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Análise da Disponibilidade de Diagnósticos Laboratoriais e Tratamentos em Micologia em Países em Desenvolvimento: Continente Africano e Leste Europeu

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Dedicatória

Aos pacientes que sofrem de doenças fúngicas no mundo todo, especialmente no continente africano e nos países não centrais.

A minha avó Maria de Lourdes Dornelles *(in memoriam)* que inspirou a mim e a tantos outros com sua determinação e amor pela educação.

RESUMO

Introdução: As doenças fúngicas representam um desafio diagnóstico e terapêutico, especialmente em países em desenvolvimento. A epidemiologia das infecções fúngicas foi descrita em muitos países do continente africano e do leste europeu, mas a disponibilidade de drogas antifúngicas e ferramentas diagnósticas em micologia médica nessas regiões era desconhecida. **Objetivos:** Descrever a capacidade diagnóstica e terapêutica no tratamento de pessoas com infecções fúngicas no continente africano e no leste europeu e analisar cada um dos centros respondedores, classificando-os de acordo com a *European Confederation of Medical Mycology Excellence Centre Initiative,* principalmente sobre o potencial de atingir ou não o estágio mínimo da classificação, chamado *Blue Status.* **Materiais e Métodos**: Foi realizada uma pesquisa online através da plataforma *clincalsurveys.com* destinada a profissionais e a pesquisadores do continente africano e do leste europeu, com perguntas específicas sobre as características do serviço de saúde, perfil de pacientes atendidos e a disponibilidade de drogas e testes diagnósticos para doenças fúngicas. As respostas foram analisadas utilizando o software SPSS 27. **Resultados**: Em relação ao continente africano, recebemos 40 respostas provenientes de 21 países diferentes. Apenas cinco instituições (12,5%) localizadas em Camarões, Quênia, Nigéria, Sudão e Uganda potencialmente preenchiam os requisitos mínimos para o *Blue Status*. Testes de suscetibilidade estavam disponíveis em 30% das instituições e detecção de antígeno de *Aspergillus spp.* em 47,5%. O acesso a medicamentos como voriconazol e posaconazol (disponível para 35,0% e 5,0% das instituições, respectivamente) foi muito limitado. Em relação ao leste europeu, 31 instituições responderam ao questionário. Dessas, 48,4%

potencialmente preenchiam os requisitos mínimos para o *Blue Status* e estavam localizadas na Rússia, Grécia, Croácia, República Tcheca, Hungria, Sérvia, Eslováquia e Eslovênia. Testes sorológicos estavam disponíveis principalmente para espécies de *Aspergillus* (80,6%). Flucitosina estava disponível para apenas 29% dos centros participantes. **Conclusão:** As regiões tem enormes lacunas no acesso a diagnósticos e a tratamentos em doenças fúngicas. Esforços unidos e direcionados são mandatórios para enfrentar os crescentes desafios da micologia médica e melhorar ainda mais os recursos de diagnóstico e tratamento. **Palavras-chave**: infecções fúngicas, micologia, diagnóstico, laboratório, antifúngicos, acesso.

ABSTRACT

Introduction: Fungal infections still pose a diagnostic and therapeutical challenge, mainly at low-and-middle-income countries. Epidemiology of these infections has been described in many countries of the Eastern Europe and the African Continent, but availability of antifungal drugs and diagnostic tools in Medical Mycology was unknow. **Aim of study:** Describe diagnostic and therapeutical capabilities in fungal infections in the African Continent and the Eastern Europe and classify which one of the responders according to the European Confederation of Medical Mycology Excellence Centre Initiative, considering if they potentially fulfill the criteria for Blue Status (initial stage). **Materials and methods:** We developed an online survey at *clincalsurveys.com* addressed to health professionals and researchers from the African Continent and the Eastern Europe, asking specifically about the institution services, the patients' profile and the availability of antifungal drugs and diagnostic tests to fungal infections. Answers were analyzed with the software SPSS 27. **Results:** We have received 40 answers from the African Continent, from 21 countries. Only five institutions (12,5%) located in Cameroon, Kenya, Nigeria, Sudan and Uganda potentially fulfill the minimum requirements for *Blue Status*. susceptibility tests were available in 30% of institutions and antigen detection for *Aspergillus spp.* in 47,5%. Access to antifungal drugs such as Voriconazole and Posaconazole (available to 35,0% and 5,0% of institutions, respectively) was very low. Considering Eastern Europe, 31 institutions answered our survey. 48,4% potentially fulfill the minimum requirements for Blue Status and were located in Russia, Greece, Croatia, Czech Republic, Hungry, Serbia, Slovakia and Slovenia. Serological testing was available mainly for *Aspergillus* (80,6%).

Flucytosine was available for only 29% of responders. **Conclusion:** Both regions have huge gaps in the diagnostic and therapeutical capabilities in fungal infections. United and targeted efforts are mandatory to face the growing challenges in medical mycology and to further improve diagnostic and treatment resources. **Keywords:** Fungal infections, mycology, diagnosis, laboratory, antifungal, access.

LISTA DE ABREVIATURAS

AIDS: Acquired Immunodeficiency Syndrome (síndrome da imunodeficiência adquirida).

ASM: American Society for Microbiology (Sociedade Americana de Microbiologia).

ECMM: The European Confederation of Medical Mycology (Confederação Europeia de Micologia Médica).

GAFFI: Global Action Fund for Fungal Infections (Fundo de Ação Global para Infecções Fúngicas).

HIV: Human Immunodeficiency Virus (virus da imunodeficiência humana).

ISHAM: International Society for Human and Animal Medical Mycology (Sociedade Internacional de Micologia Médica Humana e Animal).

MALDI-ToF: Matrix-Assisted Laser Desorption/Ionization-Time of Flight.

OMS: Organização Mundial de Saúde

PAMWG: The Pan-African Mycology Working Group (Grupo de Trabalho Pan-Africano de Micologia).

PIB: Produto Interno Bruto

TDM: Therapeutic Drug Monitoring (monitorização terapêutica de drogas).

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1.REFERENCIAL TEÓRICO

1.1 Introdução

As infecções fúngicas, a despeito de importantes avanços na micologia médica, ainda constituem um importante desafio global. Segundo informações divulgadas pelo GAFFI (*Global Action Fund for Fungal Infection*s - Fundo de Ação Global para Infecções Fúngicas), existem no mundo quase um bilhão de pessoas com micoses superficiais (acometendo pele e fâneros) e cerca de 1.5 milhão de pessoas com infecções fúngicas invasivas, colocando-se em quarto lugar entre as causas gerais de infecções[1]. Soma-se à grande prevalência destas infecções o variado espectro clínico, que pode variar entre casos leves, graves e fatais[2].

Os fatores de risco para as infecções fúngicas são variados e classicamente associados a imunossupressão, como infecção pelo HIV ((*Human Immunodeficiency Virus* - vírus da imunodeficiência humana) e uso prolongado de corticosteroides; novos tratamentos médicos, no entanto, especialmente para doenças autoimunes e neoplasias, vem aumentando o número de pacientes em risco para contrair essas infecções[3]. Em relação às pessoas vivendo com HIV/AIDS (*Acquired Immunodeficiency Syndrome* - síndrome da imunodeficiência adquirida), as doenças fúngicas podem ser responsáveis por até 50% das causas de mortalidade, podendo-se ressaltar a histoplasmose, a pneumonia por *Pneumocystis jirovecii* e a meningite criptocócica [4].

Embora tenhamos estudos a respeito da epidemiologia das infecções fúngicas, não há dados suficientes sobre a disponibilidade de ferramentas diagnósticas ou de medicações para o tratamento, fazendo com que muitas dessas doenças sejam negligenciadas e subestimadas[5]. Mesmo quando

disponível no país, o alto preço de drogas é um limitador importante no acesso ao tratamento mais adequado e eficaz[6]. Segundo estudo realizado pelo GAFFI entre 2016 e 2019, a droga Flucitosina, considerada essencial pela OMS (Organização Mundial de Saúde)[7], não está disponível em diversos países, como mostra o mapa abaixo. Além disso, o preço diário de tratamento pode variar entre USD$ 4,8 e USD$ 1844,25 [8,9].

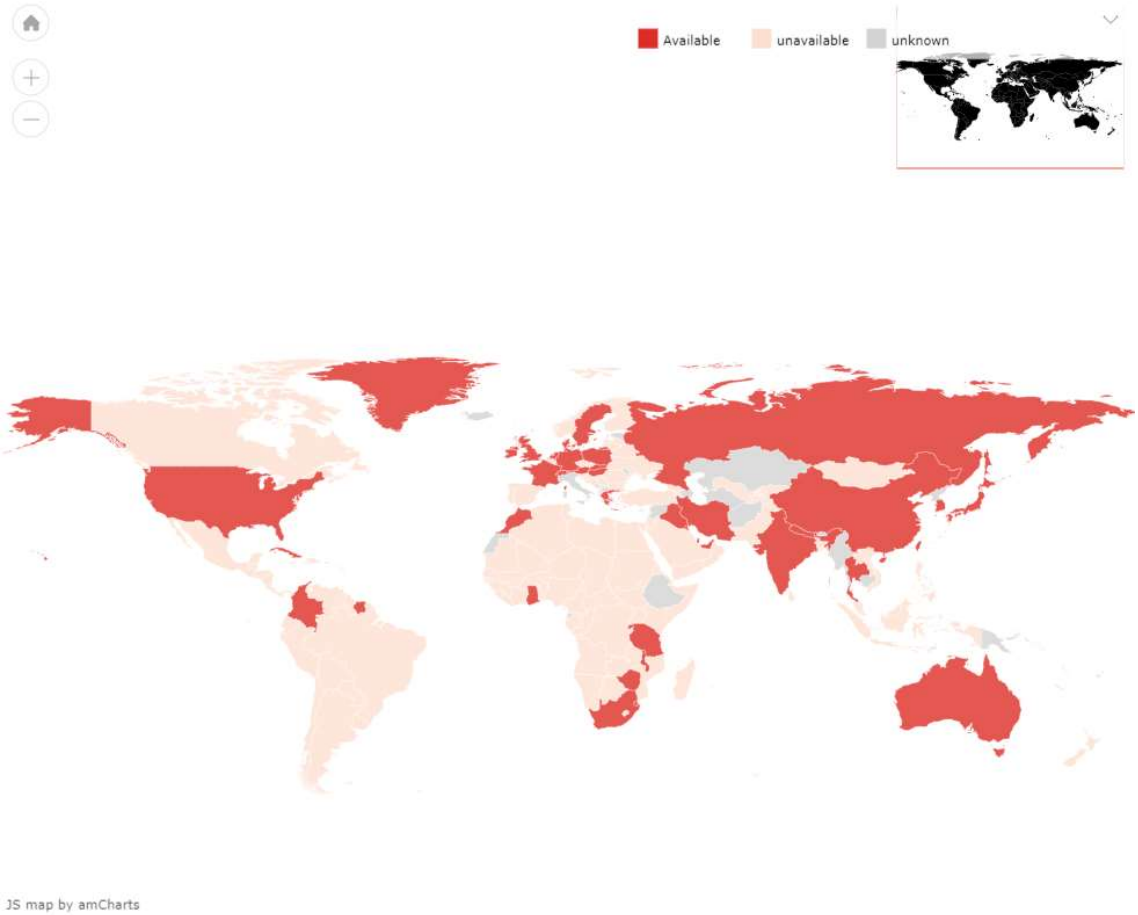

Figura 1: Disponibilidade de Flucitosina no mundo

Fonte: https://antifungalsavailability.org/maps/map/flucytosine [8]

1.2 Países em Desenvolvimento

Países em desenvolvimento podem ser definidos como aqueles que apresentam processos mais recentes de industrialização e PIBs (Produto Interno

Bruto*) per capita* menores em relação aos países desenvolvidos. Embora não exista um consenso absoluto em relação a esse conceito, consideramos “países em desenvolvimento” economias emergentes e em desenvolvimento com PIB baixo ou médio conforme definição do Fundo Monetário Internacional[10].

