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The current state of laboratory mycology in Asia/Pacific: A survey from the European Confederation of Medical Mycology (ECMM) and International Society for Human and Animal Mycology (ISHAM)

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ABSTRACT

Introduction: Invasive fungal infections (IFIs) in Asia/Pacific are a particular threat to patients with malignancies, uncontrolled diabetes mellitus or undiagnosed/untreated human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS). Adequate and early access to diagnostic tools and antifungals is essential for IFI clinical management and patient survival.

Methods: Details on institution profile, self-perception on IFI, and access to microscopy, culture, serology, antigen detection, molecular testing, and therapeutic drug monitoring for IFI were collected in a survey.

Results: As of June 2022, 235 centres from 40 countries/territories in Asia/Pacific answered the questionnaire. More than half the centres were from six countries: India (25%), China (17%), Thailand (5%), Indonesia, Iran, and Japan (4% each). Candida spp. (93%) and Aspergillus spp. (75%) were considered the most relevant pathogens. Most institutions had access to microscopy (98%) or culture-based approaches (97%). Furthermore, 79% of centres had access to antigen detection, 66% to molecular assays, and 63% to antibody tests. Access to antifungals varied between countries/territories. At least one triazole was available in 93% of the reporting sites (voriconazole [89%] was the most common mould-active azole), whereas 80% had at least one amphotericin B formulation, and 72% had at least one echinocandin.

Conclusion: According to the replies provided, the resources available for IFI diagnosis and management vary among Asia/Pacific countries/territories. Economical or geographical factors may play a key role in the incidence and clinical handling of this disease burden. Regional cooperation may be a good strategy to overcome shortcomings.

Contents

1. Introduction

Patients under immunosuppression and those with poorly controlled diabetes mellitus (DM) are at highest risk for invasive fungal infection (IFI). However, this may not apply worldwide, particularly in regions where endemic fungi are present, such as Asia/Pacific [1–4]. Furthermore, economic heterogeneity may be a key factor in recognising local disease patterns and access to diagnostic tools and drugs for IFI [3,5-10]. Laboratory diagnosis in the region might be challenging, and may take too long to yield a clinically applicable result, thereby delaying adequate patient care. Instant laboratory diagnosis is a critical factor in patient prognosis [11–13].

Environmental conditions, such as overpopulation, poverty, and climate, may be associated with an increasing incidence of IFI, even in immunocompetent individuals [14]. Uncontrolled baseline conditions, such as DM [2], long-term corticosteroid exposure [15–17], human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) [1,18], or extensive use of antibiotics [19,20], also contribute to the increasing number of patients at risk. Also, outbreaks due to contaminated surfaces or fomites [21], short-term immunosuppression (e.g., corticosteroid treatment of coronavirus disease 2019 [COVID-19] has increased the number of cases of invasive aspergillosis [22], candidiasis/candidemia [23] and mucormycosis [17,24]), or natural disasters [25] can likewise impact IFI risk. In addition, certain pathogens are known to be endemic in this region, as noted in the recently published cooperative guidelines of the European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM): *Blastomyces* spp., *Emergomyces* spp., *Histoplasma* spp., *Sporothrix* spp., and *Talaromyces* spp [26]. Other moulds and yeasts have also been reported to have high incidence rates, thereby putting even more pressure on the healthcare system [26–28].

In this study, the current laboratory diagnostic capability and antifungal drugs available in Asia/Pacific were screened to provide information for healthcare workers, patients and policymakers as an ongoing working plan of the ECMM and the ISHAM.Methods

An online electronic case report form (eCRF) was disseminated to clinical microbiologists, clinical parasitologists, infection control practitioners, infectious diseases specialists, medical mycologists, and laboratory professionals between June

2021 and April 2022. The eCRF was available online at www.clinicalsurveys.net/uc/IFI_management_capacity/ (EFS Summer 2021, TIVIAN GmbH, Cologne, Germany).

The information collected was screened to guarantee data completeness and clarity of the compiled variables. The eCRF was divided into the following domains: 1) institution profile, 2) IFI self-perception in the respective institution, 3) microscopy, 4) culture and fungal identification, 5) serology, 6) antigen detection, 7) molecular tests and 8) therapeutic drug monitoring (TDM) (Supplementary table 1).

All researchers invited to participate in this survey were affiliated to institutions in Asia/Pacific. Responses from institutions from certain transcontinental countries/territories were not included if they had already been analysed in previous publications [29–32]. To optimise survey response rates, bulk e-mails were sent, up to five times. Close collaborators of the authors were approached, for example, international societies with partners in the area, including the European Confederation of Medical Mycology (ECMM), Global Action For Fungal Infections (GAFFI), the International Society of Human and Animal Mycology (ISHAM, together with its Asia Fungal Working Group [AFWG], https://www.afwgonline.com/the-afwg) collaboration, and the Pacific Community (PC). Further, online scientific repositories) [33–37] and online accessible journals in the fields of clinical and medical mycology were assessed to identify and accrue potential participants. Additionally, online calls were sent on LinkedIn® and Twitter® social networks.

Based on the literature and epidemiological maps of endemic IFIs [26], countries/territories in which the participating institutions were located were classified as either IFI endemic or IFI non-endemic. Countries/territories were also categorised by their *per capita* GDP to highlight any differences in the availability of antifungals and diagnostic tests. Three GDP strata were established using the values from the 2021 International Monetary Fund (IMF) report: countries/territories with GDP <3000-US$, countries/territories with GDP 3000–20 000-US$ and countries/territories with GDP >20 000-US$, (Supplementary table 2) [38].

