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Evolving Lanscape of Emerging fungal Infection in Indonesia



- Consists of 17.000 islands, separated by the sea.
- Indonesia's population is 284,438,782 people (2025), the largest population in SE-Asia
- Tropical islands: warm & humid, which accommodate the growth of fungi
- The geographical situation affects the availability of health services
- Most of mycology laboratories being located in big cities in Java





 ${\sf TABLE\ 3}\quad {\sf Annual\ incidence\ and\ prevalence\ of\ the\ major\ serious\ fungal\ diseases\ in\ Indonesia}$

		Number of i	nfections pe	ear				
Infection	Incidene or prevalence	None	HIV/ AIDS	Respiratory	Cancer/ Tx	ICU	Rate/100K	Total burden
Oesophageal candidiasis	1	-	28.560	-	-	-	10	28,560
Cryptococcal meningitis	1	340	7.540	-	790	-	8.7	8,670
Pneumocystis pneumonia	I	-	15.400	-	15.400	2 8.	11.5	30,800
Histoplasmosis	1	?	1.060	?	?	?	0.4	1,060
Talaromyces marneffei infection	I	-	210	-	?	-	0.4	210
Invasive aspergillosis	1	- 1000	1.400	900	2,700	44,500	18.6	49,500
Mucormycosis	1 8	7 6b .	A	- \ \ \ \ \	530	3 4 %	0.20	530
Chronic pulmonary aspergillosis	P		A	378,700		/- \ \ \	142	378,700
Allergic bronchopulmonary aspergillosis (ABPA)	Р		11	336,200	KI	-	126	336,200
Severe asthma with fungal sensitisation (SAFS)	P		· //	443,800		i N/	166	443,800
Chronic fungal rhinosinutis	Р	294,000	-	-	CH	1/1A	110	294,000
Candidaemia	1	9300	-	-211	20,030	6,680	10	26,710
Candida peritonitis	1	- 69		CALL	/-	3,340	1.3	3,340
Recurrent vaginal candidiasis (>4 times/year)	Р	5,003,000	0	-	-	-	3,747ª	5,003,000
Tinea capitis	Р	729,000					270	729,000
Fungal keratitis	1	40,050	-	-	-	-	15	40,050
Total burden estimated		6,058,050	52,263	1,186,615	39,450	54,510		7,737,413

^aFemale population only.

Wahyuningsih et al Mycoses 2021

The burden of serious fungal disease in Indonesia

Underestimate:
Data is limited due to various constrains



Cryptococcosis – mostly in HV infection

Prev/incidence	Population	Diagnosis	Clinical Oro	VidAuthor
32/154 (20.8%)	HIV	India ink, culture, LFA	Meningitis	Sjam et al. MAJ Kedok UKI 2012
14/340 (9%)	HIV	India ink, culture, LFA	Meningitis	Imran et al. AAN 2018
2 cases	ALL & CD4 lymphocytop enic	Culture, india ink, LFA	Meningitis	Wahyuningsih et al. 2014 & 2023 presentation
16/47	HIV	Culture, india ink, LFA	Meningitis	Ganiem et al AIDS 2009
6/26	HIV	Touch biopsy	Skin lesion	Wahyuningsih et al. IJTech 2021
7%	HIV treated	LFA	None	Antara et al
58/810 (7.1%)).	HIV	LFA	WHO clinical stage 4	Ganiem et al.2014

Most of the Indonesian isolates are resistant to 5FC

Most of the isolates is C. neoformans serotype A, incl. isolates from Borneo & Papua

Pan et al PlosOne 2012 Data of Parasitology Lab



Candidemia: most study were conducted in Java,

3.5%

13.7%

Candida spp.