A despeito dos diferentes processos históricos e características socioeconômicas desses países, inequidades nos sistemas de saúde são observadas em diferentes níveis entre eles, como falta de recursos diagnósticos e terapêuticos para determinadas doenças. Nesse sentido, embora tais países concentrem o maior número de pessoas com doenças fúngicas negligenciadas, é também neles onde há maior dificuldade em obter-se dados de vida real sobre a carga-de-doença e impacto das doenças fúngicas nos sistemas de saúde e na população[11].

Assim, os debates sobre Cobertura Universal de Saúde e mais recentemente a pandemia de COVID19 reforçaram a importância da discussão sobre alocação racional de recursos em saúde pública nestes países, a fim de superar essas dificuldades históricas no acesso à saúde[12,13].

1.2.1 Continente Africano

A África é o terceiro continente mais extenso do mundo, com aproximadamente 30 milhões de quilômetros quadrados. É o segundo continente mais povoado, com mais de um bilhão de pessoas, representando cerca de um sétimo da população mundial. Dividido em 5 regiões – setentrional, ocidental, central, oriental e meridional/austral, possui 54 países independentes. Embora o continente africano tenha cerca de um quinto da população mundial e reúna diferentes fatores de risco para doenças fúngicas, com alta carga de doença

relacionada às micoses invasivas, nenhum estudo neste escopo havia sido feito sobre a África até então[14–22].

O continente é marcado por desigualdades sociais e de saúde, e muitos países possuem sistemas de saúde mal financiados e sobrecarregados[23]. Soma-se a isso grande parte da população residindo em áreas rurais, estando expostas a fatores ambientais que aumentam o risco de doenças fúngicas[24]. Ademais, a África tem a maior população absoluta vivendo com HIV/AIDS e tuberculose, que são alguns dos principais fatores de risco para infecções fúngicas[25].

É importante ressaltar que em muitas doenças fúngicas a identificação da espécie e a escolha adequada da droga são cruciais para o sucesso terapêutico. Um exemplo é *Candida auris,* que foi identificada no continente em 2009 na África do Sul e recentemente no Quênia[26,27]. As dificuldades do continente também incluem a ausência de um sistema de vigilância para infecções fúngicas, com exceção da África do Sul. Este país é também o único no continente africano com um laboratório nacional de referência em micologia[23]. Além dos desafios que o continente já vinha historicamente enfrentando, o cenário piorou ainda mais com a pandemia de COVID-19[28,29].

Esforços vem sendo feitos ao longo dos anos não só no sentido de documentar as peculiaridades do continente, mas também de completar lacunas, engajar especialistas e propor alternativas. Um dos exemplos é o da Nigéria e da organização dos micologistas no país para pautar o debate das infecções fúngicas a partir da perspectiva dos países não-desenvolvidos[30]. Ainda neste sentido, foi criado o PAMWG (*The Pan-African Mycology Working Group* - Grupo de Trabalho Pan-Africano de Micologia) da ISHAM (*International Society for*

Human and Animal Medical Mycology - Sociedade Internacional de Micologia Médica Humana e Animal), grupo de trabalho transdisciplinar que visa melhorar a interação entre os líderes regionais, promover a criação de programas educacionais de capacitação e de diretrizes clínicas e apoiar o estabelecimento de Laboratórios de Referência em Micologia[23]. Além desses, detalhamos mais abaixo os esforços relacionados a ECMM (*The European Confederation of Medical Mycology* - Confederação Europeia de Micologia Médica).

Após a realização e publicação do nosso trabalho, GAFFI realizou uma pesquisa em todo o continente africano a respeito da capacidade diagnóstica em micologia no continente, com dados de 48 países[31]. Além dos recursos diagnósticos em doenças fúngicas, também foi abordado, através de um questionário, a capacidade de exames de linfócitos T CD4, exames de imagem e biossegurança nos laboratórios.

Alguns dos principais achados desse estudo são que o ônus financeiro do diagnóstico geralmente recai diretamente sobre os pacientes e familiares, com poucos países tendo programas específicos para o tratamento de doenças fúngicas. Os autores também ressaltam a dificuldade de incorporação de testes rápidos de última geração em todo o continente.

1.2.2 Leste Europeu

Embora o continente Europeu seja associado a países com alto nível de desenvolvimento, diferentes processos históricos na região influenciaram a existência de disparidades entre os sistemas de saúde e o acesso aos mais recentes avanços tecnológicos entre esses países. Apesar de as Nações Unidas dividirem o continente europeu em cinco regiões, uma divisão em Europa

Oriental (leste) e Ocidental (oeste) ainda pode ser usada hoje, considerando características geopolíticas, históricas e culturais[10,32]. As desigualdades na Europa podem resultar em diferenças em termos de acesso a medicamentos e capacidade de diagnóstico em micologia médica [33,34].

O continente europeu não é o primeiro a ser pensado quando se discute a carga relacionada às doenças fúngicas. Entretanto, processos migratórios, viagens e o aumento da população imunocomprometida com o avanço das terapias oncológicas, por exemplo, mantêm a carga de doenças fúngicas invasivas neste continente[3,35–42].

Os dados da vida real sobre a capacidade dos centros médicos de realizar tais atividades ainda não haviam sido estudados no continente. Após a publicação do nosso trabalho sobre o leste europeu, Salmanton-García *et al* publicaram um estudo abrangendo todo o continente europeu, com 388 respostas de 45 países diferentes[43]. Os achados deste estudo foram comparados entre os países de acordo com o seu PIB *per capita*, dividido em três categorias <US$30 000 (n=54), US$30 000–$45 000 (n=167) e >US$45 000 (n=167). O estudo demonstrou uma relação diretamente proporcional entre o PIB *per capita* dos países estudados e a capacidade diagnóstica dos países. Uma limitação não observada pelos autores, no entanto, é que o PIB *per* capita usado isoladamente desconsidera as desigualdades sociais e econômicas dentro de cada país, não sendo o mais indicado para medir qualidade de vida, crescimento econômico ou nível de desenvolvimento, principalmente ao considerarmos os processos históricos do continente[44].

Ao mesmo tempo, esses achados vão ao encontro do que demonstramos em nossa pesquisa, em que países expostos com os maiores fatores de risco

para doenças fúngicas são muitas vezes aqueles com menores recursos diagnósticos e terapêuticos para essas doenças.

1.2.3 Outros Continentes

1.2.3.1 América Latina

Em nosso meio, Pasqualotto e Falci realizaram um estudo explorando os desafios pertinentes a América Latina no que se refere às ferramentas para o manejo destas doenças, evidenciando algumas disparidades regionais. O Brasil, por exemplo, teve significativamente menos acesso a testes de suscetibilidade e a antifúngicos, quando comparado aos demais países respondedores. Por outro lado, o Brasil concentrou a maioria das instituições de nível superior, com acesso a tecnologias modernas como MALDI-ToF (*Matrix-Assisted Laser Desorption/Ionization-Time of Flight*) e sequenciamento de DNA fúngico. Outra limitação regional foi o acesso a testes de suscetibilidade, realidade especialmente preocupante no atual cenário de resistência aos antifúngicos. O acesso a antifúngicos na América Latina está sintetizado na tabela abaixo, na qual evidencia-se a baixa disponibilidade de drogas consideradas essenciais pela OMS, como a Flucitosina e Anfotericina B[7,45]:

Tabela 1: Acesso a antifúngicos em países da América Latina incluindo o Brasil e somente no Brasil.

Antifúngico	*Total na América Latina (n=124)*	*Brasil (n=94)*
Fluconazol	121 (98%)	92 (98%)
Itraconazol	88 (71%)	65 (69%)
Voriconazol	68 (55%)	44 (47%)
Posaconazole	26 (21%)	13 (14%)
Isavuconazole	1 (1%)	0 (0%)
Anfotericina B desoxicolato	89 (72%)	68 (72%)
Anfotericina B Lipossomal	60 (49%)	40 (43%)
Outras formulações lipídicas de anfotericina B	52 (42%)	43 (46%)
Micafungina	51 (41%)	45 (48%)
Anidulafungina	39 (32%)	30 (32%)
Caspofungina	37 (30%)	15 (16%)
Flucitosina	10/55 (18%)	7/40 (18%)

Fonte: adaptada de Falci[45]

Segundo Falci e Pasqualotto, o acesso a TDM (*Therapeutic Drug Monitoring* - monitorização terapêutica de drogas) é bastante restrito no continente, disponível para voriconazol em 16% dos laboratórios, seguido de itraconazol (10%) e posaconazol (4%). Ao mesmo tempo, um número bastante superior afirmou ter acesso a essas drogas, como ilustrado na tabela acima. A impossibilidade de TDM pode levar a piores desfechos, com piores efeitos adversos relacionados a toxicidade, além de dificultar o uso racional destas drogas, o que seria ainda mais necessário em cenários com recursos reduzidos[45].

