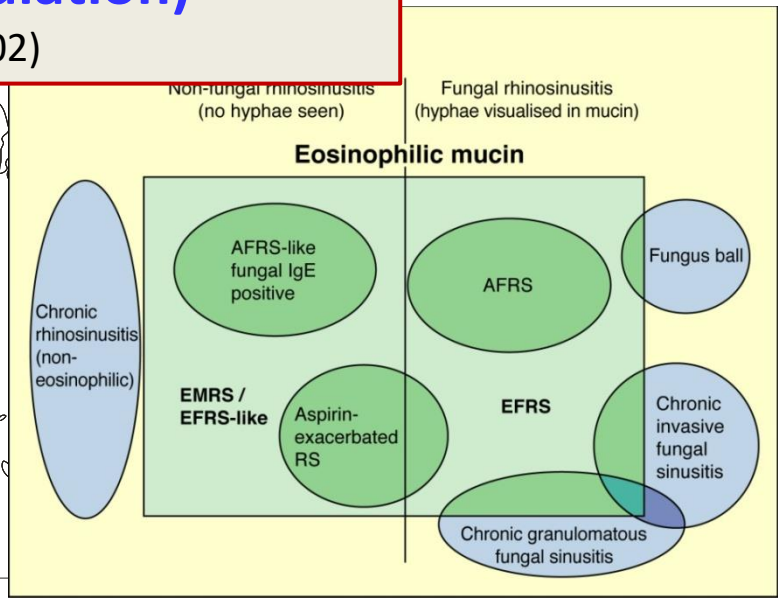
Fungal Rhinosinusitis: A Categorizatio and Definitional Schema Addressing Current Controversies

Arunaloke Chakrabarti, MD; David W. Denning, FRCP, FRCPATH; B. J. Ferguson, MD; Jens Ponikau, MD; Walter Buzina, MD; Hirohito Kita, MD; Bradley Marple, MD; Naresh Panda, MS; Stephan Vlaminck, MD; Catherine Kauffmann-Lacroix; Ashim Das, MD; Paramjeet Singh, MD; Saad J. Taj-Aldeen, PhD; A. Serda Kantarcioglu, PhD; K. K. Handa, I Ashok Gupta, MS; M. Thungapatra, PhD; M. R. Shivaprakash, MD; Amanjit Kaur, MD; Annette Fothergill; B. D. Radotra, MD



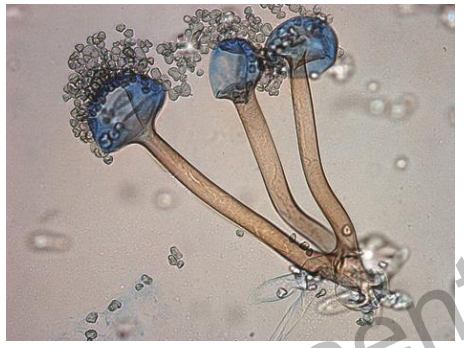
Recent study in north India – 1.4% adult suffer from CRS, 8.1% of them are FRS (0.11% of population)

(Chakrabarti A, *et al*. Mycoses 2015; 58: 294-302)



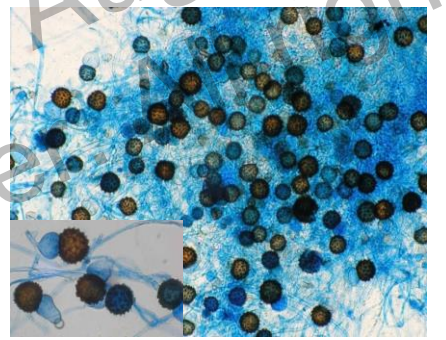
Difference of mucormycosis in Asia vs. western world

- The rise of mucormycosis in China & India phenomenal; 70 times higher rate in India compared to western world (14/100,000 population); recent outbreak of CAM in India
- Among underlying diseases uncontrolled diabetes overshadows all other risk factors
- Many new *Mucorales* have emerged causing infections