C. parapsilosis

Prev/incidence	Species (dominant)	Populations	Type of study	Authors
12.3 %	C. albicans & C. topicalis	Adult Sepsis –tert hosp	retrospective	Kalista et al. 2017
74 pts, 4 years	C. parap, C. trop, C. alb	adult, pediatric, tert hosp	retrospective	Wulandari et al 2021, Semarang
NA	C. trop, C. alb.	sputum >, blood, urine, tert hosp	retrospective	Sahetapy et al 2022 , Bali
117 cases 2011-2014	C. trop, C. alb	adult, pediatric, tert hosp	retrospective	Mursinah et al 2016
123 cases11 years	C. alb, C. paraps	adult	retrospective	Wiwing et al 2024
48 cases, 3 years	C. alb, C. trop	adult, pediatric, tert hosp	retrospective	Faizah et al 2024
19 (16.5%) /115	NA	adult, tert hosp.	prospective	Sedono et al. 2023
141 (3,9%) /3600, 3 years	NA NA	Neonates	Retrospective	Wijayanto et al. 2009

ICU

Neurological patients with

sepsis/fever

Retrospective

Prospective

Maulana et al 2019, Bandung

Rinawati et al. 2022

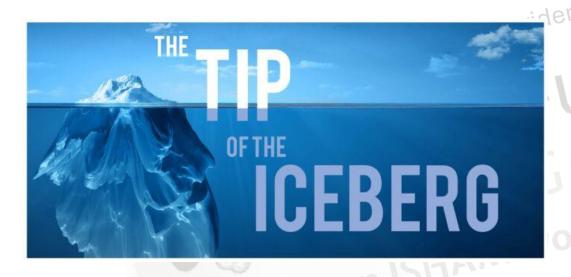
Candidemia

- A previous study conducted in 1998 (Jakarta) on adults identified *C. albicans* as the causative agent of invasive candidiasis (Wahyuningsih et al., JCM 2000).
- 10 later; neonates in PICU, Jakarta, *C. tropicalis* was the causative agent (Wahyuningsih et al., MKI 2008).
- As for *Candida auris*, there have been no reports of it causing invasive candidiasis.





Mucormycosis considered rare case



Indonesia:
Cause is *R. arrhizus/oryzae*

In the 2000s

4 cases of mucormycosis was identified in the Mycology laboratory:

- 3 cases with haematology malignancy rhino sinusitis & disseminated DPJP Prof. Dr. Ari Haryanto
- 1 case of abdominal wall mucormycosis that appear after C surgery DPJP Dr. Gentur Sujatmiko

In 2010 – one case with renal mucormycosis - DPJP Prof. Dr. Ponco Birowo.



Mucormycosis – Indonesia

- Mostly caused by R. arrhizus/R. oryzae
- Sinusitis, rhino-orbito-cerebral mucormycosis, pulmonary mucormycosis, renal mucormycosis, & skin
- Underlying disease:
 - Diabetes mellitus

 - Hematology malignancy
 No clear upol No clear underlying disease
- Age: adult & children

Mucormycosis: reported cases



Marpaung et al JIPD 2018, 5(1): 42-5; Nelwan et al. Acta Med Indones 2021, 53(3):349-51; Wulandari et al J Indones Oral Mc Soc. 2024; TN Putra et al. J Mycol Infect 2024; 29(3): 170-174; Octora et al. 2022 http://creativecommons.org/licenses/by-nc/4.0/; Dhiyantari et al J Narra 2023; Rochmah et al

Pneumocystis jiroveci

WAHYUNINGSIH ET AL.

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TARIF 3	Annual incidence and prevalence of the major serious fungal diseases in Indonesia	

Infection		Number o	f infections p					
	Incidene or prevalence	None	HIV/ AIDS Respiratory		Cancer/ Tx ICU		Rate/100K	Total burden
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- Patients treated in the ICU
- HIV; using Mab: 8/55 (14.6%); PCP & PTB: 3/5 pts with positive AFB



Talaromycosis

- T. artroroseus & T. marneffei isolated from HIV & non-HIV patients (Surja et al Medical Mycology, 2019)
- Skin lesion in HIV infected patient; case report (Widaty et al. Dermatology Online 2020; Wahyuningsih et al IJ Tech 2021)
- Lung infection (Darma et al SAGE Open Med Case Reports 2017)
- Skin lesion (Karo et al, Earth and Environmental Sci 125 (2018)
- Its reservoir *R. sumatrensis* is endemic in Sumatera. but the report is scarce.

Wikipedia

Underestimate??



- Rhizomys sumatrensis or Indomalayan bamboo rat is distributed in SE Asia including Sumatera, Indonesia
- Known for its role as the reservoir & source of infection for talaromycosis marneffei
- In Jakarta, where we found talaromycosis artroroseus, the source of infection is *Rattus rattus* (house rat)
- This suggests that other rat species may serve as reservoirs of *Talaromyces* in nature.