Em relação a micoses negligenciadas, a histoplasmose e a paracoccidioidomicose são as mais relevantes no continente, estando entre principais causas de morte por doenças infecciosas e parasitárias. A variabilidade de sintomas, baixo índice de suspeição entre profissionais da

saúde e a alta prevalência de tuberculose no continente são fatores de confusão para o diagnóstico precoce, evidenciando a importância da disponibilidade de testes diagnósticos específicos[11,46]. É importante ressaltar que, a despeito da relevância epidemiológica, principalmente para populações vivendo em áreas tropicais, a maioria das micoses sistêmicas ainda não são consideradas como doenças negligenciadas pela OMS.

1.2.3.2 Ásia

No continente asiático, Chindamporn *et al* conduziu um estudo similar, com 241 respostas de sete países: China (71), Índia (104), Indonésia (11), Filipinas (26), Cingapura (4), Taiwan (18) e Tailândia (7). Os autores destacam que embora microscopia e cultura sejam amplamente disponíveis, há praticamente nenhum acesso a métodos avançados de diagnóstico como PCR, galactomanana e β-D-glucana nos laboratórios respondedores da Indonésia, Filipinas e Tailândia. Ademais, TDM é realizado em apenas 21 laboratórios.

No continente asiático, há uma urgente necessidade de desenvolvimento de infraestrutura, treinamento de profissionais e acesso a testes avançados não baseados em cultura para melhor manejo das infecções fúngicas [47,48].

1.3 ECMM

Esta confederação europeia tem sido uma voz atuante no enfrentamento às inequidades em relação às doenças fúngicas. A ECMM tem como principais objetivos melhorar o diagnóstico, tratamento, resultado e sobrevivência de pessoas com doenças fúngicas invasivas. Algumas de suas frentes de atuação incluem a criação de *guideline*s, inclusive em parceria com a ISHAM e a ASM

(*American Society for Microbiology* - Sociedade Americana de Microbiologia) para o enfretamento de infecções fúngicas, levando em consideração que a maioria dos documentos já existentes não consegue fornecer orientações voltadas a países em desenvolvimento[49–51]. Além disso, preocupam-se em estabelecer *networking* e apoio mútuo entre os pesquisadores ao redor do globo, reconhecendo individualmente àqueles de maior relevância na produção científica mundial e também os centros mais capacitados[52].

Uma das iniciativas da ECMM é o *Excellence Centre*, que busca atestar os centros de excelência no manejo de micoses invasivas e colocá-los como referência para outros centros. De acordo com uma auditoria baseada nas melhores práticas disponíveis para o diagnóstico e tratamento de doenças fúngicas, os centros podem ser classificados em *Blue Status, Silver, Gold ou Diamond*, em ordem crescente de adequação aos critérios clínicos, laboratoriais e educacionais[50].

A classificação inicial, chamada *Blue Status,* possui critérios clínicos e laboratoriais. Os critérios laboratoriais consistem em:

1) Identificação de espécies fúngicas de importância médica;

2) Realizar testes de suscetibilidade de acordo com procedimentos-padrão;

3) Realizar antígeno ELISA para *Aspergillus* ou ensaio equivalente;

4) Possuir teste de antígeno criptocócico.

Já os critérios clínicos dependem, em parte, do tipo de paciente atendido pela instituição e incluem acesso a tomografia computadorizada ou ressonância magnética em pacientes imunossuprimidos com suspeita de pneumonia ou neuroinfecção; acesso a broncoscopia e obtenção de lavado broncoalveolar;

acesso a azóis, anfotericina B e equinocandinas, acesso à cirurgia quando apropriado e acesso a Unidade de Terapia Intensiva conforme necessidade. [52]

2. REFERÊNCIAS BIBLIOGRÁFICAS

1. Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden killers: Human fungal infections. Sci Transl Med. 2012;4(165).
2. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases—estimate precision. Vol. 3, Journal of Fungi. MDPI AG; 2017.
3. Friedman DZP, Schwartz IS. Emerging fungal infections: New patients, new patterns, and new pathogens. Journal of Fungi. 2019;5(3).
4. World Health Organization. WHO fungal priority pathogens list to guide research, development and public health action. Vol. 1, Licence: CC BY-NC-SA 3.0 IGO. 2022. 1–48 p.
5. Queiroz-Telles F, Fahal AH, Falci DR, Caceres DH, Chiller T, Pasqualotto AC. Neglected endemic mycoses. Lancet Infect Dis [Internet]. 2017;17(11):e367–77. Available from: http://dx.doi.org/10.1016/S1473-3099(17)30306-7
6. Tudela JLR, Denning DW. Recovery from serious fungal infections should be realisable for everyone. Lancet Infect Dis. 2017;17(11):1111–3.
7. OMS. World Health Organization Model List of Essential Medicines. Mental and Holistic Health: Some International Perspectives [Internet]. 2019;21:119–34. Available from: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1
8. AmCharts. Flucytosine Available [gráfico interativo]. GAFFI- 2022. Available from: https://antifungalsavailability.org/maps/map/flucytosine
9. Kneale M, Bartholomew JS, Davies E, Denning DW. Global access to antifungal therapy and its variable cost. Journal of Antimicrobial Chemotherapy. 2016;71(12):3599–606.

10. International Monetary Fund. World Economic Outlook: Countering the Cost-of-Living Crisis [Internet]. 2022. 1–186 p. Available from: www.imfbookstore.org
11. Queiroz-Telles F, Fahal AH, Falci DR, Caceres DH, Chiller T, Pasqualotto AC. Neglected endemic mycoses. Lancet Infect Dis [Internet]. 2017;17(11):e367–77. Available from: http://dx.doi.org/10.1016/S1473-3099(17)30306-7
12. Jain V. Financing global health emergency response: outbreaks, not agencies. J Public Health Policy [Internet]. 2020;41(2):196–205. Available from: https://doi.org/10.1057/s41271-019-00207-z
13. Penman-Aguilar A, Talih M, Huang D, Moonesinghe R, Bouye K, Beckles G. Measurement of Health Disparities, Health Inequities, and Social Determinants of Health to Support the Advancement of Health Equity. Physiol Behav. 2017;176(10):139–48.
14. Chekiri-Talbi M, Denning DW. Burden of fungal infections in Algeria. European Journal of Clinical Microbiology and Infectious Diseases. 2017;36(6):999–1004.
15. Badiane AS, Ndiaye D, Denning DW. Burden of fungal infections in Senegal. Mycoses. 2015;58:63–9.
16. Faini D, Maokola W, Furrer H, Hatz C, Battegay M, Tanner M, et al. Burden of serious fungal infections in Tanzania. Mycoses. 2015;58:70–9.
17. Guto JA, Bii CC, Denning DW. Estimated burden of fungal infections in Kenya. J Infect Dev Ctries. 2016;10(8):777–84.
18. Mandengue CE, Denning DW. The burden of serious fungal infections in Cameroon. Journal of Fungi. 2018;4(2):1–9.
19. Bongomin F, Olum R, Nsenga L, Namusobya M, Russell L, de Sousa E, et al. Estimation of the burden of tinea capitis among children in Africa. Vol. 64, Mycoses. 2021. 349–363 p.

20. Kwizera R, Musaazi J, Meya DB, Worodria W, Bwanga F, Kajumbula H, et al. Burden of fungal asthma in Africa: A systematic review and meta-analysis. PLoS One. 2019;14(5):1–17.

21. Bongomin F, Fayemiwo SA. Epidemiology of fungal diseases in africa: A review of diagnostic drivers. Curr Med Mycol. 2021;7(1):63–70.

22. Zaki SM, Denning DW. Serious fungal infections in Egypt. European Journal of Clinical Microbiology and Infectious Diseases. 2017;36(6):971–4.

23. Oladele RO, Akase IE, Fahal AH, Govender NP, Hoenigl M, Gangneux JP, et al. Bridging the knowledge gap on mycoses in Africa: Setting up a Pan-African Mycology Working Group. Mycoses. 2020;63(3):244–9.

24. Brauer VS, Rezende CP, Pessoni AM, de Paula RG, Rangappa KS, Nayaka SC, et al. Antifungal agents in agriculture: Friends and foes of public health. Biomolecules. 2019;9(10):1–21.

25. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis [Internet]. 2017;17(8):873–81. Available from: http://dx.doi.org/10.1016/S1473-3099(17)30243-8

26. Magobo RE, Corcoran C, Seetharam S, Govender NP. Candida auris-associated Candidemia, South Africa. Emerg Infect Dis. 2014;20(7):1250–1.

27. Adam RD, Revathi G, Okinda N, Fontaine M, Shah J, Kagotho E, et al. Analysis of Candida auris fungemia at a single facility in Kenya. International Journal of Infectious Diseases [Internet]. 2019;85:182–7. Available from: https://doi.org/10.1016/j.ijid.2019.06.001

28. Nargesi S, Bongomin F, Hedayati MT. The impact of covid-19 pandemic on aidsrelated mycoses and fungal neglected tropical diseases: Why should we

worry? PLoS Negl Trop Dis [Internet]. 2021;15(2):1–5. Available from: http://dx.doi.org/10.1371/journal.pntd.0009092

29. Dada DA, Aku E, David KB. Covid-19 pandemic and antiretrovirals (Arv) availability in nigeria: Recommendations to prevent shortages. Pan African Medical Journal. 2020;35(Supp 2):1–3.

30. Oladele RO, Osaigbovo II, Ayanlowo OO, Otu AA, Hoenigl M, Cornely OA, et al. The role of medical mycology societies in combating invasive fungal infections in low- and middle-income countries: A Nigerian model. Mycoses. 2019;62(1):16–21.

31. Global Action Fund for Fungal Infections - GAFFI. Diagnostic Survey Report. Kigalli; GAFFI. 2022. Available from: https://gaffidocuments.s3.eu-west-2.amazonaws.com/Gaffi+Survey+Africa+2022+EN+Final_3.pdf

32. Asad Alam, Mamta Murthi, Ruslan Yemtsov, Edmundo Murrugarra, Nora Dudwick, Ellen Hamilton and ET. Growth, poverty, and inequality : Eastern Europe and the former Soviet Union [Internet]. Development TIB for R and, editor. The World Bank; 2005. 69–80 p. Available from: http://www.worldbank.org/content/dam/Worldbank/GEP/GEP2015a/pdfs/GEP15a_web_full.pdf

33. Scholz N. Addressing health inequalities in the European Union [Internet]. 2020. Available from: http://www.europarl.europa.eu/thinktank

34. European Commission. European Semester: Thematic Factsheet Addressing Inequalities. 2017;9.

35. Arsenijević VA, Denning DW. Estimated burden of serious fungal diseases in Serbia. Journal of Fungi. 2018;4(3):1–13.

36. Mareș M, Moroti-Constantinescu VR, Denning DW. The burden of fungal diseases in Romania. Journal of Fungi. 2018;4(1):1–7.