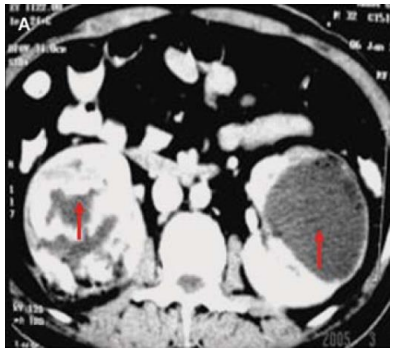


Rhizopus microsprus

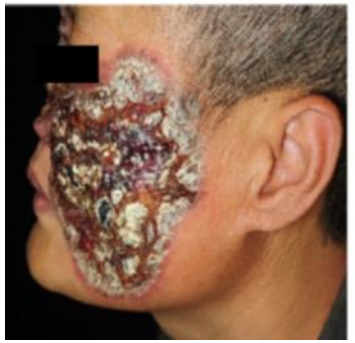
Mucor irregularis



Rhizopus homothallicus



Renal mucor

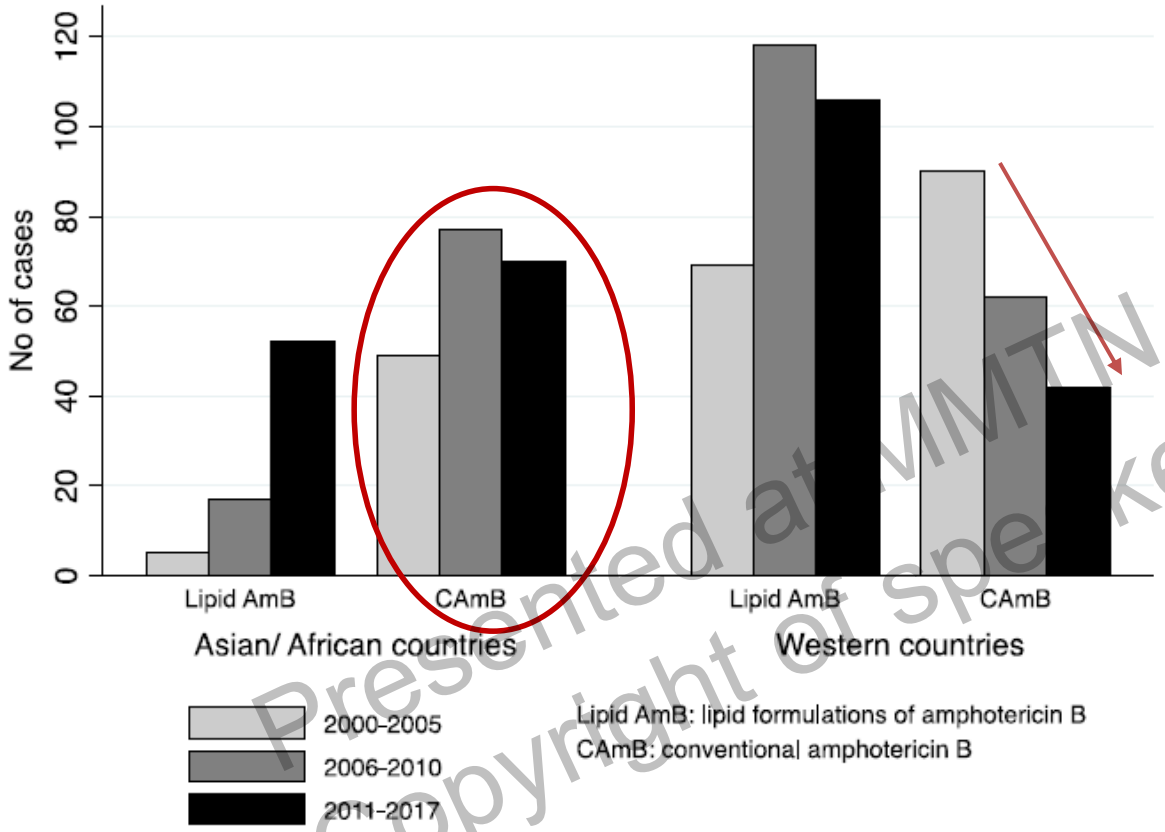


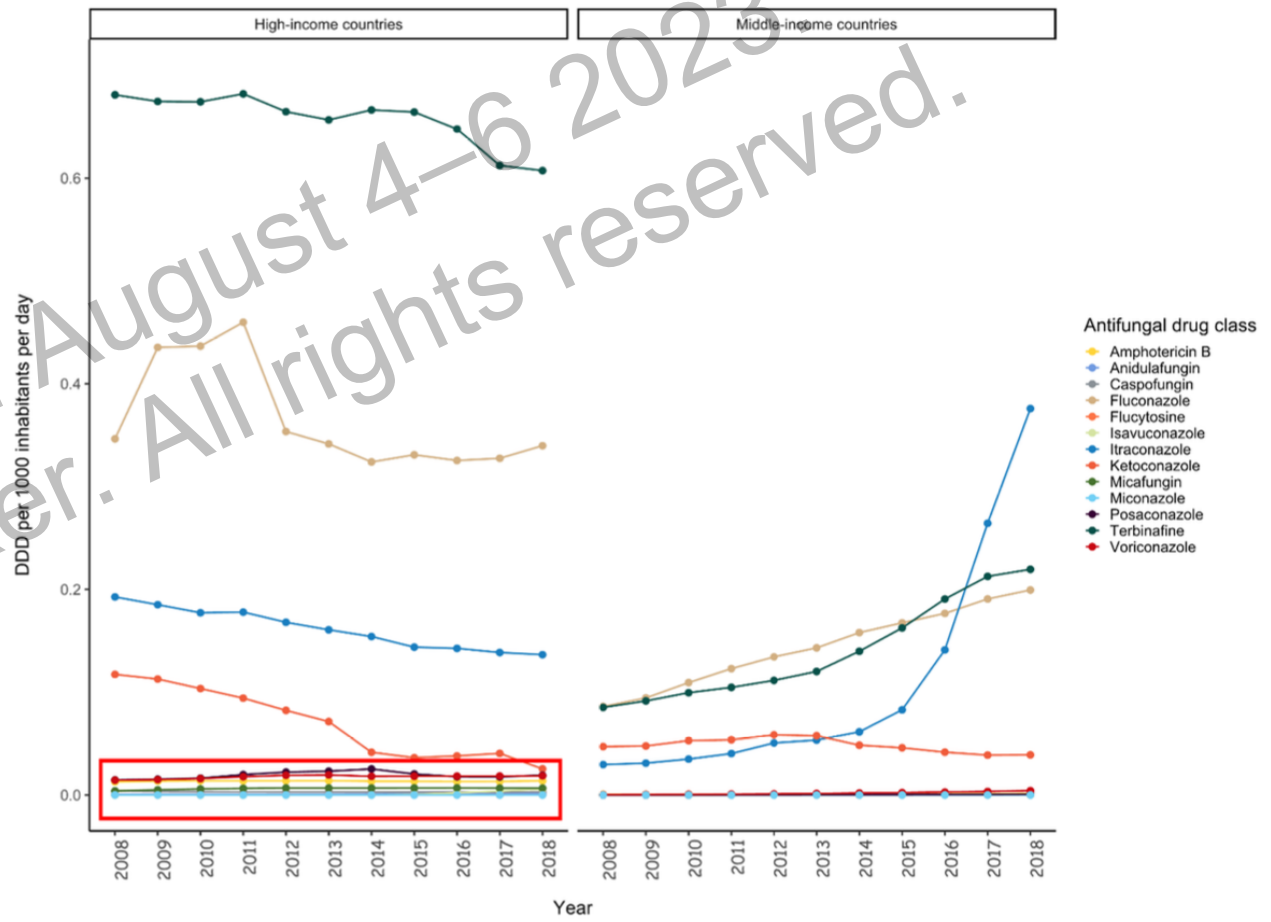
Chronic cutaneous

- New disease spectrum – isolated renal mucormycosis, chronic cutaneous mucormycosis
- Delay in seeking medical attention
- Management challenges due to cost of therapy (25.7% could not afford therapy)

Prakash & Chakrabarti. J Fungi 2019; 5: 26; Prakash & Chakrabarti. Microorganisms. 2021;9:523; Patel A, *et al.* Clin Microbiol Infect. 2020;26: 944.e9–944.e15

Antifungal use in developed & developing countries