Suitability of the responding institutions as potential Blue ECMM Excellence centres was assessed, to determine which accreditation levels the respondents' institutions could attain if an application was submitted [39]. ECMM Blue status is the basic level in the scale of Excellence centres from the ECMM, which evaluates the diagnostic and clinical capacities of applying institutions, building an international collaborative network in IFI.

Categorical data were summarised with frequencies and percentages. Proportions were compared between countries/territories according to their GDP and within IFI endemic countries/territories, with Fisher's exact test (variables with at least one cell with expected value <5) and X^2 test (variables with all cells with expected value >5), as appropriate. *P*-values of <0.05 were considered statistically significant. SPSS v27.0 was used for statistical analyses (SPSS, IBM Corp., Chicago, IL, United States).

2. Results

A total of 235 sites replied to the online open call between June 2021 and April 2022. Almost 60% of the participants were from six countries/territories: India (n=58, 24.7%), China (n=39, 16.6%), Thailand (n=11, 4.7%), and Indonesia, Iran, and Japan (n=10, 4.3% each) (Figure 1, Supplementary table 3). Haematological diseases were treated in 83.8% (n=197) of the institutions. The majority of institutions also took care of individuals with solid tumours (n=183, 77.9%), provided parenteral nutrition (n=180, 76.6%), or had neonatal intensive care (ICU) services (n=179, 76.2%) (Table 1).

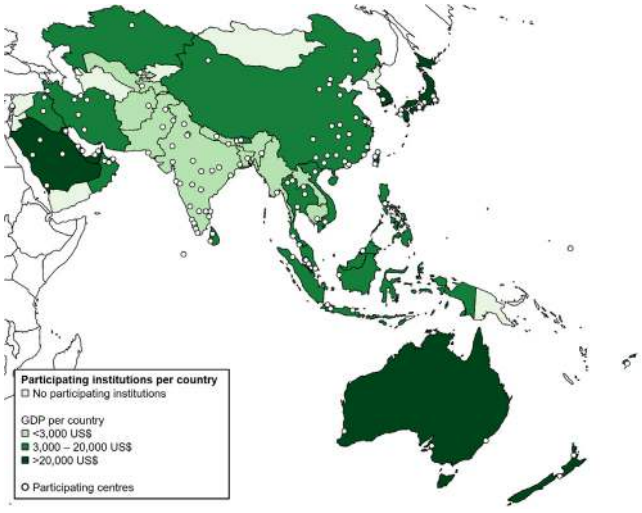

Figure 1. Map of participating Asian/Pacific institutions per country/territory
GDP, gross domestic product; **IFI**, invasive fungal infection.
In cases where there is more than one participating centre in the same city, a single point is pictured.
Number of sites per country/territory:
A) Countries/territories and territories with no participating institutions: *American Samoa, Christmas Island, Cocos (Keeling) Islands, Cook Islands, French Polynesia, Guam, Jordan, Kiribati, Kyrgyzstan, Marshall Islands, Mongolia, Nauru, New Caledonia, Niue, Norfolk Island, North Korea, Northern Mariana Islands, Palau, Papua New Guinea, Pitcairn Islands, Samoa, Solomon Islands, Syria, Timor-Leste, Tokelau, Tonga, Turkmenistan, Tuvalu, Vanuatu, Wallis and Futuna, and Yemen (n=0, each).*
B) Countries/territories and territories without report of endemic IFI: *Iran (n=10), Lebanon (n=7), Oman and Saudi Arabia (n=5, each), Kazakhstan, Kuwait, and Sri Lanka (n=3, each), Iraq, New Zealand, United Arab Emirates and Uzbekistan (n=2, each), Afghanistan, Bahrain, Federated States of Micronesia, Fiji, Maldives, Qatar, and Tajikistan (n=1, each).*
C) Countries/territories and territories with report of endemic IFI and GDP <3000-US$: *India (n=58), Pakistan (n=9), Bangladesh (n=5), Nepal (n=3), and Cambodia, Laos, and Myanmar (n=1, each).*
D) Countries/territories and territories with report of endemic IFI and GDP 3000–20 000-US$: *China (n=39), Thailand (n=11), Indonesia (n=10), Malaysia (n=9), Vietnam (n=4), Philippines (n=2), and Bhutan (n=1).*
E) Countries/territories and territories with report of endemic IFI and GDP >20 000-US$: *Japan (n=10), Australia and Taiwan (n=5, each), Singapore (n=4), South Korea (n=3), and Brunei, Hong Kong SAR, and Macau SAR (n=1, each).*

IFI incidence was self-assessed as very low or low by 118 sites (50.2%). Of those sites that considered their IFI incidence high or very high, the majority (n=39, 16.6%) were in countries/territories with endemic mycoses (endemic countries/territories: n=33/39, 84.6%; non-endemic countries/territories: n=6/39, 15.4%). When asked specifically about mucormycosis, two-thirds of the sites (n=156, 66.4%) regarded the local incidence as very low to low. Of those with a high to very high self-assessed mucormycosis incidence (n=11, 4.7%), 45.5% (n=5) of these were in India. Regarding the most important pathogens, 218 (92.8%) sites stated *Candida* spp., 177 (75.3%) *Aspergillus* spp., 104 (44.3%) *Cryptococcus* spp., and 93 (39.6%) Mucorales (Table 1, Supplementary table 2).

Overall, microscopic techniques were available at 231 (98.3%) of the respondent sites but there were variations in stain type. China/India ink (n=204, 86.8%) and potassium hydroxide (KOH, n=194, 82.6%) were the most common stains. Silver stain (n=113, 48.1%) and calcofluor white (n=103, 43.8%) were unavailable in around half the institutions. Statistically significant differences were observed in availability of Giemsa and KOH stains depending on the country's/territory's GDP (Giemsa P=0.046, KOH $P \leq 0.007$). Microscopy was reported as always used at 118 (50.2%) sites, and rarely or never used at 36 (15.3%) sites. Direct microscopy was performed on almost half the occasions when IFI was suspected (Table 2).