37. Klimko N, Kozlova Y, Khostelidi S, Shadrivova O, Borzova Y, Burygina E, et al. The burden of serious fungal diseases in Russia. Mycoses. 2015;58(July):58–62.

38. Osmanov A, Denning DW. Burden of serious fungal infections in Ukraine. Mycoses. 2015;58:94–100.

39. Sinkó J, Sulyok M, Denning DW. Burden of serious fungal diseases in Hungary. Mycoses. 2015;58:29–33.

40. Drgona L, Khachatryan A, Stephens J, Charbonneau C, Kantecki M, Haider S, et al. Clinical and economic burden of invasive fungal diseases in Europe: Focus on pre-emptive and empirical treatment of Aspergillus and Candida species. European Journal of Clinical Microbiology and Infectious Diseases. 2014;33(1):7–21.

41. Benedict K, Richardson M, Vallabhaneni S, Jackson BR, Chiller T. Emerging issues, challenges, and changing epidemiology of fungal disease outbreaks. Lancet Infect Dis [Internet]. 2017;17(12):e403–11. Available from: http://dx.doi.org/10.1016/S1473-3099(17)30443-7

42. Chrdle A, Mallátová N, Vašáková M, Haber J, Denning DW. Burden of serious fungal infections in the Czech Republic. Mycoses. 2015;58:6–14.

43. Salmanton-garcía J, Hoenigl M, Gangneux J pierre, Segal E, Alastruey-izquierdo A, Akdagli SA, et al. Review The current state of laboratory mycology and access to antifungal treatment in Europe : a European Confederation of Medical Mycology survey. 2022;47–56.

44. Costanza R, Hart M, Posner S, Talberth J. Beyond GDP : The Need for New Measures of Progress Beyond GDP : The Need for New Measures of Progress. Boston University. 2009;(4):1–47.

45. Falci DR, Pasqualotto AC. Clinical mycology in Latin America and the Caribbean: A snapshot of diagnostic and therapeutic capabilities. Mycoses. 2019;(January):368–73.

46. Pasqualotto AC, Queiroz-Telles F, Chebabo A, Leitao TMJS, Falci DR, Xavier MO, et al. The “Histoplasmosis Porto Alegre manifesto”-Addressing disseminated histoplasmosis in AIDS. PLoS Negl Trop Dis. 2023;17(1):e0010960.

47. Chindamporn A, Chakrabarti A, Li R, Sun PL, Tan BH, Chua M, et al. Survey of laboratory practices for diagnosis of fungal infection in seven Asian countries: An Asia Fungal Working Group (AFWG) initiative. Med Mycol. 2018;56(4):416–25.

48. Chen M, Xu Y, Hong N, Yang Y, Lei W, Du L, et al. Epidemiology of fungal infections in China. Front Med. 2018;12(1):58–75.

49. Chen SCA, Perfect J, Colombo AL, Cornely OA, Groll AH, Seidel D, et al. Global guideline for the diagnosis and management of rare yeast infections: an initiative of the ECMM in cooperation with ISHAM and ASM. Lancet Infect Dis. 2021;21(12):e375–86.

50. Hoenigl M, Gangneux JP, Segal E, Alanio A, Chakrabarti A, Chen SCA, et al. Global guidelines and initiatives from the European Confederation of Medical Mycology to improve patient care and research worldwide: New leadership is about working together. Mycoses. 2018;61(11):885–94.

51. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology

in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19(12):e405–21.

52. Koehler P, Denis B, Denning DW, Gangneux JP, Hoenigl M, Kontoyiannis DP, et al. European confederation of medical mycology expert consult—An ECMM excellence center initiative. Mycoses. 2020;63(6):566–72.

3. OBJETIVOS

Geral:

Determinar e avaliar a capacidade diagnóstica e terapêutica quanto a infecções fúngicas invasivas em países em desenvolvimento no continente africano e no leste europeu.

Específicos:

a) Avaliar os métodos laboratoriais usados para diagnóstico das infecções fúngicas nestes países;

b) Avaliar o acesso às terapias antifúngicas nestes países;

c) Classificar os laboratórios de micologia destes países conforme as definições da Confederação Europeia de Micologia Médica (ECMM).

4. ARTIGOS CIENTÍFICOS REDIGIDOS EM INGLÊS

“The current state of clinical mycology in Africa: a European Confederation of Medical Mycology and International Society for Human and Animal Mycology survey”

Revista Lancet Microbe

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Review

The current state of clinical mycology in Africa: a European Confederation of Medical Mycology and International Society for Human and Animal Mycology survey

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Africa, although not unique in this context, is a favourable environment for fungal infections, given the high burden of risk factors. An online survey was developed asking about laboratory infrastructure and antifungal drug availability. We received 40 responses (24·4% response rate) of 164 researchers contacted from 21 African countries. Only five institutions (12·5%) of 40 located in Cameroon, Kenya, Nigeria, Sudan, and Uganda potentially fulfilled the minimum laboratory requirements for European Confederation of Medical Mycology Excellence Centre blue status. Difficulties included low access to susceptibility testing for both yeasts and moulds (available in only 30% of institutions) and *Aspergillus* spp antigen detection (available in only 47·5% of institutions as an in-house or outsourced test), as well as access to mould-active antifungal drugs such as amphotericin B deoxycholate (available for 52·5% of institutions), itraconazole (52·5%), voriconazole (35·0%), and posaconazole (5·0%). United and targeted efforts are crucial to face the growing challenges in clinical mycology.

Introduction

Approximately a fifth of the world's people live in Africa, a continent with a propitious environment for fungal infections. The continent is marked by social and health inequalities, with a national health insurance scheme absent in most countries. Additionally, a large proportion of its population live in rural settings and are exposed to environmental factors that increase the risk for fungal diseases.[1] Africa has the largest population living with HIV, AIDS, and tuberculosis globally, which are major risk factors for fungal infections.[2,3] Meanwhile, access to treatment for these three conditions is still low in many countries, and has become even worse with the COVID-19 pandemic.[4–6] This problem is mainly attributed to poorly funded and overburdened health systems in many African countries;[7,8] thus dealing with the probably high burden of fungal infections is a challenge.

Despite the global importance of superficial and invasive mycoses, there is still little information regarding the epidemiology of fungal infections in some areas of the world, including in Africa.[9] Medical mycology has made important advances, but non-specific signs and symptoms and the rapid progression of fungal disease in immunocompromised patients continue to present a challenge to clinicians and laboratories.[10] Notable limitations include few resources and investments in clinical mycology and diagnostic resources, as well as difficulties in accessing antifungal therapy. A poor awareness of fungal diseases among health-care professionals and policy makers, as well as the unaffordability of, toxicity of, and little access to antifungal treatment options are some of the challenges facing the continent.[11–13]

With few exceptions (such as testing for cryptococcal antigen), advances within the past 5 years in non-culture-based diagnostics have not reached most low-income and middle-income countries (LMICs). Therefore, it is necessary to assess the present status of the diagnosis of fungal infections in these regions to guide health professionals, patients, and policy makers.[12] Africa has not yet been comprehensively evaluated for its capability to diagnose and treat fungal diseases. These studies are important not only for epidemiological purposes, but also to guide the appropriate implementation of preventive, diagnostic, and therapeutic measures in medical mycology. Hence, under the umbrella of the European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM), we surveyed African institutions to obtain an overview of the current state of mycological laboratory capacities and availability of antifungal treatment in the field of invasive fungal diseases.

Procedure

We designed a cross-sectional survey with 29 questions (appendix pp 1–7) about the profile and size of institutions, antifungal drug availability, laboratory infrastructure, and methods used to identify pathogens and antifungal susceptibility, as well as antigen detection and molecular tests. The survey was open from June 1, 2019, to May 31, 2020, and was released online on the ISHAM and ECMM websites and sent out to their members based in Africa. We contacted 164 African researchers directly by email based on their email address from PubMed publications. Reminders were sent to the authors in cases of non-response.

The institutions were classified according to whether the laboratories potentially met the ECMM criteria for blue, silver, gold, or diamond status, or did not meet the criteria. The minimal requirements for the blue status are the identification of relevant yeasts and moulds, susceptibility testing on yeasts and moulds according to standard procedures, and the performance of antigen

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Review

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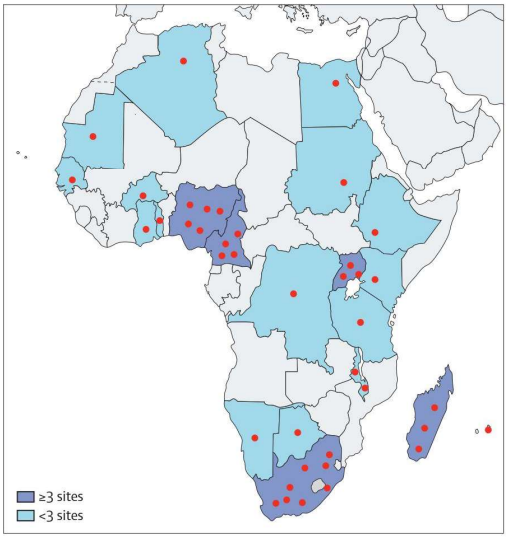

Figure 1: **Location of African institutions participating in this survey**
Key indicates the number of institutions that responded in each country.

ELISA for *Aspergillus* spp (galactomannan) and cryptococcal antigen. The criteria used for the classification of mycology centres are not restricted to the laboratory, but also consider the clinical and epidemiological dimensions, involvement in clinical trials, and in part depend on the type of patients cared for (appendix p 8).[14] This classification procedure was not an accreditation visit or round organised by the ECMM. Instead, we only checked the level at which centres were likely to be accredited if they had formally applied.

Findings

We received 40 responses (24·4% response rate) of the 164 researchers contacted, encompassing 40 different institutions from 21 different countries with all African sub-regions represented (figure 1). Countries with researchers that responded were South Africa (n=8), Nigeria (n=5), Cameroon (n=4), Madagascar (n=3), Uganda (n=3), Malawi (n=2), Algeria (n=1), Botswana (n=1), Burkina Faso (n=1), Democratic Republic of the Congo (n=1), Egypt (n=1), Ethiopia (n=1), Ghana (n=1), Kenya (n=1), Mauritania (n=1), Mauritius (n=1), Namibia (n=1), Senegal (n=1), Sudan (n=1), Togo (n=1), and Tanzania (n=1). Our survey was answered by laboratory professionals (n=22), professors (n=11), attending physicians (n=4), infection control practitioners (n=1), and other professionals who did not fit any of these categories (n=2).