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

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

'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

- **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

Though high incidence of mucormycosis in India is well known

- **Incidence is very high in India associated with uncontrolled diabetes**
- **Comparison of incidence /1,000,000 population**
  - **US** **-1.7cases/1,000,000** (allogenic HSCT – 0.29%; SOT-0.07%)
  - **Europe** **-0.43-1.2cases/1,000,000**
  - **India** **-140 cases/1,000,000**

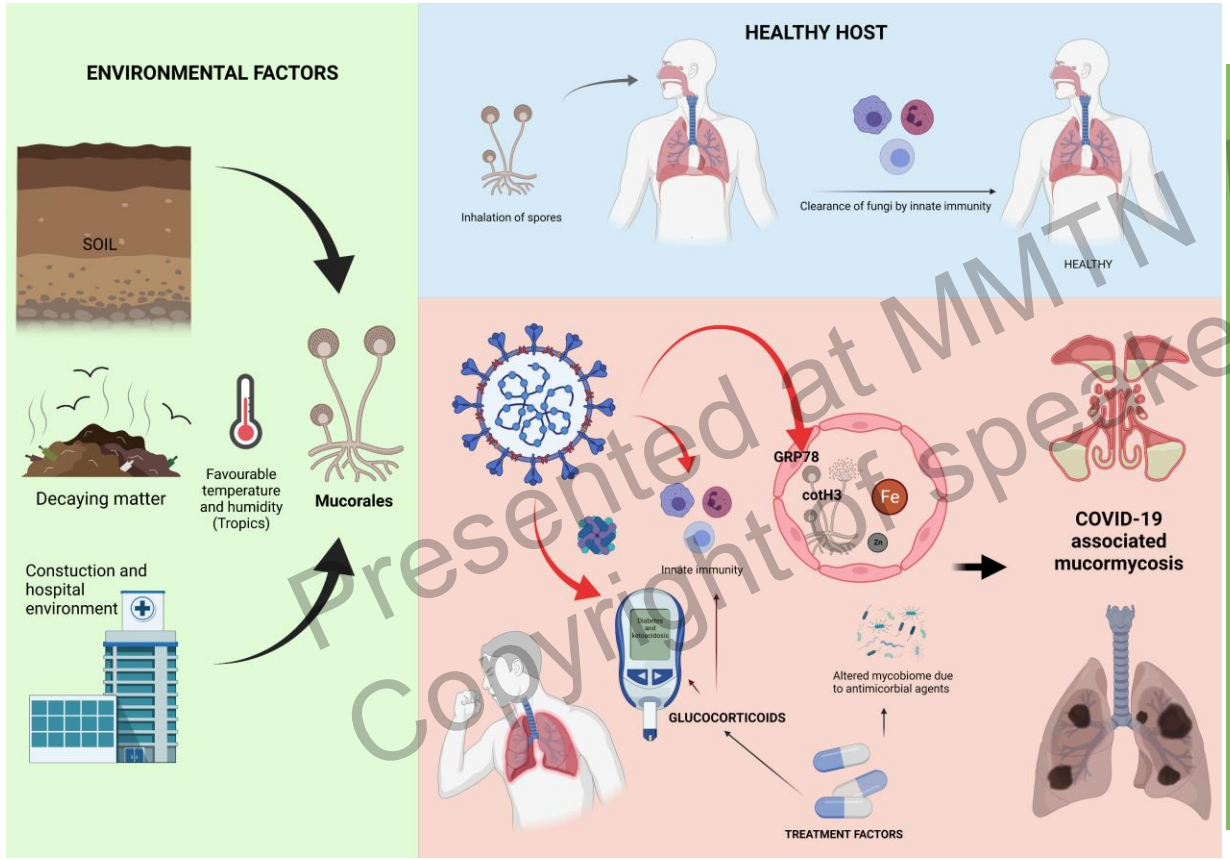
But, COVID-19 associated mucormycosis is unprecedented – A STORM