Table 1
Baseline characteristic of participating institutions in Asia/Pacific.

	Overall *(n=235)*		*<3000-US$ (n=89)*		*3000–20 000-US$ (n=102)*		*>20 000-US$ (n=44)*	
	n	%	n	%	n	%	n	%
Institution profile								
Type of institution								
Day-Hospital	10	4.3	5	5.6	2	2.0	3	6.8
Dialysis Clinic	11	4.7	6	6.7	3	2.9	2	4.5
Federal Institute / Research Hospital	24	10.2	12	13.5	9	8.8	3	6.8
Oncology Clinic	15	6.4	8	9.0	5	4.9	2	4.5
Private Hospital	49	20.9	39	43.8	5	4.9	5	11.4
Private Laboratory	6	2.6	4	4.5	1	1.0	1	2.3
Public Hospital	77	32.8	23	25.8	38	37.3	16	36.4
University Hospital	103	43.8	24	27.0	54	52.9	25	56.8
Other	22	9.4	8	9.0	14	13.7	0	0.0
Target patients								
COVID-19	175	74.5	79	88.8	57	55.9	39	88.6
Hematology	197	83.8	75	84.3	81	79.4	41	93.2
HIV/AIDS	167	71.1	72	80.9	61	59.8	34	77.3
Neonatal Intensive Care Unit	179	76.2	73	82.0	70	68.6	36	81.8
Oncology	183	77.9	69	77.5	76	74.5	38	86.4
Parenteral nutrition	180	76.6	70	78.7	71	69.6	39	88.6
Solid organ transplantation	126	53.6	43	48.3	51	50.0	32	72.7
Stem cell transplantation	106	45.1	33	37.1	44	43.1	29	65.9
Access to microbiology laboratory?	232	98.7	89	100.0	99	97.1	44	100.0
Yes, in place	223	94.9	86	96.6	94	92.2	43	97.7
Yes, outsourcing laboratory services	9	3.8	3	3.4	5	4.9	1	2.3
Mycological diagnostic procedures performed?	228	97.0	85	95.5	99	97.1	44	100.0
Always in our institution	144	61.3	64	71.9	55	53.9	25	56.8
Part in our institution / part outsourced	78	33.2	20	22.5	39	38.2	19	43.2
Totally outsourced	6	2.6	1	1.1	5	4.9	0	0.0
IFI incidence								
Very low	40	17.0	16	18.0	18	17.6	6	13.6
Low	78	33.2	28	31.5	39	38.2	11	25.0
Moderate	75	31.9	29	32.6	29	28.4	17	38.6
High	31	13.2	13	14.6	12	11.8	6	13.6
Very high	8	3.4	2	2.2	2	2.0	4	9.1
Incidence mucormycosis								
Very low	110	46.8	38	42.7	40	39.2	32	72.7
Low	46	19.6	21	23.6	21	20.6	4	9.1
Moderate	37	15.7	23	25.8	8	7.8	6	13.6
High	8	3.4	3	3.4	4	3.9	1	2.3
Very high	3	1.3	2	2.2	1	1.0	0	0.0
Most important pathogen(s)								
Aspergillus spp.	177	75.3	71	79.8	72	70.6	34	77.3
Candida spp.	218	92.8	82	92.1	96	94.1	40	90.9
Cryptococcus spp.	104	44.3	34	38.2	50	49.0	20	45.5
Fusarium spp.	57	24.3	26	29.2	21	20.6	10	22.7
Histoplasma spp.	32	13.6	15	16.9	17	16.7	0	0.0
Mucorales	93	39.6	49	55.1	32	31.4	12	27.3

COVID-19, coronavirus disease 2019; **HIV/AIDS**, human immunodeficiency virus/acquired immunodeficiency syndrome; **IFI**, invasive fungal infection; **spp.**, species; **USS**, United States dollar.

Culture-based diagnosis was available at 229 (97.4%) of the replying sites, although not all reported fungal media were available in similar proportions. Only three mycological agars were accessible in more than half the centres: Sabouraud dextrose agar (SDA, n=197, 83.8%), SDA combined with chloramphenicol (n=162, 68.9%), and potato dextrose agar (n=131, 55.7%). Lactrimel agar was accessible at only 17 sites (7.2%). Access to lactrimel agar was significantly more common in countries/territories with higher GDP (<3000-US$: n=2, 2.2%; 3000–20 000-US$: n=7, 6.9%; >20 000-US$: n=8, 18.2%; P=0.005). Access to pathogen-specific identification tests was reported in 207 (88.1%) of the institutions, mainly through classical phenotypic mycology (n=154, 65.5%) or automated identification systems (n=152, 64.7%). Availability of deoxyribonucleic acid (DNA) sequencing and matrix-assisted laser desorption/ionization–time-of-flight–mass spectrometry (MALDI–TOF–MS) was significantly different according to the country's/territory's GDP, both in the overall sample and within endemic countries/territories (P<0.001). Broth microdilution using Clinical and Laboratory Standards Institute (CLSI) standards was the most common method reported for antifungal susceptibility testing (Table 2, Supplementary table 2).

Antibody detection tests were available in only 149 (63.4%) of the sites, with the following distribution: *Aspergillus* spp. (n=139, 59.1%), *Candida* spp. (n=92, 39.1%), and *Histoplasma* spp. (n=63, 26.8%). Access to serological tests was mainly outsourced, except for *Aspergillus* spp. (n=93, 66.9% onsite vs. n=46, 33.1% outsourced). There was a linear gradient in access to serology in general, and *Aspergillus* spp. specifically, with countries/territories with lower GDP having reduced access (P<0.001 in both cases); however, availability of *Histoplasma* spp. serology was greater in countries/territories with GDP <3000-US$ (n=25, 28.1%) than in those with GDP 3000–20 000-US$ (n=18, 17.6%) and this was statistically significant (P=0.002) (Table 2).