Antifungal susceptibility test – Talaromyces spp

Table 1. Result of antifungal susceptibility test using Sensititre™ YeastOne ToviderS and

	William inhibitory concentration (MIC)										
Antifungal		- 5	T. atroroseus								
agents	TM7	TM1&2	TM3	TM4	TM5	TM6	TM8	TM9	TM10	T. atroroseus	
Anidulafungin	4	>8	>8	>8	>8	>8	>8	>8	>8	>8	
Micafungin	>8	>8	>8	>8	>8	>8	0.12	>8	>8	0.12 - > 8	
Caspofungin	4	>8	>8	>8	>8	>8	0.5	>8	>8	0.5 - > 8	
5-Flucytosine	2	>64	4	8	>64	>64	0.06	32	8	0.06->64	
Posaconazole	≤0.008	0.5	0.25	0.25	>8	0.5	0.25	0.5	0.25	0.25 - > 8	
Voriconazole	0.03	>8	4	8	>8	>8	0.12	>8	8	0.12 - > 8	
Itraconazole	≤0.015	1	0.25	0.25	>16	0.5	0.12	0.5	0.5	0.12 - > 16	
Fluconazole	4	>256	>256	>256	>256	>256	64	>256	>256	64->256	
Amphotericin B	1	3 40	2 2	4	>8	4	0.5	2	2	0.5 - > 8	

T. marneffei, Talaromyces marneffei.

- Susceptibility of *T. atroroseus* is variable & strain dependent,
- susceptibility test is important for its treatment

T. atroroseus, Talaromyces atroroseus.

aspergillosis

Acute; invasive aspergillosis Chronic form – pulmonary

Aspergillosis:

- Invasive lung infection: usually in ICU
 - o A study conducted in the ICU of 6 hospitals in Jakarta, showed the prevalence of IPA is 7.7% (31/405)
 - Diagnosis probable: clinical, radiology, risk factors & Mostly A. flavus
 - A sino pulmonary diseases (FPPL is A. fumigatus)



PTB & aspergillosis

The chronic form, has similar symptom with PTB



- 800
- Indonesia: 2nd second largest TB cases in the world,
- 2015-2023, TB incidence increased by 19%, & deaths by 26%
- 2025, on March detected 889.000 cases; 134.000 death/year
- Is the death only caused by TB? Co-infection with mycosis?



Epidemiology of CPA in Indonesia

Study of CPA in Indonesia												
Author	Populations	Prevalence	Method Diagnosis of CPA	Coinfection								
Setianingrum et al. Thorax 2022; 77 :821–8. (Jakarta)	Confirmed, unconfirmed TB	Proven 12 (6%) Probable 5 (2%) Possible 15 (7%) CPA, 6% at the starting & 8% at the end of TB therapy,	Asp Ig/culture, radiology & clinical	TB & Aspergillus								
Dewi et al Med Mycol 2023	Confirmed & unconfirmed TB	26.9% confirmed 18.2% unconfirmed	Ab detection	Histoplasma								
Suroso et al <u>J Fungi</u> (<u>Basel</u>). 2024; 10(8): 529.	MDR TB	32%	Ab detection	Histoplasma								
Wangko et al, MSJ. 2021; 3(1):1 -7	Post treatment PTB	25/72 (34,7%)	Ab detection	-								

CPA – Pulmonary Tb (PTB)

- Studies have shown that Aspergillus antibodies are present in patients with PTB.
- Further research is needed among PTB patients to assess the extent of this issue.
- It is important to consider fungal infections when managing tuberculosis.
- The treatment for aspergillosis is different from that for Tb
- Antifungal medications, such as itraconazole, are necessary for treating CPA.