Among responders, 29 (72·5%) were from university hospitals or national institutes of research, seven (17·5%) were from public hospitals not related to universities, two (5%) were private hospitals not related to universities, and one (2·5%) was an oncology clinic. One institution (2·5%) was an independent laboratory that served both private and public hospitals. The number of beds per institution ranged from 10 to 2880 (median, 300 beds), the number of adult intensive care unit beds ranged from 6 to 125 (median, 19 beds), and the number of paediatric and neonatal intensive care unit beds ranged from 4 to 300 (median, 20 beds).

Institutions served patients living with HIV or AIDS (n=38 [95·0%]), patients with oncological (n=33 [82·5%]) and haematological malignancies (n=35 [87·5%]), patients requiring parenteral nutrition (n=24 [60·0%]), and patients who had received a solid organ transplantation (n=6 [15·0%]) or a haematopoietic stem-cell transplantation (n=4 [10·0%]).

Nearly all institutions (n=39 [97·5%]) reported having a microbiology laboratory in place, although one institution outsourced general laboratory services. Focusing specifically on mycological diagnostic tools, three (7·5%) institutions reported no access at all to such services, 14 (35·0%) performed some tests within the institution and outsourced some tests to other laboratories, and 23 (57·5%) always perfomed the tests within the institution.

When asked about the most relevant fungi affecting patients in their institutions, most responses were: *Candida* spp (n=34 [85·0%]), followed by *Cryptococcus* spp (n=22 [55·0%]), *Aspergillus* spp (n=16 [40·0%]), *Fusarium* spp (n=8 [20·0%]), *Histoplasma* spp (n=5 [12·5%]), and Mucorales (n=4 [10·0%]).

When a fungal infection was suspected, 21 (52·5%) institutions reported always performing direct microscopy on clinical specimens, five (12·5%) reported performing it most of the time, seven (17·5%) reported performing it half of the time, five (12·5%) reported performing it rarely, and two (5·0%) reported that direct microscopy was never performed. Although 34 (85·0%) used microscopy to diagnose cryptococcosis, only eight (20·0%) performed a silver stain when pneumocystosis was suspected. Access to fluorescent dyes was also restricted, being available in only nine (22·5%) institutions. India or China ink was available for 31 (77·5%) institutions, followed by potassium hydroxide (n=28 [70·0%]), silver stain (n=28 [70·0%]), Giemsa stain (n=22 [55·0%]), and calcofluor white (n=4 [10·0%]).

To identify fungi at the species level, biochemical tests were the most commonly used tools, in 28 (70%) institutions. Automated identification by a VITEK system (an automated system for antibiotic susceptibility testing and microbiology identification; bioMérieux, Marcy-l'Étoile, France) or other commercial methods were accessible in 18 (45·0%) institutions, followed by mounting medium (n=11 [27·5%]), Matrix-Assisted Laser Desorption or Ionization-Time of Flight (MALDI-ToF; n=7 [17·5%]), and DNA sequencing (n=8 [20·0%]). Automated blood culture monitoring was available for 19 institutions (47·5%).

Susceptibility testing was available for 25 (62·5%) participants, but only in 12 (30%) institutions was access

to susceptibility tests covering both yeasts and moulds available. E-test strips were available in 14 (35·0%) institutions, 14 (35·0%) had access to VITEK, 11 (27·5%) to broth microdilution following Clinical and Laboratory Standards Institute standards, and seven (17·5%) to broth microdilution following European Committee on Antimicrobial Susceptibility Testing standards.

When serological testing was considered, antibody detection was mostly available for *Aspergillus* spp (n=9 [22·5%]), and in ten (25·0%) institutions antibody detection for *Aspergillus* spp was available at an outsourced laboratory. Anti-*Aspergillus* IgE was not evaluated in the survey. *Candida* spp antibody detection was available for five (12·5%) institutions, the same number had access to the test for *Candida* spp at an outsourced laboratory, *Histoplasma* spp antibody detection was performed in one institution only (2·5%), and 12 (30%) had access to the test for *Histoplasma* spp at an outsourced laboratory.

The availability of antigen detection tests was low in the study, as illustrated in figure 2. Regarding *Histoplasma* species, only two (5·0%) centres indicated access to in-house antigen testing, even though 12 (30·0%) had access through an outsourced laboratory. *Cryptococcus* lateral flow assay was available for 24 (60·0%) institutions, three of which were exclusively through an outsourced laboratory, whereas *Cryptococcus* latex testing was performed in 16 (40·0%) institutions, and another two (5·0%) had access to the test through an outsourced laboratory. *Aspergillus* antigen detection (by galactomannan enzyme immunoassay, lateral flow assay, or lateral flow device) was available for 11 (27·5%) institutions locally and for eight (20·0%) exclusively through an outsourced laboratory. 16 (40·0%) of all institutions that answered the survey did not have access to antigen testing even through outsourced laboratories.

Access to fungal molecular diagnostics was even more restricted, as shown in table 1. For example, in-house molecular tests for *Pneumocystis* spp were available for seven (17·5%) institutions, and six (15·0%) had access to these methods through an outsourced laboratory.

Only five (12·5%) institutions fulfilled the minimum laboratory requirements for blue status according to ECMM criteria. These five institutions were located in Cameroon, Kenya, Nigeria, Sudan, and Uganda. Seven (17·5%) other institutions fulfilled three of four blue status criteria, whereas 16 (40%) fulfilled two, 11 (27·5%) institutions fulfilled one criterion, and only one (2·5%) institution did not fulfil any of the criteria. Although South Africa is the only African country with a surveillance system for fungal infections and a national mycology reference laboratory,[8] none of the responders from this country performed an antigen ELISA for *Aspergillus* spp or equivalent assays instead.

The availability of antifungal therapy in Africa is detailed in table 2. Therapeutic drug monitoring (TDM) was available for itraconazole in seven (17·5%) institutions in house and in two (5%) institutions at an outsourced laboratory. Regarding TDM for other antifungal agents, voriconazole was available in four (10·0%) institutions, posaconazole in one (2·5%) institution, and 5-flucytosine in three (7·5%) centres in total, both in-house and outsourced.

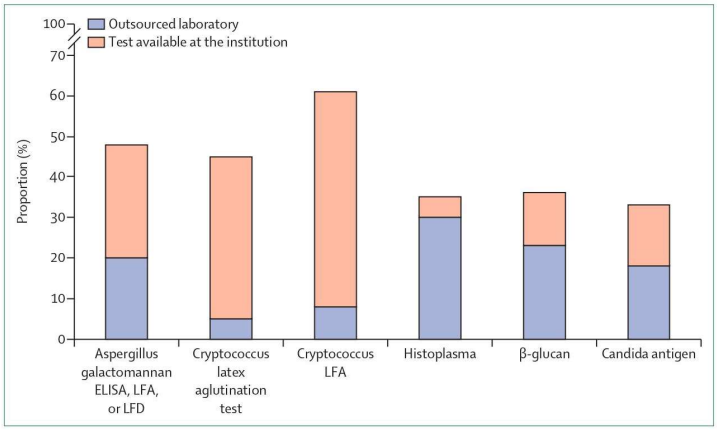

Figure 2: **Antigen detection availability in African institutions**
LFA=lateral flow assay. LFD=lateral flow device.

	Number of institutions with molecular tests available in-house	Number of institutions with molecular tests performed at outsourced laboratories	Total
Candida spp	8 (20·0%)	7 (17·5%)	15 (37·5%)
Aspergillus spp	5 (12·5%)	7 (17·5%)	12 (30·0%)
Pneumocystis spp	7 (17·5%)	6 (15·0%)	13 (32·5%)
Other fungi	5 (12·5%)	6 (15·0%)	11 (27·5%)

Data shown as n (%). Percentages calculated out of 40 responses.

Table 1: **Molecular test (of any sort) availability in-house and at outsourced laboratories according to the fungal pathogen**

Discussion

We report for the first time the availability of diagnostic tools and capacity for treatment of fungal infections in Africa. Other investigators have indicated some of the African laboratories' strengths and weaknesses, but they usually focused on specific African sub-regions (sub-Saharan Africa mainly) and diseases, such as HIV or AIDS.[15–18] Our survey included institutions with distinct profiles (such as university hospitals and public and private hospitals with different numbers of beds) and from different sub-regions of Africa.

The low numbers of responders might reflect the fact that there are few mycologists on the continent. Even though the sample in this survey was a convenience sample, it did provide a snapshot from the entire

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See Online for appendix

For the **ECMM criteria** see https://www.ecmm.info/ecmm-excellence-centers/

	Number of institutions with antifungal drug availability in Africa (n=40)
Fluconazole	36 (90·0%)
Isavuconazole	1 (2·5%)
Itraconazole	21 (52·5%)
Posaconazole	2 (5·0%)
Voriconazole	14 (35·0%)
Amphotericin B deoxycholate	21 (52·5%)
Liposomal amphotericin B	7 (17·5%)
Amphotericin B lipid complex	4 (10·0%)
Other lipid formulations of amphotericin B	4 (10·0%)
Anidulafungin	2 (5·0%)
Caspofungin acetate	8 (20·0%)
Micafungin sodium	9 (22·5%)
5-flucytosine	11 (27·5%)
Terbinafine	25 (62·5%)

Data shown as n (%). Percentages calculated out of 40 responses.

Table 2: **Antifungal drug availability in Africa**

continent. Only three (7·5%) institutions, located in Ethiopia (n=1), Nigeria (n=1), and Togo (n=1), reported no access to mycological diagnosis. However, we should highlight that some countries are not represented in our sample and might have an even more vulnerable situation when it comes to the diagnosis and treatment of fungal infections, mainly if we consider those countries with a lower human development index, lower gross national income per person, and worse indicators related to multidimensional poverty, than the countries included here.[1,2] Nevertheless, the high prevalence of university hospitals and national centres of research (72·5%) among responders might overestimate the available resources. In Africa, challenges posed by fungal infection are huge and diverse. The burden of fungal infection, both cutaneous and invasive, is high, and is well documented in many studies.[19–30] Deaths due to cryptococcal disease, which are associated with HIV infection, exceed 200 000 per year.[29,31] A study evaluating non-culture-based methods, performed with inpatients in South Africa, showed that one in ten inpatients had evidence of an invasive mycosis (including cryptococcosis, pneumocystosis, and histoplasmosis).[32] Additionally, a high incidence of co-infection with tuberculosis was observed, complicating the diagnosis and management of these patients, particularly because of drug–drug interactions. The authors of this previous study estimated that 60% of invasive fungal diseases were missed,[32] corroborating the urgent need for improving diagnostic capacities in this region.