More than three-quarters of the responding facilities (n=186, 79.1%) perform antigen detection for different fungi, either onsite or by outsourcing to other laboratories. Of these, access to *Aspergillus* antigen tests was reported by 165 (70.2%) of the sites, with statistically significant differences between coun-

Table 2
Comparison of available diagnostic techniques for mycological diagnosis in Asia/Pacific.

	Overall *(n=235)*		*<3000-US$ (n=89)*		*3000–20 000-US$ (n=102)*		*>20 000-US$ (n=44)*		*P* value	
	n	%	n	%	n	%	n	%		
Microscopy	231	98.3	87	97.8	101	99.0	43	97.7	0.674	*
Methodologies										
Calcofluor white	103	43.8	39	71.9	38	71.6	26	59.1	0.054	§
Giemsa stain	160	68.1	64	89.9	73	84.3	23	52.3	0.046	§
China/India ink	204	86.8	80	92.1	86	78.4	38	86.4	0.497	§
Potassium hydroxide	194	82.6	82	48.3	80	45.1	32	72.7	0.007	§
Silver stain	113	48.1	43	34.8	46	45.1	24	54.5	0.594	§
Others	92	39.1	31	0.0	46	0.0	15	34.1		
Microscopy frequency when IFI suspected										
Never	12	5.1	4	4.5	7	6.9	1	2.3		
Rarely	24	10.2	9	10.1	10	9.8	5	11.4		
Sometimes	37	15.7	7	7.9	23	22.5	7	15.9		
Often	43	18.3	11	12.4	22	21.6	10	22.7		
Always	118	50.2	58	65.2	39	38.2	21	47.7		
Access to fluorescence dye?	120	51.1	44	49.4	51	50.0	25	56.8	0.693	§
Direct examination in body fluids when cryptococcosis suspected	207	88.1	79	88.8	89	87.3	39	88.6	0.964	§
Yes, China/India ink	196	83.4	76	85.4	82	80.4	38	86.4		
Yes, other dyes	11	4.7	3	3.4	7	6.9	1	2.3		
Silver stain when pneumocystis suspected	95	40.4	38	42.7	37	36.3	20	45.5	0.497	§
Direct microscopy when mucormycosis suspected	106	45.1	47	52.8	39	38.2	20	45.5	0.133	§
Culture and fungal identification	229	97.4	88	98.9	99	97.1	42	95.5	0.420	§
Blood cultures when fungemia suspected	170	72.3	65	73.0	68	66.7	37	84.1	0.098	§
Fungal culture methods										
Agar Niger	65	27.7	20	22.5	32	31.4	13	29.5	0.377	§
Chromogen	61	26.0	16	18.0	34	33.3	11	25.0	0.056	§
Lactrimel agar	17	7.2	2	2.2	7	6.9	8	18.2	0.005	*
Potato dextrose agar	131	55.7	46	51.7	59	57.8	26	59.1	0.618	§
SDA	197	83.8	77	86.5	84	82.4	36	81.8	0.754	§
SDA + Chloramphenicol	162	68.9	68	76.4	68	66.7	26	59.1	0.106	§
SDA + Gentamicin	99	42.1	45	50.6	36	35.3	18	40.9	0.108	§
Selective agar (Chloramphenicol + Cycloheximide)	112	47.7	46	51.7	48	47.1	18	40.9	0.501	§
Others	76	32.3	26	29.2	33	32.4	17	38.6		
Available tests for specific identification	207	88.1	76	85.4	90	88.2	41	93.2	0.435	§
Automated identification (i.e., VITEK, other commercial tests)	152	64.7	55	61.8	64	62.7	33	75.0	0.290	§
Biochemical tests (classic mycology)	154	65.5	54	60.7	70	68.6	30	68.2	0.482	§
DNA sequencing	85	36.2	12	13.5	48	47.1	25	56.8	<0.001	§
MALDI – TOF – MS	101	43.0	21	23.6	44	43.1	36	81.8	<0.001	§
Mounting medium	92	39.1	38	42.7	37	36.3	17	38.6	0.658	§
Antifungal susceptibility tests?	197	83.8	70	78.7	84	82.4	43	97.7	0.014	§
For yeasts	95	40.4	46	51.7	30	29.4	19	43.2		
For moulds	2	0.9	1	1.1	1	1.0	0	0.0		
For both	90	38.3	21	23.6	48	47.1	21	47.7		
Available antifungal susceptibility test technologies										
Broth microdilution, using CLSI standards	114	48.5	32	36.0	57	55.9	25	56.8	0.011	§
Broth microdilution, using EUCAST standards	37	15.7	9	10.1	21	20.6	7	15.9	0.135	§
E-test	87	37.0	38	42.7	33	32.4	16	36.4	0.338	§
VITEK	117	49.8	50	56.2	44	43.1	23	52.3	0.181	§
Maximum identification capability										
Yeasts	233	99.1	87	97.8	102	100.0	44	100.0		
Genus	32	13.6	19	21.3	7	6.9	6	13.6		
Genus / species	118	50.2	51	57.3	54	52.9	13	29.5		
Genus / species / complex	44	18.7	11	12.4	20	19.6	13	29.5		
Genus / species / complex / cryptic species	39	16.6	6	6.7	21	20.6	12	27.3		

(*continued on next page*)

Table 2 (*continued*)