Histoplasmosis

Histoplasmosis in Indonesia

- The first case of disseminated histoplasmosis was identified in a 7-year-old boy from Lumajang, East Java, by Muller in 1932.
- Since then many literatures reported cases of disseminated form, especially in Java, but chronicpulmonary histoplasmosis (CPH) never been reported.
- CPH, & disseminated form often diagnosed as TB infection



Cases of disseminated histoplasmosis in Indonesia since 1932

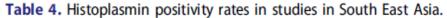


- Java: Jakarta, Bogor, Sukabumi, Bandung (West Java), Brebes, Pemalang, DI Yogyakarta (Central Java), Surabaya, Gersik, Lumajang (East Java).
- Bali: cases of disseminated histoplasmosis (Parwati T, pers comm)
- Celebes: Manado, HIV with skin dissemination (Tuda J, pers comm)
- Borneo: laryngeal ulcer; which part of Borneo? (Dowe et al Med J Aust, 1953)



Histoplasma skin test

- 2019- 2020, HST was carried out in six cities: Jakarta, Bandung, Sukabumi, Semarang, Surabaya, Malang and Manado.
- The subjects: chronic pulmonary disorders such as post-TB/chronic TB/COPD
- 290 patients: 166 (57,2%) were male.
- 5 positive; 3 males & 2 females (50-74 years old).



High prevalence of skin test, in line with case's reported

No	Area	Percent positive (%)	Dilution used	Population studied	Reference
1	Myanmar (Burma)- Upper	8.4	1:100	3558 prisoners/ prison staff	[31]
2	Myanmar (Burma)- Lower	14.5			[31]
3	Myanmar (Burma)- Rangoon	27.1		- A \	[31]
4	Myanmar(Burma)- Maguee	86.4		16/1	[31]
5	Philippines- Manila	6.4	1:100	2577 navy recruits	[32]
6	Philippines-Luzon Island	26.0	**	143 electric company employees	[33]
7	Thailand-Bangkok	5.6	N/A	497 medical/nursing students	[34]
8	Thailand-Northern region	14.0	1:100	4211 prisoners	[35]
9	Thailand-Central region	9.0			[35]
10	Thailand-Southern region	36.0	- 1	(.KU)	[35]
11	Indonesia-Jakarta (adults/children)	12.5/2.7	N/A	2542 students/nurses/hospital patients	[36]
12	Indonesia-Surabaya	32.0	N/A	281 school children/villagers	[37]
13	Indonesia-Kedisan (Bali)	63.6	1:100	340 school children/villagers	[37]
14	Indonesia-Medan	13.6	1:200	1265 medical Student	[38]
15	Malaysia-Sarawak	0.5	1:100	181 school children/hospital patients	[39]
16	Vietnam-Saigon	33.7	1:100	303 school children/villagers	[37]
17	Malaysia-Kuala Lumpur	10.5	N/A	224 adult residents	[26]
18	Malaysia-Sabah	11.8	N/A	3824 adult residents	[40]

^{*}Histolyn-CYL.

N/A - Information not available.

Emerging Microbes & Infections 2019, VOL. 8 https://doi.org/10.1080/22221751.2019.1644539







PTB & the existence of Histoplasma antibodies



Fig 1. The distribution of anti-*H. capsulatum* IgG antibody-positive serum specimens from pulmonary TB patients at seven TB referral hospitals in Indonesia. The original map was obtained from an openly available source https://www.naturalearthdata.com/. The figure was developed with QGIS 3.32.1 and https://biorender.com/.

A study conducted in 7 TB referral hospitals in Indonesia 39 of 306 (12.7%); (DR-TB patients (15.9%, 18/114), DS-TB (13.0%, 15/115), & unconfirmed TB



Our study of CPH among PTB patients

- Bandung area, West Java: n 122 PTB patients
- Confirmed TB; Ab to Histo 16.9%; A. fumigatus 26.9%
- Unconfirmed TB; Histo-Ab 4% & A. f 18.2%
- 1/3 pts with positive Ab histo had elevated levels of AB against A. fumigatus (p <0.001).

Discribution of patients with positive and negative anti-Histoplasma [16] and anti-Aspergillus antibody results.

Variable	Total (n = 50)	%
Positive <i>Histoplasma</i> IgG	14	28%
Negative <i>Histoplasma</i> antibodies	34	68%
Indeterminate result of <i>Histoplasma</i> antibodies	2	4%
Positive Aspergillus IgG/IgM	16	32%
Negative Aspergillus antibodies	34	68%
Mixed positive <i>Histoplasma</i> and <i>Aspergillus</i> antibodies	6	6%
Both were negative	24	48%

Medan, North Sumatera; 50 pts withMDR TB



The emergence of resistant strains

0,0

> J Fungi (Basel). 2022 Apr 16;8(4):411. doi: 10.3390/jof8040411.