Few studies assessing mycological practices around the world have been performed,[33–37] and fewer so in LMICs.[18,38,39] Sufficient numbers of responders are a challenge in this type of approach: the sample size was also a limitation for Falci and Pasqualotto[38] (129 responses from 14 countries [96 from Brazil, nine from Mexico, five from Colombia, three from Uruguay, three from Guatemala, two from Argentina, two from Chile, two from Paraguay, two from Venezuela, one from Barbados, one from Ecuador, one from Honduras, one from Peru, and one from French Guiana], of which 74% were from one country only) and Chindamporn and colleagues[39] (241 laboratories from seven countries answered the survey out of nearly 900 who were directly contacted, a response rate of approximately 26%). Despite this, data from these snapshots are interesting tools to be used for the advocacy of laboratory capacity improvements. Our data can be combined with those from these previous papers, indicating that there is an unequivocal absence of adequate diagnostic tools to manage fungal disease burden in these regions (Asia, Africa, and Latin America).

In many mycoses, choosing the most appropriate therapy and accurately identifying the causative fungal species is crucial. One example is *Candida auris*, a multidrug resistant pathogen that was retrospectively identified in 2009 in South Africa and in 2011 in Kenya.[40,41] Nevertheless, few laboratories reported having the capacity to correctly identify *C auris*, which includes modern technology such as MALDI-ToF or molecular methods. Institutions that answered the survey here seemed to be reasonably prepared for HIV-associated infections such as cryptococcosis, reporting rates of more than 75% for cryptococcal antigen test and India ink availability. However, opportunistic infections with an unclear epidemiological characterisation in Africa, such as histoplasmosis[42] and emergomycosis,[43] are under-recognised, with less than 40% of institutions reporting access to *Histoplasma* antigen detection.

It is to be noted that it is necessitated that tertiary hospitals attending to patients with non-HIV immunocompromising conditions are aware of the rampant increase of antifungal resistance. However, a concerning 37·5% of institutions in this study do not perform antifungal susceptibility tests. Consequently, we anticipate a catastrophic scenario because multiple risk factors for fungal infections in Africa are combined with an absence of diagnostic tools and limited resources, which in turn is likely to exaggerate the global trend in antifungal resistance, not only in medicine but also in agriculture, with deficient epidemiological tools to monitor its advance in the continent.[44]

The worldwide rise of antifungal resistance as a threat not only to public health but also to food security has been previously noted,[45,46] but not enough action has been taken in the field, especially from policy makers. The use of antifungal agents in agriculture is common and necessary, but their unadvertised use and few regulations might aggravate the problem, mainly in LMICs, which economically depend on crops and commodities.[47] Thus, antifungal resistance has become a problem in onychomycosis and other superficial mycoses, as well as in systemic mycoses.[48]

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Regarding treatment, the unavailability of WHO essential drugs[49] is concerning. Fundamental agents had low availability in the institutes included here. Amphotericin B deoxycholate was available in only 21 (52·5%) institutions, and liposomal amphotericin B in seven (17·5%; table 2). Itraconazole was available only in 21 (52·5%), voriconazole in 14 (35·0%), and posaconazole in two (5·0%) institutions. 5-flucytosine was available in 11 (27·5%) institutions. Only fluconazole had a reasonable availability (90·0%), but this is insufficient to overcome the great burden of fungal infection in Africa, especially without the other components of the antifungal armamentarium. For example, in cryptococcal meningitis, monotherapy with fluconazole is related to substantially higher mortality[50] in comparison with the combination of 5-flucytosine and amphotericin B. Additional issues include *Cryptococcus neoformans* resistance and immune reconstitution inflammatory syndrome in patients living with HIV; however, fluconazole is unfortunately the only treatment available in many African settings.[51,52] When considering dermatophytosis, a high burden and growing resistance in Africa also represents a challenge. According to Bongomin and colleagues,[53] one in every five children in Africa has tinea capitis. If the availability of the appropriate diagnosis tools is low, then adequate treatment seems to be an equally relevant debility. The low availability of TDM is also a worrying sign, because the appropriate use of necessary drugs such as voriconazole and itraconazole is largely dependent on it.[54] TDM is an important tool to adjust drug doses, control toxicity, and result in the rational use of drugs, and is even more necessary in scenarios with reduced resources. Few institutions reported access to TDM and most only had access to TDM testing from outsourced institutions (which results in long turnaround times and, consequently, a lessening in the clinical usefulness of these tests). Moreover, it would also be necessary to consider the access to routine laboratory results to better treat and prevent antifungal toxicity, such as monitoring liver and kidney function. Delay in obtaining such results might result in worse outcomes in patients with fungal diseases.[55]

We aimed to contact as many African institutions and researchers as possible, and the small number of responders in such a diverse continent is probably the most notable limitation of our study. We tried to reach them through their institutional email addresses available in published papers and also through ISHAM and ECMM, which also advertised the study on social media. Additionally, the questionnaire was in English only, which might have created language barrier difficulties for some of the participants. The questionnaire also had to be kept short to facilitate the answers, and some important points were left out, such as the cost of treatments and capabilities of obtaining rapid results of laboratory tests, which might be imperative to handling antifungal toxicity. In addition to the sample size, we were not able to include all relevant mycoses in Africa in the questionnaire, such as dermatophytosis and blastomycosis.[53,56]

In Africa there is an urgent need to improve the structure of health laboratories and overall capacity of the system to tackle the burden of fungal infection. Efforts and collaborations have been made in the last few decades, mainly against fungal infections related to HIV and AIDS, and accomplished many objectives (such as access to cryptococcal antigen tests) through partnerships and structured networks. However, our survey shows that there is more work yet to be done to achieve the necessary framework to address the challenges of all fungal infections, especially non-HIV related infections.[57] There are notable deficits in the availability of diagnostic tests, especially newer technologies such as MALDI-ToF and molecular methods, and non-culture-based methods for the diagnosis of invasive mycoses. Chromogenic media could also optimise the diagnosis at a lower cost. Furthermore, access to adequate treatment is hampered by the low availability of essential drugs. Efforts from and collaborations between health-care professionals, academia, researchers, policy makers, and all other stakeholders are necessary to support the improvement of the diagnostic and therapeutic capacity in caring for people affected by all fungal infections in Africa.

Search strategy and selection criteria

We searched for articles written in English in the PubMed database from May 1, 2019, to May 31, 2021, without any restrictions on the date of publication of the articles included in the search, considering combined terms such as "Africa", "antifungal", "invasive fungal infections", "dermatophytosis", "mycology", "resistance", "agriculture", "laboratory", "access", "treatment", "susceptibility testing", "toxicity", "fluconazole", "amphotericin", "therapeutic drug monitoring", "epidemiology", "burden", "low- and middle-income countries", "cryptococcus", and "HIV". We used guidelines (the WHO guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV and WHO guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents, and children) and the essential medicine list from WHO as consult material as well as the 2019 UN Report on Human Development and Multidimensional Poverty Index to better contextualise our data. When pertinent, we revised the references of the selected articles.

Contributors

CD contributed to the formal analysis, literature search, creating the figures, and writing of the original draft of the manuscript. DRF contributed to the formal analysis, literature search, and writing of the original draft. ROO, FB, BKO, NPG, JPG, CL-F, AA, JG, COM, RR-R, AC, and JFM contributed to writing, reviewing, and editing the manuscript. MH and OAC contributed to the conceptualisation, study design, literature search, data collection, and writing, reviewing, and editing of the manuscript. CB contributed to the data collection, and writing, reviewing, and editing of the manuscript. JS contributed to

creating the figures, and writing, reviewing, and editing of the manuscript. ACP contributed to the conceptualisation, study design, data collection, formal analysis, project administration, and writing of the original draft. CD, DRF, MH, and ACP verified the underlying data.

Declaration of interests

DRF received payments for educational material from Gilead Sciences; honoraria for lectures from Gilead Sciences, Merck Sharp & Dohme, Pfizer, and United Medical; support for attending meetings and travel from Merck, Sharp & Dohme, Gilead Sciences, Pfizer, and United Medical; and participated on an advisory board of Merck, Sharp & Dohme and GlaxoSmithKline, outside the submitted work. AA received honoraria from Gilead Sciences and Pfizer; and travel grants from Astellas, outside the submitted work. JS received research grants from the Ministry of Education and Research and Basilea Pharmaceuticals; and received travel grants from the German Society for Infectious Diseases and Meta-Alexander Foundation, outside the submitted work. JPG received funds for participating at educational activities organised on behalf of Astellas, Biotoscana, Gilead Sciences, Merck, Sharp & Dohme, and Scynexis; and received research funds from Cidara, Fabbrica Italiana Sintetici, Gilead Sciences, and Scynexis, outside the submitted work. OAC reports grants from Actelion, Amplyx, Astellas, Basilea, Cidara, Da Volterra, The Deutsche Forschungsgemeinschaft, F2G, German Federal Ministry of Research and Education, German Research Foundation, Gilead Sciences, Immunic, Janssen, Medicines Company, MedPace, Melinta Therapeutics, Merck, Sharpe & Dohme, Pfizer, and Scynexis; and personal fees from Actelion, Allecra Therapeutics, Al-Jazeera Pharmaceuticals, Amplyx, Astellas, Basilea, Biosys, Cidara, Da Volterra, Entasis, F2G, Gilead Sciences, Grupo Biotoscana, IQVIA, Matinas, MedPace, Menarini, Merck, Sharpe & Dohme, Mylan, Nabriva, Noxxon, Octapharma, Paratek, Pfizer, Pharmaceutical Solutions Industry, Roche Diagnostics, Scynexis, and Shionogi, outside the submitted work. JFM received grants from F2G and Pulmozyme; has been a consultant to Merck Sharpe & Dohme and Scynexis; and has received speaker's fees from Gilead, Teva Pharmaceutical Industries, and United Medical. NPG received research grants from the National Institutes of Health, Centers for Disease Control and Prevention, Bill & Melinda Gates Foundation, and the UK Medical Research Council, outside the submitted work. ROO has received grants from Gilead Sciences and Pfizer; payment for lectures from Pfizer; and participated on an advisory board for Pfizer, outside the submitted work. BKO received research funds from The Foundation for Technological Innovation, outside the submitted work; and the funds to organise a symposium from Immuno-Mycologics. COM has received grants from Gilead Sciences and Merck Sharp & Dohme Australia; received payment for lectures from Gilead Sciences, Merck Sharp & Dohme, and Pfizer; and participated in a data safety monitoring board for Gilead Sciences and Merck Sharp & Dohme, outside the submitted work. ACP received research grants support from Gilead Sciences, Immuno-Mycologics, Merck, Sharp & Dohme, and Pfizer; and has given paid talks and consulted for Gilead Sciences, Immuno-Mycologics, Merck, Sharp & Dohme, Pfizer, Teva, and United Medical, outside the submitted work. MH received research funding from Astellas, Euroimmun, the National Institutes of Health US, Gilead, Pfizer, and Scynexis, outside the submitted work. All other authors declare no competing interests.