	Overall *(n=235)*		*<3000-US$ (n=89)*		*3000–20 000-US$ (n=102)*		*>20 000-US$ (n=44)*		*P* value	
	n	%	n	%	n	%	n	%		
Moulds	233	99.1	88	98.9	101	99.0	44	100.0		
Genus	92	39.1	42	47.2	34	33.3	16	36.4		
Genus / species	141	60.0	46	51.7	67	65.7	28	63.6		
Serology	149	63.4	44	49.4	66	64.7	39	88.6	<0.001	§
Aspergillus spp.	139	59.1	40	44.9	62	60.8	37	84.1	<0.001	§
Onsite	93	39.6	21	23.6	49	48.0	23	52.3		
Outsourced	46	19.6	19	21.3	13	12.7	14	31.8		
Candida spp.	92	39.1	25	28.1	48	47.1	19	43.2	0.022	§
Onsite	55	23.4	9	10.1	36	35.3	10	22.7		
Outsourced	37	15.7	16	18.0	12	11.8	9	20.5		
Histoplasma spp.	63	26.8	25	28.1	18	17.6	20	45.5	0.002	§
Onsite	27	11.5	10	11.2	10	9.8	7	15.9		
Outsourced	36	15.3	15	16.9	8	7.8	13	29.5		
Antigen detection	186	79.1	66	74.2	79	77.5	41	93.2	0.032	§
Aspergillus overall	165	70.2	58	65.2	68	66.7	39	88.6	0.012	§
Aspergillus LFD	56	23.8	20	22.5	26	25.5	10	22.7	0.509	§
Onsite	31	13.2	11	12.4	15	14.7	5	11.4		
Outsourced	25	10.6	9	10.1	11	10.8	5	11.4		
Aspergillus GM ELISA	148	63.0	48	53.9	64	62.7	36	81.8	0.007	§
Onsite	93	39.6	29	32.6	41	40.2	23	52.3		
Outsourced	55	23.4	19	21.3	23	22.5	13	29.5		
Aspergillus GM LFA	70	29.8	28	31.5	32	31.4	10	22.7	0.900	§
Onsite	31	13.2	12	13.5	15	14.7	4	9.1		
Outsourced	39	16.6	16	18.0	17	16.7	6	13.6		
Candida antigen	68	28.9	21	23.6	31	30.4	16	36.4	0.309	§
Onsite	36	15.3	8	9.0	18	17.6	10	22.7		
Outsourced	32	13.6	13	14.6	13	12.7	6	13.6		
Cryptococcus overall	159	67.7	56	62.9	68	66.7	35	79.5	0.158	§
Cryptococcus LFA	115	48.9	46	51.7	51	50.0	18	40.9	0.487	§
Onsite	86	36.6	34	38.2	38	37.3	14	31.8		
Outsourced	29	12.3	12	13.5	13	12.7	4	9.1		
Cryptococcus LAT	113	48.1	36	40.4	53	52.0	24	54.5	0.187	§
Onsite	79	33.6	20	22.5	42	41.2	17	38.6		
Outsourced	34	14.5	16	18.0	11	10.8	7	15.9		
Histoplasma	51	21.7	22	24.7	17	16.7	12	27.3	0.245	§
Onsite	17	7.2	9	10.1	6	5.9	2	4.5		
Outsourced	34	14.5	13	14.6	11	10.8	10	22.7		
Beta-glucan	103	43.8	36	40.4	40	39.2	27	61.4	0.033	§
Onsite	55	23.4	14	15.7	26	25.5	15	34.1		
Outsourced	48	20.4	22	24.7	14	13.7	12	27.3		
Molecular tests	155	66.0	46	51.7	71	69.6	38	86.4	<0.001	§
Aspergillus PCR	103	43.8	27	30.3	52	51.0	24	54.5	0.004	§
Onsite	65	27.7	15	16.9	36	35.3	14	31.8		
Outsourced	38	16.2	12	13.5	16	15.7	10	22.7		
Candida PCR	104	44.3	27	30.3	59	57.8	18	40.9	<0.001	§
Onsite	67	28.5	16	18.0	42	41.2	9	20.5		
Outsourced	37	15.7	11	12.4	17	16.7	9	20.5		
Pneumocystis PCR	103	43.8	31	34.8	40	39.2	32	72.7	<0.001	§
Onsite	61	26.0	19	21.3	24	23.5	18	40.9		
Outsourced	42	17.9	12	13.5	16	15.7	14	31.8		
Mucorales PCR	69	29.4	22	24.7	34	33.3	13	29.5	0.427	§
Onsite	37	15.7	13	14.6	19	18.6	5	11.4		
Outsourced	32	13.6	9	10.1	15	14.7	8	18.2		
PCR for other fungi	85	36.2	17	19.1	47	46.1	21	47.7		
Onsite	49	20.9	7	7.9	30	29.4	12	27.3		
Outsourced	36	15.3	10	11.2	17	16.7	9	20.5		
Other molecular tests	82	34.9	23	25.8	41	40.2	18	40.9		
Onsite	46	19.6	14	15.7	22	21.6	10	22.7		
Outsourced	36	15.3	9	10.1	19	18.6	8	18.2		

* compared with Fisher's Exact test; §, compared with chi-squared (X^2) test.**CLSI**, Clinical and Laboratory Standards Institute; **DNA**, deoxyribonucleic acid; **ELISA**, enzyme-linked immunosorbent assay; **E-test**, epsilometer test; **EUCAST**, European Committee on Antimicrobial Susceptibility Testing; **GM**, galactomannan; **IFI**, invasive fungal infection; **LAT**, latex agglutination test; **LFA**, lateral flow assay; **LFD**, lateral flow device; **MALDI – TOF – MS**, matrix-assisted laser desorption/ionization – time-of-flight mass spectrometer; **PCR**, polymerase chain reaction; **SDA**; Sabouraud dextrose agar; **spp.**, species; **US$**, United States dollar.