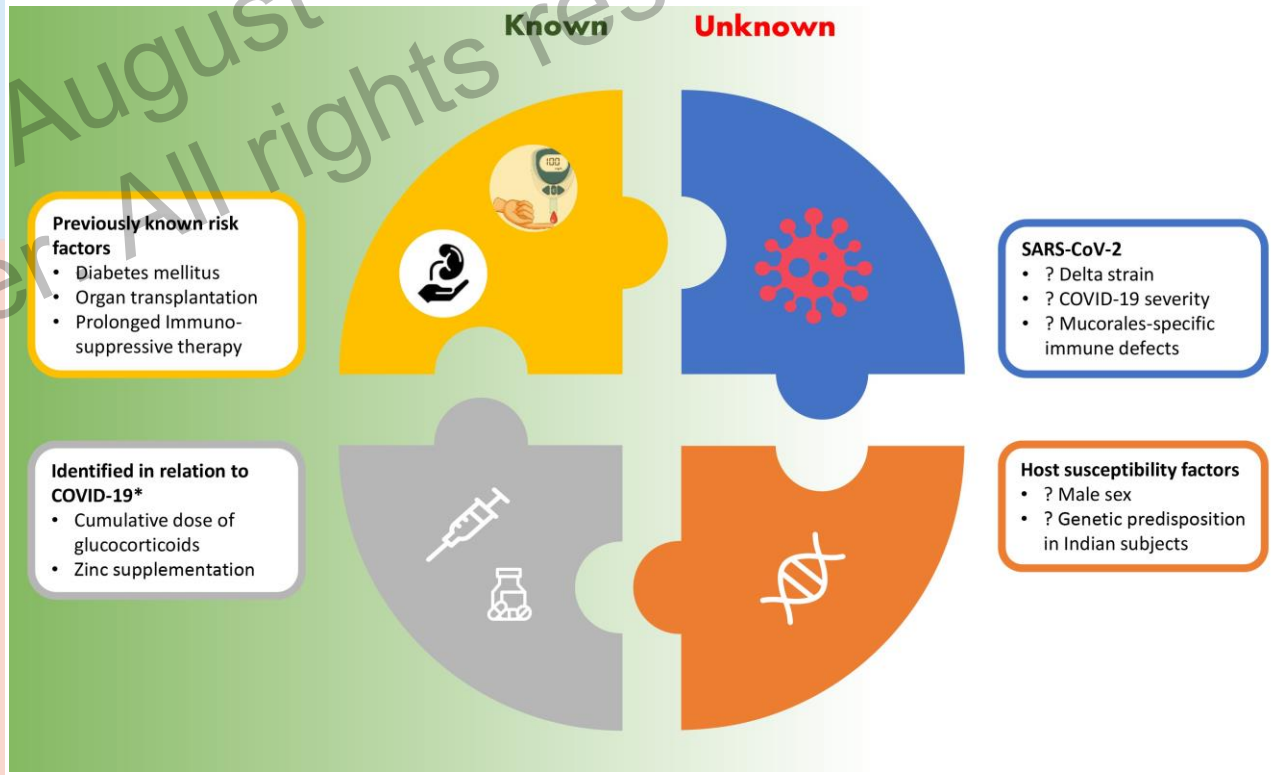
Lawley B., et al. 2004. *Appl. Environ. Microbiol.* 70: 5963; Redman RS., et al. 1999. *Appl. Environ. Microbiol.* 65: 5193; Prakash & Chakrabarti J Fungi 2019; 5: 26; Checinska A. et al. 2015 Microbiome 3:50; Prakash H, *et al.* Med Mycol 2020; 58: 11