Unravelling the Molecular Identification and Antifungal Susceptibility Profiles of Aspergillus spp Isolated from Chronic Pulmonary Aspergillosis Patients in Jakarta, Indonesia: The Emergence of Cryptic Species

Anna Rozaliyani ¹ ², Asriyani Abdullah ³, Findra Setianingrum ¹ ², Wellyzar Sjamsuridzal ⁴, Retno Wahyuningsih ¹ ⁵, Anom Bowolaksono ⁴, Ayu Eka Fatril ¹, <u>Robiatul Adawiyah</u> ¹ ², Mulyati Tugiran ¹ ², Ridhawati Syam ¹ ², Heri Wibowo ¹ ³, Chris Kosmidis ⁶ ⁷, David W Denning ⁶ ⁷

59 isolates: 19% were susceptible to AMB, 53% to voriconazole, 78% to itraconazole; Cryptic spp > non-cryptic species.

> PLoS One. 2012;7(3):e32868. doi: 10.1371/journal.pone.0032868. Epub 2012 Mar 13.

Resistance of Asian Cryptococcus neoformans serotype A is confined to few microsatellite genotypes

Weihua Pan ³¹, Kantarawee Khayhan, Ferry Hagen, Retno Wahyuningsih, Arunaloke Chakrabarti, Anuradha Chowdhary, Reiko Ikeda, Saad J Taj-Aldeen, Ziauddin Khan, Darma Imran, Ridhawati Sjam, Pojana Sriburee, Wanqing Liao, Kunyaluk Chaicumpar, Natnicha Ingviya, Johan W Mouton, Ilse Curfs-Breuker, Teun Boekhout, Jacques F Meis, Corné H W Klaassen

Resistant to 5FC

Periodical Dermato Venereology 2015

Uji Kepekaan Griseofulvin, Ketokonasol, Itrakonasol, dan Terbinafin terhadap Spesies Dermatofit dengan Metode Mikrodilusi

(Susceptibility test of Griseofulvin, Ketoconazole, Itraconazole, and Terbinafine to Dermatophyte Species Using Microdilution Method)

Dyah Ratri Anggarini*, Hari Sukanto*, Linda Astari*, Pepy Dwi Endraswari**

All T. rubrum are susceptible to AF " MIC_{80} 16.7% isolates sensitive to griseofulvin, 23.3% to ketoconazole, 16.7% to 80itraconazole & 20% to terbinafine."

			% Uji kepekaan antifungi										
No	Jenis Spesies jamur	Flukonazol						Vorikonazol					
		S (N)	S(%)	I(N)	I(%)	R(N)	R(%)	S (N)	S(%)	I(N)	I(%)	R(N)	R(%)
1	Candida albicans	11	64.7	5	29.4	21	28.4	15	62.5	2	28.6	22	28.6
2	Candida parapsilosis complex	1	5.9	1	5.9	0	0.0	1	4.2	1	14.3	0	0.0
3	Candida glabrata	0	0.0	4	23.5	7	9.5	3	12.5	0	0.0	8	10.4
4	Candida tropicalis	4	23.5	0	0.0	10	13.5	0	0.0	3	42.9	10	13.0
5	Candida sp	1	5.9	6	35.3	35	47.3	4	16.7	1	14.3	36	46.8
6	Candida krusei	0	0.0	1	5.9	0	0.0	1	4.2	0	0.0	0	0.0
7	Candida utilis	0	0.0	0	0.0	1	1.4	0	0.0	0	0.0	1	1.3
		17	100.0	17	100.0	74	100.0	24	100.0	7	100.0	77	100.0

Candida from patients with malignancies, showing emerging resistance to fluconazole & voriconazole (Pertiwi & Wahyuningsih 2024 unpubslihed.

Conclusion

- Indonesia is a tropical country that is conducive to the growth of fungi.
- The specific problem lies in the availability of Mycology laboratories Underlying conditions promote fungal diseases
- Important to identify mycotic diseases in special populations, such as those with TB, HIV, etc.
- The emergence of f-AMR: provide more data, to make accurate & useful decision to manage mycoses & prevent the emergence of f-AMR.

Terima kasih

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