tries/territories (*P*=0.012). Conversely, no differences were observed in access to point-of-care (POC) testing, such as lateral flow devices (LFD, n=56, 23.8%, *P*=0.509) or lateral flow assays (LFA, n=70, 29.8%, *P*=0.9). However, the option to perform enzyme-linked immunosorbent assay (ELISA, n=148, 63.0%) was inequitably distributed (GDP <3000-US$: n=48, 53.9%; GDP 3000–20 000-US$: n=64, 62.7%; GDP >20 000-US$: n=36, 81.8%; *P*=0.007). *Cryptococcus* LFA (n=115, 48.9%), *Cryptococcus* latex agglutination test (LAT, n=113, 48.1%) and ß-D-glucan (n=103, 43.8%) were available in almost half the responding sites (Table 2).

Access to polymerase chain reaction (PCR) and other molecular tests was reported in 155 (n=66.0%) institutions, with similar proportions for *Aspergillus* (n=103, 43.8%), *Candida* (n=104, 44.3%) or *Pneumocystis* (n=103, 43.8%) PCR (Table 2).

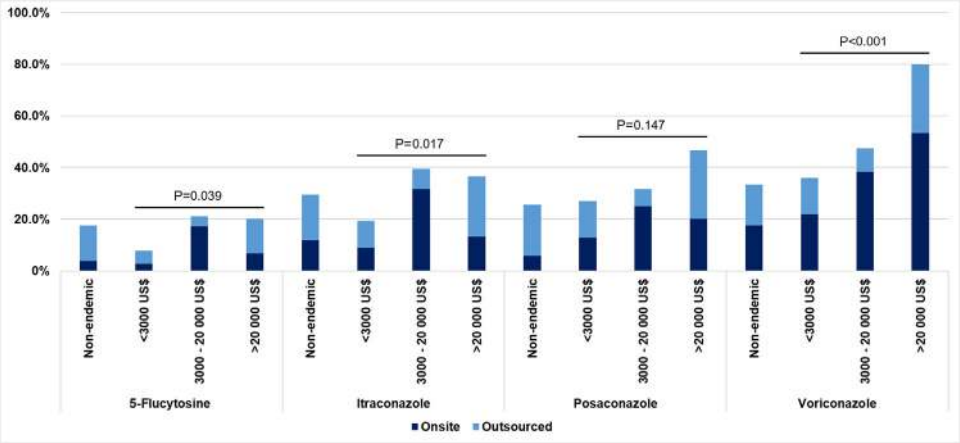

Figure 2. Histogram of the access to therapeutic drug monitoring in analysed Asian/Pacific institutions
USS, United States dollar.

Table 3
Comparison of available drugs for clinical management in Asia/Pacific.

	Overall *(n=235)*		*<3000-US$ (n=89)*		*3000–20 000-US$ (n=102)*		*>20 000-US$ (n=44)*		*P* value	
	n	%	n	%	n	%	n	%		
Available antifungals										
Amphotericin B	188	80.0	73	82.0	77	75.5	38	86.4	0.268	§
Amphotericin B deoxycholate	144	61.3	57	64.0	64	62.7	23	52.3	0.392	§
Amphotericin B lipid complex	67	28.5	32	36.0	27	26.5	8	18.2	0.084	§
Amphotericin B liposomal	135	57.4	62	69.7	37	36.3	36	81.8	<0.001	§
Amphotericin B - other formulations	32	13.6	19	21.3	9	8.8	4	9.1		
Echinocandins	170	72.3	61	68.5	70	68.6	39	88.6	0.029	§
Anidulafungin	81	34.5	37	41.6	21	20.6	25	56.8	<0.001	§
Caspofungin	131	55.7	54	60.7	53	52.0	37	84.1	0.001	§
Micafungin	132	56.2	37	41.6	51	50.0	29	65.9	0.032	§
Triazoles	219	93.2	85	95.5	92	90.2	42	95.5	0.321	*
Fluconazole	217	92.3	84	94.4	91	89.2	42	95.5	0.363	*
Isavuconazole	78	33.2	25	28.1	12	11.8	16	36.4	0.001	§
Itraconazole	164	69.8	70	78.7	80	78.4	39	88.6	0.327	§
Posaconazole	120	51.1	48	53.9	41	40.2	31	70.5	0.003	§
Voriconazole	184	78.3	70	78.7	75	73.5	39	88.6	0.126	§
Flucytosine	102	43.4	31	34.8	36	35.3	35	79.5	<0.001	§
Terbinafine	120	51.1	47	52.8	46	45.1	27	61.4	0.182	§

* compared with Fisher's Exact test; §, compared with chi-squared (X^2) test.**USS**, United States dollar.

Triazoles were accessible at 219 (93.2%) centres, mainly fluconazole (n=217, 92.3%) and voriconazole (n=184, 78.3%). Concerning mould-active azoles [40], there was at least one available at 208 (88.5%) sites, with no statistically significant difference between GDP strata. Nevertheless, individual site access to mould-active azoles was unequally distributed for these antifungals (isavuconazole: n=78, 33.2%, *P*=0.001; itraconazole: n=164, 69.8%, *P*=0.327; posaconazole: n=120, 51.1%, *P*=0.003; and voriconazole: n=184, 78.3%%, *P*=0.126). At least one amphotericin B formulation was available in 188 (80.0%) facilities, primarily the deoxycholate formulation (n=144, 61.3%). Echinocandins (specifically micafungin [n=132, 56.2%] and caspofungin [n=131, 55.7%]), terbinafine, and flucytosine were accessible in 170 (72.3%), 120 (51.1%) and 102 (43.3%) institutions, respectively. There were statistically significant differences in access to several antifungals (liposomal amphotericin B [LAMB], anidulafungin, caspofungin, micafungin, isavuconazole, posaconazole, flucytosine, and terbinafine). For all antifungals, except micafungin, centres from endemic countries/territories with GDP <3000-US$ had greater availability than those with 3000–20 000-US$. Nevertheless, countries/territories with a GDP >20 000-US$ had the broadest antifungal formulary (Table 3, Supplementary table 4). Availability of therapeutic drug monitoring (TDM) was evaluated for flucytosine, itraconazole, posaconazole and voriconazole; the latter being the most widely available (n=184, 78.3%), although access varied according to GDP (*P*<0.001) (Figure 2).