Myriad hypothesis

- High Mucorales spores around garbage & construction of makeshift COVID 19 facilities
- Contamination of oxygen supplies, respiratory equipment, humidifier water
- Reused face masks and zinc supplements

Soman & Sunavala. Editorial. J Assoc Physicians India 2021; 88





Muthu V, *et al*. Mycopathologia 2021; 186: 739-54

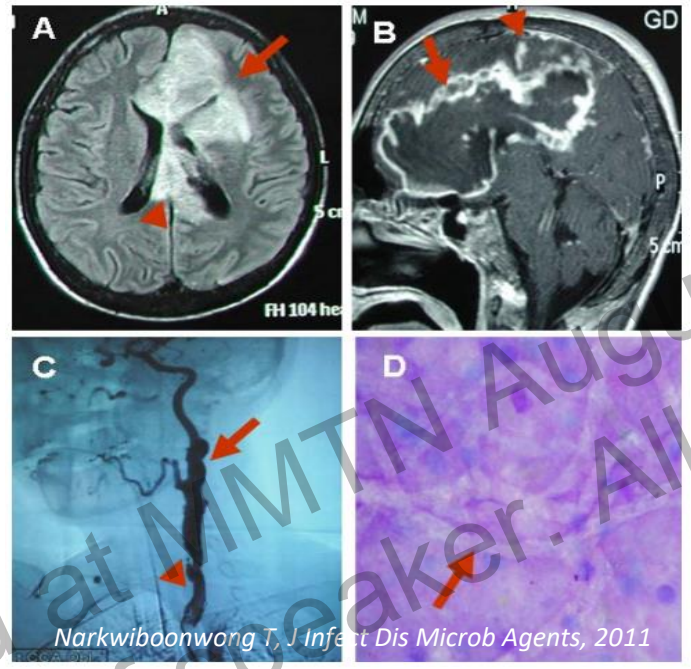
Muthu, Agarwal, Chakrabarti. Indian J Med Microbiol 2023; 44: 100382

Certain unique fungal diseases & clinical manifestations in Asia-Pacific region

Human pythiosis in Asia

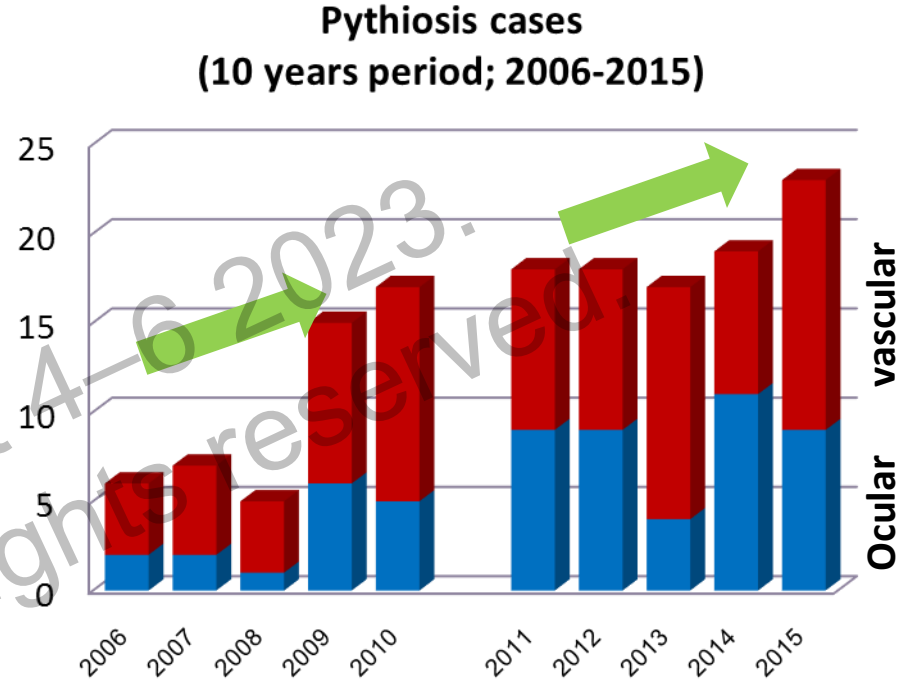
Vascular pythiosis

Cerebral pythiosis



Ocular pythiosis

(sub) Cutaneous form



Highest number in Thailand

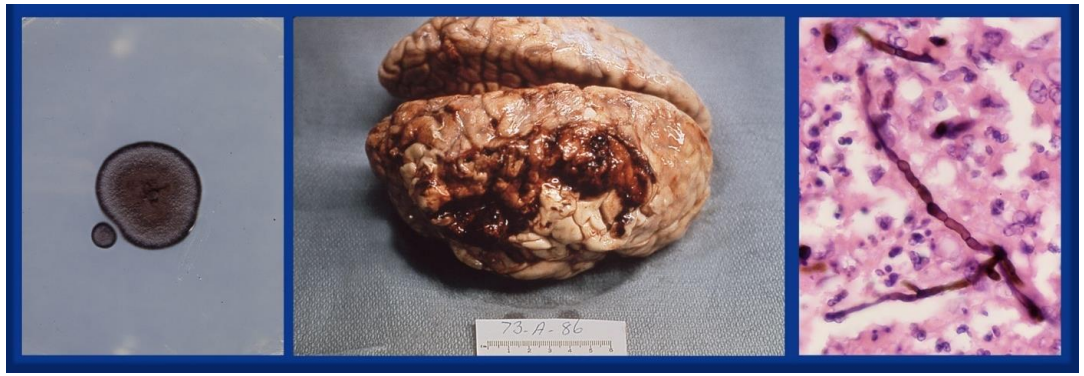
Krajaejun T, *et al.* Clin Infect Dis 2006; 43: 569-76