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References

1 Oxford Poverty and Human Development Initiative, United Nations Development Programme. Charting pathways out of multidimensional poverty: achieving the SDGs. 2020. http://hdr.undp.org/sites/default/files/2020_mpi_report_en.pdf (accessed Jan 15, 2021).

2 United Nations Development Programme. Human Development Report 2019. 2019. http://hdr.undp.org/sites/default/files/hdr2019.pdf (accessed Jan 15, 2021).

3 WHO. Tuberculose (TB). https://www.afro.who.int/health-topics/tuberculosis-tb (acessed March 23, 2021).

4 Dada DA, Aku E, David KB. COVID-19 pandemic and antiretrovirals (ARV) availability in Nigeria: recommendations to prevent shortages. *Pan Afr Med J* 2020; **35** (suppl 2): 149.

5 UNAIDS. COVID-19 could affect the availability and cost of antiretroviral medicines, but the risks can be mitigated. June 22, 2020. https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2020/june/20200622_availability-and-cost-of-antiretroviral-medicines (acessed March 23, 2021).

6 Nargesi S, Bongomin F, Hedayati MT. The impact of COVID-19 pandemic on AIDS-related mycoses and fungal neglected tropical diseases: why should we worry? *PLoS Negl Trop Dis* 2021; **15:** e0009092.

7 Oladele RO, Osaigbovo II, Ayanlowo OO, et al. The role of medical mycology societies in combating invasive fungal infections in low- and middle-income countries: a Nigerian model. *Mycoses* 2019; **62:** 16–21.

8 Oladele RO, Akase IE, Fahal AH, et al. Bridging the knowledge gap on mycoses in Africa: setting up a Pan-African Mycology Working Group. *Mycoses* 2020; **63:** 244–49.

9 Global Action Fund for Fungal Infections. Hidden crisis: how 150 people die every hour from fungal infection while the world turns a blind eye. August, 2017. https://www.gaffi.org/wp-content/uploads/GAFFI-Final-Brochure-Aug-2017-pages.pdf (acessed March 23, 2021).

10 Cornely OA, Lass-Flörl C, Lagrou K, Arsic-Arsenijevic V, Hoenigl M. Improving outcome of fungal diseases - guiding experts and patients towards excellence. *Mycoses* 2017; **60:** 420–25.

11 Friedman DZP, Schwartz IS. Emerging fungal infections: new patients, new patterns, and new pathogens. *J Fungi (Basel)* 2019; **5:** 5.

12 Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. *Sci Transl Med* 2012; **4:** 165rv13.

13 Oladele R, Otu AA, Olubamwo O, et al. Evaluation of knowledge and awareness of invasive fungal infections amongst resident doctors in Nigeria. *Pan Afr Med J* 2020; **36:** 297.

14 Hoenigl M, Gangneux JP, Segal E, et al. Global guidelines and initiatives from the European Confederation of Medical Mycology to improve patient care and research worldwide: new leadership is about working together. *Mycoses* 2018; **61:** 885–94.

15 Alemnji GA, Zeh C, Yao K, Fonjungo PN. Strengthening national health laboratories in sub-Saharan Africa: a decade of remarkable progress. *Trop Med Int Health* 2014; **19:** 450–58.

16 Gray IP, Carter JY. An evaluation of clinical laboratory services in sub-Saharan Africa. Ex africa semper aliquid novi? *Clin Chim Acta* 1997; **267:** 103–28.

17 Zhang HL, Omondi MW, Musyoka AM, et al. Challenges of maintaining good clinical laboratory practices in low-resource settings: a health program evaluation framework case study from east Africa. *Am J Clin Pathol* 2016; **146:** 199–206.

18 Eduful SK, Ocansey BK, Dadzie EA, et al. The current state of medical mycology laboratory practice in Ghana: preliminary data from a FIKI Ghana and GMMG survey. The 7th Laboratory Professionals Annual Meeting of the Celebrate LAB West Africa, Accra, Ghana; April 21–22, 2021.

19 Ocansey BK, Pesewu GA, Codjoe FS, Osei-Djarbeng S, Feglo PK, Denning DW. Estimated burden of serious fungal infections in Ghana. *J Fungi (Basel)* 2019; 11; **5:** 38.

20 Badiane AS, Ndiaye D, Denning DW. Burden of fungal infections in Senegal. *Mycoses* 2015; **58** (suppl 5): 63–69.

21 Chekiri-Talbi M, Denning DW. Burden of fungal infections in Algeria. *Eur J Clin Microbiol Infect Dis* 2017; **36:** 999–1004.

22 Faini D, Maokola W, Furrer H, et al. Burden of serious fungal infections in Tanzania. *Mycoses* 2015; **58** (suppl 5): 70–79.

23 Guto JA, Bii CC, Denning DW. Estimated burden of fungal infections in Kenya. *J Infect Dev Ctries* 2016; **10:** 777–84.

24 Koffi D, Bonouman IV, Toure AO, et al. Estimates of serious fungal infection burden in Côte d'Ivoire and country health profile. *J Mycol Med* 2021; **31:** 101086.

25 Kwizera R, Musaazi J, Meya DB, et al. Burden of fungal asthma in Africa: a systematic review and meta-analysis. *PLoS One* 2019; **14:** e0216568.

26 Mandengue CE, Denning DW. The burden of serious fungal infections in Cameroon. *J Fungi (Basel)* 2018; **4:** 1–9.

27 Oladele RO, Denning DW. Burden of serious fungal infection in Nigeria. *West Afr J Med* 2014; **33:** 107–14.

28 Parkes-Ratanshi R, Achan B, Kwizera R, Kambugu A, Meya D, Denning DW. Cryptococcal disease and the burden of other fungal diseases in Uganda; where are the knowledge gaps and how can we fill them? *Mycoses* 2015; **58** (suppl 5): 85–93.

29 Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* 2017; **17:** 873–81.

30 Zaki SM, Denning DW. Serious fungal infections in Egypt. *Eur J Clin Microbiol Infect Dis* 2017; **36:** 971–74.

31 Nyazika TK, Tatuene JK, Kenfak-Foguena A, et al. Epidemiology and aetiologies of cryptococcal meningitis in Africa, 1950-2017: protocol for a systematic review. *BMJ Open* 2018; **8:** e020654.

32 van Schalkwyk E, Mhlanga M, Maphanga TG, et al. Screening for invasive fungal disease using non-culture-based assays among inpatients with advanced HIV disease at a large academic hospital in South Africa. *Mycoses* 2020; **63:** 478–87.

33 Lasseter G, McNulty CAM, Palmer M, Yoxall H, Kibbler C. Developing best practice for fungal specimen submission--fungal audit of general practice. *Mycoses* 2012; **55:** 476–82.

34 Schelenz S, Owens K, Guy R, et al. National mycology laboratory diagnostic capacity for invasive fungal diseases in 2017: evidence of sub-optimal practice. *J Infect* 2019; **79:** 167–73.

35 Morris AJ, Arthur IH, Kidd SE, et al. Mycological testing of clinical samples in Australasian pathology laboratories: wide diversity and room for improvement. *Pathology* 2016; **48:** 531–34.

36 Rosner ER, Reiss E, Warren NG, Shadomy HJ, Lipman HB. Evaluation of the status of laboratory practices and the need for continuing education in medical mycology. *Am J Clin Pathol* 2002; **118:** 278–86.

37 Schelenz S, Barnes RA, Kibbler CC, Jones BL, Denning DW. Standards of care for patients with invasive fungal infections within the United Kingdom: a national audit. *J Infect* 2009; **58:** 145–53.

38 Falci DR, Pasqualotto AC. Clinical mycology in Latin America and the Caribbean: a snapshot of diagnostic and therapeutic capabilities. *Mycoses* 2019; **62:** 368–73.

39 Chindamporn A, Chakrabarti A, Li R, et al. Survey of laboratory practices for diagnosis of fungal infection in seven Asian countries: an Asia Fungal Working Group (AFWG) initiative. *Med Mycol* 2018; **56:** 416–25.

40 Adam RD, Revathi G, Okinda N, et al. Analysis of *Candida auris* fungemia at a single facility in Kenya. *Int J Infect Dis* 2019; **85:** 182–87.

41 Magobo RE, Corcoran C, Seetharam S, Govender NP. *Candida auris*-associated candidemia, South Africa. *Emerg Infect Dis* 2014; **20:** 1250–51.

42 Develoux M, Amona FM, Hennequin C. Histoplasmosis caused by *Histoplasma capsulatum* var. duboisii: a comprehensive review of cases from 1993 to 2019. *Clin Infect Dis* 2021; **73:** e543–49.

43 Govender NP, Grayson W. Emergomycosis (*Emergomyces africanus*) in advanced HIV disease. *Dermatopathology (Basel)* 2019; **6:** 63–69.

44 Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. *Lancet Infect Dis* 2017; **17:** e383–92.

45 Verweij PE, Snelders E, Kema GH, Mellado E, Melchers WJ. Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use? *Lancet Infect Dis* 2009; **9:** 789–95.

46 Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. *Science* 2018; **360:** 739–42.

47 Brauer VS, Rezende CP, Pessoni AM, et al. Antifungal agents in agriculture: friends and foes of public health. *Biomolecules* 2019; **9:** 521.

48 Gupta AK, Renaud HJ, Quinlan EM, Shear NH, Piguet V. The growing problem of antifungal resistance in onychomycosis and other superficial mycoses. *Am J Clin Dermatol* 2021; **22:** 149–57.

49 WHO. World Health Organization model list of essential medicines. *Ment Holist Heal Some Int Perspect* 2019; **21:** 119–34.

50 Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med* 2018; **378:** 1004–17.