Of the 235 responding facilities, 68 (28.9%) fulfilled the criteria to be certified with ECMM Blue level status.

3. Discussion

Herein is presented data collected from 235 institutions in 40 countries/territories. To the best of our knowledge, this is the first survey to evaluate the IFI diagnostic and clinical management capabilities of Asia/Pacific. Similar analyses were restricted to smaller areas, such as Australasia [41] or South-East Asia [10,42,43].

Given the number of countries/territories with endemic IFI areas [26,44,45], and the economic differences prevailing, similar country/territory groupings were compared in this study. The relevance of such grouping was observed, among others, in the self-reporting IFI incidence. Sites from countries/territories classified as endemic reported that the IFI risk incidence at their institutions was moderate, high, or very high more frequently than sites from non-endemic countries/territories, which indicates that endemic IFIs are a reason for increased laboratory burden. These differences were also noted when the sites were asked specifically about perceived mucormycosis incidence. Of note, this survey was ongoing while there was an active epidemic of COVID-

19-associated mucormycosis in India [24]. *Candida* spp. and *Aspergillus* spp. were considered to be the most important pathogens amongst all endemic countries/territories, which is consistent with data published from other regions [29–32]. Interestingly, Mucorales were perceived as more relevant in countries/territories with a GDP <3000-US$, probably because of the presence of countries/territories with a high incidence of uncontrolled DM, such as India. Moreover, comparable to other areas with tropical regions, the significance of cryptococcosis was pertinent (Africa 55.0% [29], the Caribbean and Latin America 67.0% [30], Asia/Pacific 44.3%).

Overall, access to microscopy for IFI diagnosis was confirmed in almost every site (98.3%), with similar availability as reported in other regions [29–31]. Nevertheless, there were differences in access to Giemsa and KOH stains; the lower the GDP, the higher the availability of these stains, probably because of their low costs [46]. Interestingly, the highest proportion of sites performing direct microscopy for suspected mucormycosis was reported from countries/territories with the lowest income, possibly biased by the elevated IFI incidence due to Mucorales in South-East Asia [2,3,24].

Culture-based methodologies were available across almost all the presented country/territory groups (97.4%). These numbers are similar to those recently reported from Europe (98.7%) [32], and notably higher than those from South-East Asia (89.2%) in 2018 [42], or the Caribbean and Latin America (78.0%) in 2019, implying recent regional improvements in resources for mycotic disease [30]. Species identification and susceptibility testing are particularly relevant to Asia/Pacific, as several new fungal pathogens, including *Candida auris*, were first described in this region [47,48]. Feasibility of the newest and more costly platforms, i.e., DNA sequencing and MALDI–TOF–MS, for the detection of new species was inequitably distributed among replying sites (13.5-56.8% and 23.6-81.8% respectively), with the higher GDP countries/territories reaching equivalent accessibility to Europe [32], and others closer to African or Caribbean and Latin American resource levels [30]. This supports a link between the cost and the accessibility of such techniques in certain regions [49,50], and consequential challenges in a timely diagnosis. The availability of antifungal susceptibility testing in Asia/Pacific (overall 83.8%) is close to that in Europe (93.6%) [32], and much higher than in Africa (62.5%) [29] or the Caribbean and Latin America (61.0%) [30]. These results are encouraging in that acceptable regional standards for IFI management are attainable, but there is still room for improvement.

Preferred diagnostic tests for endemic mycoses reported from Asia/Pacific, according to current guidelines, include microscopy and in vitro cultures, in some cases with clear recommendations for specific stains and culture media [26]. Therefore, considering the overall levels of access to microscopy (98.3%) and culture (97.4%) from the replying sites, Asia/Pacific is becoming appropriately placed to diagnose endemic mycoses, as recommended by the World Health Organization (WHO) and its list of essential in vitro diagnostics for IFI, although access to such tools might vary geographically [51]. In the case of histoplasmosis diagnosis, serological and antigen tests are more useful, but these are not widely available in the analysed setting (26.8% and 21.7%, respectively), thereby hindering correct diagnosis and clinical management [26].

Notable capabilities for diagnosis of opportunistic fungi were reported, with 60-70% of the centres surveyed able to conduct antigen detection (e.g., for *Aspergillus* spp. and *Cryptococcus* spp.) and the majority performing the tests in-house. The prevalence for antigen-based diagnostics is followed by beta-glucan (~40%); least popular were those for *Candida* spp. and *Histoplasma* spp. (~20%). This marks an improvement in fungal antigen diagnostic capability in the region compared with a previous survey [42], in which 23% of centres had galactomannan detection capability vs. 66-88% in this study. These findings are in line with a survey in 2020 [10], in which 60.6% and 21.2% of centres reported access to galactomannan and beta-glucan, respectively.