Country	Pythiosis Cases	Reference
Malaysia (Kuala Lumpur)	*Pythium* keratitis disposable contact lens wear, and swimming in the Kelang River	Badenoch et al., 2001; Br J Opthalmol 2001; 85: 502
India (Telangana)	13 *Pythium* keratitis cases during 2010-2012	Sharma S et al. Cornea 2015; 34: 438-42
China (Hainan)	*Pythium* keratitis in a boy who was scraped by twigs while climbing a tree	Hong H et al. Am J Case Rep 2016; 17: 982-8
Israel	Contact lens-related *Pythium* keratitis	Tanhehco TY et al. Eye Contact Lens 2011; 37: 96

Trichosporonosis

- **Frequently encountered in Thailand, Taiwan & Japan**
- **Thailand**
  - **6% of all fungemia cases** & cannot be distinguished from candidemia (Anunnatsiri *et al.* Int J Infect Dis 2009; 13: 90)
  - Majority cases in ICUs, with malignancies, CVC, antibiotic exposure (Ruan *et al.* CID 2009; 49: e11)
- **Japan** (Suzuki *et al*. Eur J Haematol 2010; 84: 441)
  - **Breakthrough infection (91%) after micafungin therapy** & mortality (76%)
  - Only 12% cases beta-glucan positive
- **Taiwan** (Ruan *et al*. CID 2009; 49: e11)
  - **84% positive for *T. asahii***, then *T. dermatis, T montevideense*
- Other than fungemia, pulmonary, soft tissue infection & meningitis

Cerebral phaeohyphomycosis due to *Cladophialophora bantiana*

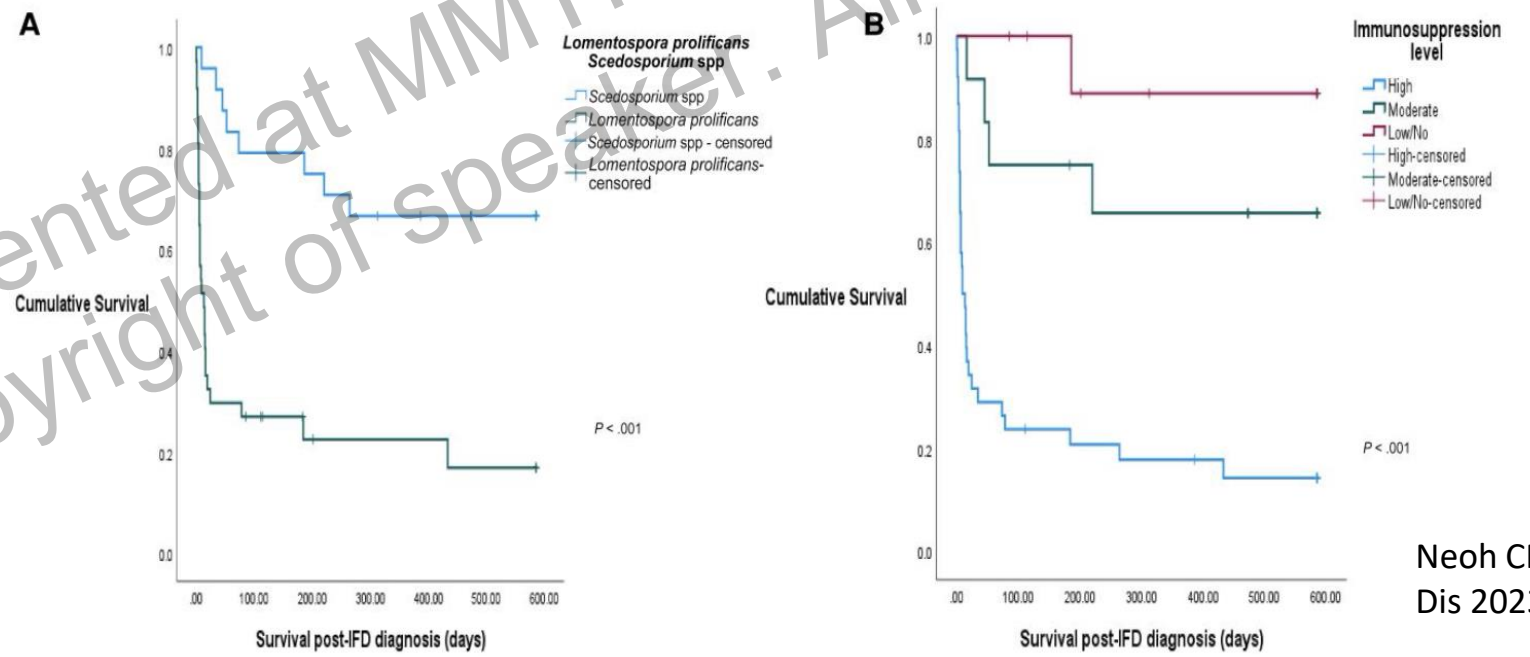


Place	No. of cases	Age M/F	Immunocompromised	Mortality	Con. AMB	Lipid AMB	Vorico-nazole
World	102	39 76:26	36.3%	63.5%	15/46 (32.6%)	6/16 (37.5%)	3/14 (21.4%)
Asia	51	32 43/8	17.7%	50.0%	12/21 (57.1%)	3/4 (75.0%)	2/3 (66.7%)
India	41	32 36/5	14.6%	50.0%	11/19 (57.9%)	1/1 (100%)	1/2 (50%)

Chakrabarti A, *et al*. Med Mycol 2016; 54: 111-119

Invasive *Scedosporium* & *Lementospora prolificans* infections in Australia

- 47.5% disseminated infection
- **Prolonged neutropenia (44.3%), immunosuppression (80.3%) are major risk factors**
- **Only 36.1% attained treatment success at 18 months**
- **Outcome was poor particularly with *L. prolificans* infections or in highly immunosuppressed population**



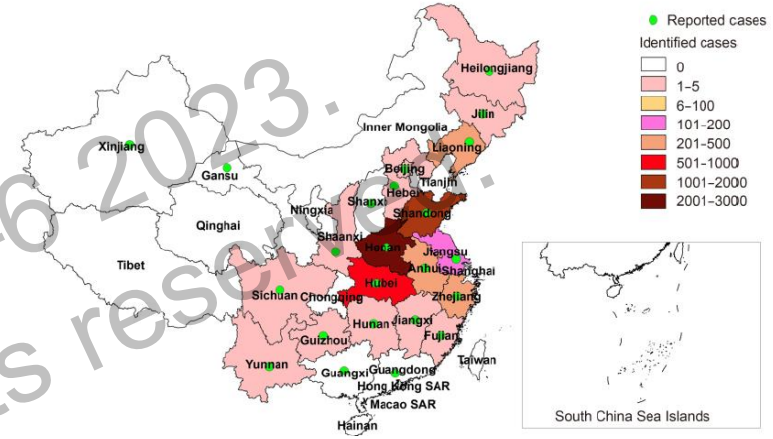
Neoh CF, *et al*. Open Forum Infect Dis 2023; 10: ofad 059

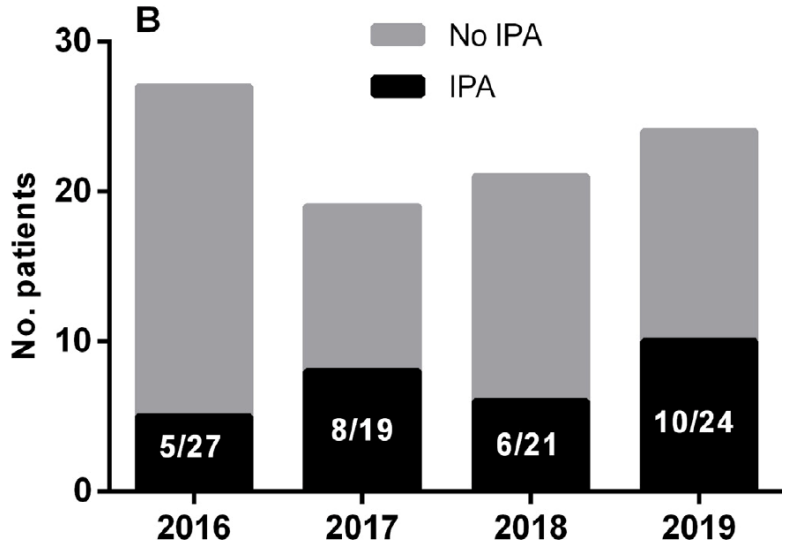
International Journal of Infectious Diseases 105 (2021) 646–652

Invasive pulmonary aspergillosis is a frequent complication in patients with severe fever with thrombocytopenia syndrome: A retrospective study

Ying Xu[a], Mingran Shao[b], Ning Liu[a], Jian Tang[a], Qin Gu[a], Danjiang Dong[a]

- **SFTS virus (bunyavirus) first isolated from Chinese patient in 2011; many thousands of cases reported**
- **Now the virus has also been isolated from patients in South Korea, Japan**
- **Regional clustering in hilly area during May-July & September**
- **Spread by ticks & also human to human**
- **Invasive pulmonary aspergillosis common with high fatality rate**