The current study provides a novel overview of availability and antifungal usage in Asia/Pacific. At least one triazole was present in 93.2% of the analysed sites, mainly fluconazole (92.3%) and voriconazole (78.3%, the most frequent mould-active azole). Similarly, amphotericin B products were widely available in Asia/Pacific, with at least one systemic formulation accessible in 80.0% of sites, aligning with the WHO list of essential systemic antifungal drugs [52]. Access to other antifungals from this list, such as LAMB, was suboptimal, with availability at only 57.4% (n=135) of sites. Moreover, access to other antifungals from the list, such as echinocandins (at least one in 72.3% of the sites, anidulafungin in 34.5%, caspofungin in 55.7%, and micafungin in 56%), itraconazole (69.8%) or flucytosine (43.4%), need to be further improved. Similar lower accessibility was reported for newer antifungals that are not on the WHO list: isavuconazole (33.2%) and posaconazole (51.1%). Although there do not appear to be any earlier references in the literature on the availability of newer generation azole and echinocandin drugs in Asia/Pacific, the authors perceive these trends as promising, albeit lower than those in Western countries/territories, and expect them to continue to increase in this developing region.

Nonetheless, certain patient cohorts, particularly those with endemic mycoses or mucormycosis, remain at risk. LAMB, e.g., for *Blastomyces* spp., *Histoplasma* spp., *Emergomyces* spp., and *Talaromyces* spp., and itraconazole, e.g., for *Sporothrix* spp., are the recommended first-line drugs, or maintenance therapies, for endemic mycoses [26], but access to these antifungals (57.1% and 85.3% in endemic countries/territories, respectively) is not granted. For cases of mucormycosis, LAMB is the recommended first-line drug, with isavuconazole and posaconazole as alternatives [53]; however, again, not all institutions have access to the recommended first-line drug. Interestingly, in endemic countries/territories, the gradient for accessibility of antifungals, except for micafungin, was as follows (from most to least available): countries/territories with GDP >20 000-US$, countries/territories with GDP <3000-US$, and countries/territories with GDP 3000–20 000-US$. Antifungals were most accessible in countries with a better overall economic context (i.e., countries with a GDP >20 000-US$). The greater accessibility to antifungals in the poorest stratum (i.e., countries with GDP <3000-US$) compared with richer countries in the GDP 3000–20 000-US$ group may be related to the higher incidence and IFI impact in these poorer countries, as reported from India during the recent COVID-19-associated mucormycosis outbreak [16,17,24]. However, as repeatedly described in the literature, institutional availability of a specific drug does not guarantee the comprehensive treatment of patients with first-line therapy as this may not be affordable for all eligible recipients [10].

Access to TDM is limited during the administration of flucytosine (15.7%), itraconazole (30.2%), posaconazole (30.6%), or voriconazole (44.7%), although Asia/Pacific appears in a better position than Africa and the Caribbean and Latin America [29,30]. In the case of Asia/Pacific countries/territories, access to voriconazole TDM is most notable, given its wide utility as a mould-active antifungal in a region with a higher prevalence of genotype CYP2C19 (high metaboliser status) patients [54].

The current study results have several limitations. First, several countries/territories did not respond to the request to take part in the survey; possible reasons for this include active armed conflicts, lack of local contacts, smaller country/territory populations and fewer facilities. Also, there were more respondents from sites that are comparably well equipped and have a higher annual budget allowance; therefore, potentially overestimating regional capabilities. Second, the size of some countries/territories and, therefore, the number of responding sites (i.e., India in GDP <3000-US$ and China in GDP 3000–20 000-US$) could bias the data reported

from within comparable economic strata, yielding less heterogeneous results. Third, the contemporaneous COVID-19 pandemic and associated mycoses in some of these countries/territories [16,17,22-24] may have limited the capacity to respond. Fourth, further analysis is needed to determine the specific formulation of the triazoles prescribed, given the variation in pharmacodynamics and pharmacokinetics between different formulations. Fifth, the survey did not measure the quality metrics of diagnostic and therapeutic strategies in Asia/Pacific; this is an important future research objective. Lastly, country/territory or subregional level analyses might be more relevant, as Asia/Pacific has an enormous variability in reported IFI epidemiology, such as climate and host factors, or economic resources, and these may be key determinants of the local diagnostic and clinical management capabilities for IFI.

The current IFI diagnostic status and therapeutic capabilities in Asia/Pacific are heterogeneous because of a range of reasons, including the presence of endemic IFI, overall IFI burden and economic resources of the countries. Significant progress has already been made, however, including opportunities for collaborative partnerships (e.g., academic societies) to leverage online resources via social media and to provide the administrative infrastructure to enable regional collaborators to conduct important research studies. Thus, partnerships are required to advance the understanding, diagnostics and management of IFI, and to augment fungal surveillance data to support best practices in Asia/Pacific. This includes the conduct and publication of more studies from Asia/Pacific, and the advancement of educational initiatives, including masterclasses, online educational content that includes pre-specified curricula and confirms that learning goals are met (e.g., CME programs), online educational activities through websites (e.g., AFWG-ISHAM, www.afwgonline.com/mmtn/), and social channels to facilitate discussion via online forums of topics most relevant to Asia/Pacific. Ultimately, the exchange of expertise between infectious disease and mycology professionals will strengthen support across the region, ensuring that knowledge transfer achieves regional improvements in the quality of IFI diagnosis and treatment for patients in Asia/Pacific.

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JSG reports speaker honoraria from Gilead and Pfizer, outside of the submitted work.

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RW has received speaker honoraria from Pfizer and Astellas, outside of the submitted work.

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Ethical Approval

N/A

Sequence Information

N/A

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Author contributions

JSG, MH, and OAC conceived the study idea.

JSG, MH, and OAC contributed to study design.

JSG collected and validated the data, did the statistical plan and analysis, and drafted the first version of the manuscript.

All authors contributed to data collection and interpretation, manuscript writing and review of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106718.

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