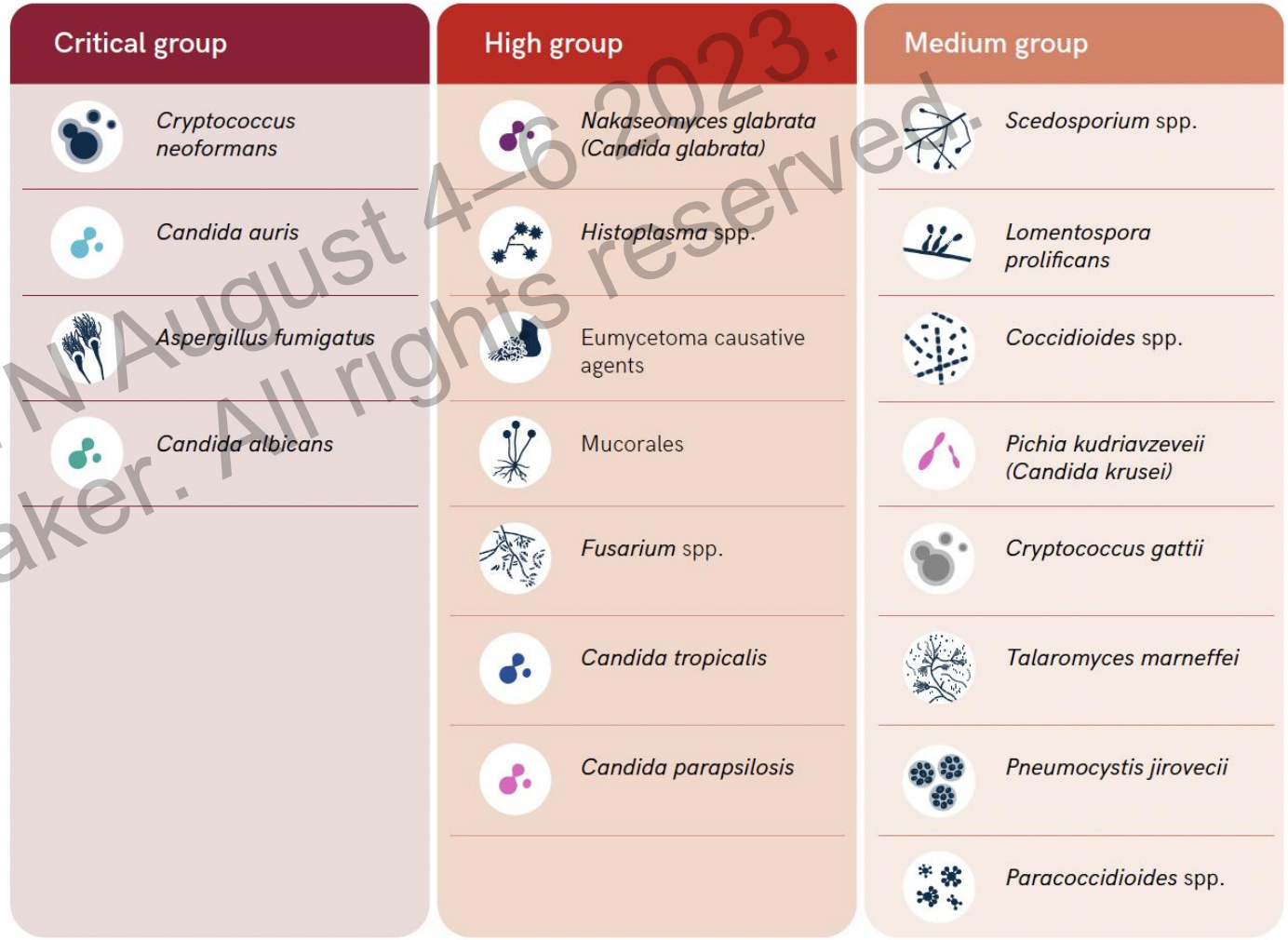
32% proven or probable IPA

Zhan J, *et al*. Virol Sin 2017; 32: 51-62

WHO priority fungal pathogens (released on 25.10.2022)

Prioritization linked to

- **Public health importance**
- **Antifungal resistance top priority**



- **Major knowledge gap in burden of resistance**
- **Epidemiology of antifungal resistance vary significantly by region**

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

Summary

- Prevalence of fungal disease is vey high with unique spectrum of agents
- Among endemic fungi, Talaromycosis (restricted), histoplasmosis, occasionally blastomycosis & emergomycosis
- Among yeast, *C. tropicalis* & *T. ashii* prevalence unique, high prevalence of *C. auris*
- Aspergillosis – real incidence not known; *A. flavus* prevalent in tropical area
- Mucormycosis – high incidence in India & China; association with diabetes; wide spectrum of agents; caused big outbreak with COVID 19 in India
- Outbreak due to rare fungi – affects large number of patients, difficult to diagnose & treat
- *P. insidiosum* infection prevalent in Thailand & India; *Scedosporium & Lementospora* in Australia; black fungus *Cladophialophora bantiana* in India
- However, awareness among clinicians is still lacking; few laboratories in majority countries
- AFWG is playing important role – training, education, research, networking

THANK YOU