51 Hope W, Stone NRH, Johnson A, et al. Fluconazole monotherapy is a suboptimal option for initial treatment of cryptococcal meningitis because of emergence of resistance. *MBio* 2019; **10:** e02575–19.

52 Cotton MF, Rabie H, Nemes E, et al. A prospective study of the immune reconstitution inflammatory syndrome (IRIS) in HIV-infected children from high prevalence countries. *PLoS One* 2019; **14:** e0211155.

53 Bongomin F, Olum R, Nsenga L, et al. Estimation of the burden of tinea capitis among children in Africa. *Mycoses* 2021; **64:** 349–63.

54 Stott KE, Hope WW. Therapeutic drug monitoring for invasive mould infections and disease: pharmacokinetic and pharmacodynamic considerations. *J Antimicrob Chemother* 2017; **72:** i12–18.

55 Bellmann R, Smuszkiewicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. *Infection* 2017; **45:** 737–79.

56 Maphanga TG, Birkhead M, Muñoz JF, et al. Human blastomycosis in South Africa caused by *Blastomyces percursus* and *Blastomyces emzantsi* sp. nov., 1967 to 2014. *J Clin Microbiol* 2020; **58:** 1–19.

57 Cole DC, Govender NP, Chakrabarti A, Sacarlal J, Denning DW. Improvement of fungal disease identification and management: combined health systems and public health approaches. *Lancet Infect Dis* 2017; **17:** e412–19.

“**The current state of Clinical Mycology in Eastern and South-Eastern Europe”**

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Brief Report

Brief Report

The current state of Clinical Mycology in Eastern and South-Eastern Europe

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Abstract

The ability of medical centers in Eastern and South-Eastern Europe to diagnose and treat fungal infections remains unknown. In order to investigate that, here we conducted a cross-sectional online survey, released at both The International Society for Human & Animal Mycology (ISHAM) and European Confederation of

Medical Mycology (ECMM) websites. A total of 31 institutions responded to the questionnaire. Most centers (87.1%, n = 27) had access to *Aspergillus* spp. ELISA galactomannan testing as well as to *Cryptococcus* spp. antigen testing (83.9%, n = 26). Serological tests were mostly available for *Aspergillus* species (80.6%, n = 25); and most institutions reported access to mold-active antifungal drugs (83.9%; n = 26), but 5-flucytosine was available to only 29% (n = 9) of the participant centers. In conclusion, this study represents the first attempt to document the strengths and limitations of the Eastern and South-Eastern European region for diagnosing and treating fungal diseases.

Lay Summary

Our article is about the availability of diagnostic and treatments tools related to fungal infections in the countries of Eastern and South-Eastern region. Surveys like these are important to understand the gaps and point towards the fungal infections as a global health issue.

Key words: fungal infection, mycology, diagnosis, laboratory, antifungal agents.

Fungal infections still pose a challenge, due to combination of factors including poor awareness of health care workers, limited availability of diagnostic tools, treatment-related toxicities and limited access to antifungal drugs. The epidemiology of fungal infections has been described in many countries around the globe including Eastern and South-Eastern Europe,[1–6] including epidemiology of rare mold and rare yeast infections,[7–9] but knowledge on the availability of antifungal drugs and diagnostic tools in Clinical Mycology in the region remains poorly studied. Moreover, inequities within Europe may result in differences in terms of access to medicines and diagnostic capacity in medical mycology.[10]

In order to fill this gap of information, we developed a cross-sectional online survey (www.clinicalsurveys.net, Questback GmbH, Cologne, Germany) that included 29 questions covering different topics in the field of clinical mycology. The survey remained open from June 2019 to May 2020 and was released online at the International Society of Human and Animal Mycology (ISHAM) and the European Confederation of Medical Mycology (ECMM) websites. Institutions were classified according to whether the laboratories potentially met the ECMM criteria for Blue Status, the initial category of the Excellence Centre Initiative (https://www.ecmm.info/ecmm-excellence-centers), which are: (i) the ability to identify relevant yeasts and molds; (ii) performance of susceptibility testing on yeasts and molds according to standard procedures; (iii) performance of *Aspergillus* antigen (galactomannan) test; (iv) availability of cryptococcal antigen testing.[11] This did not configure an ECMM accreditation, but rather suggested possible candidates for Blue Status, if there was an application from these institutions. Croatia already has an accredited ECMM Excellence Centre Silver since 2018, University Hospital Centre Zagreb Department of Clinical and Molecular Microbiology, and this center did not answer to this survey. The ECMM accreditation process is part of a project which aims to provide expert consultation free of charge in difficult-to-treat invasive fungal infections clinical cases (ECMM Expert Consultation Service).[11]

We received 31 answers, from 11 different countries (Figure 1), including Greece (n = 9), Croatia (n = 5), Russia (n = 5), Estonia (n = 3), Serbia (n = 2), Slovakia (n = 2), Czech Republic (n = 1), Hungary (n = 1), Lithuania (n = 1), Romania (n = 1) and Slovenia (n = 1). Among responders, only Russia and Serbia are not part of the European Union. The survey was answered by laboratory professionals (n = 12), academics (n = 8), attending physicians (n = 3), infectious diseases specialists (n = 2), institution directors (n = 2) and other professionals who did not fit any of these categories (n = 3). One responder did not inform their position. Among responders, 74.2% (n = 23) were university hospitals or national institutes of research, 19.4% (n = 6) were public hospitals, 6.5% (n = 2) were oncology clinics, 3.2% (n = 1) were private hospitals and one was an independent laboratory (provides diagnosis to health institutions but does not perform treatment). Multiple selections were allowed in this item.

Regarding performance of microscopy, potassium hydroxide was available for 71.0% (n = 22) of institutions, India/China ink for 64.5% (n = 20), Giemsa stain for 54.8% (n = 17), silver stain for 16.1% (n = 7) and calcofluor white for 38.7% (n = 12). Fluorescent dyes in general were available for 61.3% (n = 19). Automated blood culture monitoring was available for 80.6% (n = 26) of institutions.

For fungal species identification, automated identification by VITEK or other commercial methods was available for 67.7% (n = 21) of institutions; biochemical tests (classic mycology) were available for 54.0% (n = 17), Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-ToF) for 48.4% (n = 15), 32.3% used mounting medium (n = 12), and DNA sequencing was accessible for 29.0% (n = 9).

Susceptibility testing was available for both yeasts and molds in 67.7% (n = 21) of institutions and for yeasts only in 22.6%

Figure 1. Distribution of European institutions participating in this survey. In blue, there are countries from institutions that answered the survey. The marker indicates countries where at least one institution potentially fulfilled the minimum requirements for ECMM Blue Status.

(n = 7). Institutions used E-test strips (77.4%, n = 24), VITEK (41.9%, n = 13), and broth microdilution, following the Clinical and Laboratory Standards Institute (CLSI) (35.5%, n = 11) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards (41.9%, n = 13).

Regarding the availability of serological testing, it was mostly available for *Aspergillus* spp. (80.6%, n = 25). This was followed by *Candida* spp. (64.5%, n = 20), *Histoplasma* spp. (16.1%, n = 5) and *Paracoccidioides* spp. (9.7%, n = 3).

Most institutions (87.1%, n = 27) had access to *Aspergillus* spp. ELISA galactomannan testing, and 12.9% (n = 4) had access to the *Aspergillus* spp. lateral flow assay (LFA). *Cryptococcus* spp. latex testing was available for 83.8% (n = 26) of responders; *Cryptococcus* spp. LFA for 3.2% (n = 1), *Histoplasma* spp. antigen detection for 12.9% (n = 4), 1.3-β-Glucan for 51.6% (n = 16) and *Candida* spp. antigen detection for 54.8% (n = 17) of institutions.

The availability of molecular tests in Eastern and South-Eastern Europe is described in Table 1, and the availability of antifungal drugs is summarized in Table 2.

Therapeutic drug monitoring (TDM) was locally available for itraconazole in 19.4% (n = 6) of institutions, for posaconazole in 32.3% (n = 10), for voriconazole in 29% (n = 9), and for 5-flucytosine in 6.5% (n = 2).

Regarding ECMM requirements for Blue Status, 48.4% (n = 15) of institutions potentially fulfilled the minimum laboratory requirements. These centers were located in Russia (n = 5), Greece (n = 4), Croatia (n = 1), Czech Republic (n = 1), Hungary (n = 1), Serbia (n = 1), Slovakia (n = 1), Slovenia (n = 1).

Considering that antifungal resistance is a growing global health problem,[12] participant institutions were not ready to properly face this challenge, once they reported low access to diagnostic tools, including TDM. The most accessible TDM was to posaconazole, and that was available at only 32.3% (n = 10) of institutions. The limited availability of molecular tests showed in our survey can also pose a problem, resulting in delayed diagnoses.

For instance, 5-flucytosine, considered essential by the World Health Organization, was available to only 29.0% (n = 9) of participant centers, which is alarming considering the high mortality of HIV-associated cryptococcal meningoencephalitis.[13] Although limited, the region has better availability of 5-flucytosine than other regions of the globe, such as Latin America and Africa (18 and 27%, respectively). At the same time, amphotericin B was available in any of its formulations in 83.9% (n = 26) of institutions in our survey, and in 72% in Latin America and 52.5% in Africa.[14,15]

Continuous work is necessary in order to reduce health inequities within the European continent and beyond, guaranteeing access to healthcare services in its three dimensions: coverage, affordability and availability of care. According to the World Health Organization, HIV/AIDS is more prevalent in Eastern countries when compared to other European subregions, as well as respiratory underlying conditions, considered important risk factor for fungal infections. For example, of the 136,449 people diagnosed with HIV/AIDS in Europe in 2019, 79.0% were diagnosed in the East (n = 107,842).[16] In some countries, efforts have been made to document the burden of fungal diseases. One example is Hungary, in which the number of difficult to treat and potentially life-threatening mycoses was estimated as at least

Table 1. Molecular tests availability according to the fungal pathogen.

	Molecular tests availability at the institution	Molecular tests performed at outsourced laboratories	Total
Aspergillus spp.	29.9% (n = 9)	16.1% (n = 5)	45.2% (n = 14)
Candida spp.	41.9% (n = 13)	9.7% (n = 3)	51.6% (n = 16)
Pneumocystis spp.	48.4% (n = 15)	3.2% (n = 1)	51.6% (n = 16)
Other fungi	22.6% (n = 7)	6.5% (n = 2)	29.0% (n = 9)

Table 2. Availability of antifungal drugs in Eastern and South-Eastern Europe.

Antifungal drug	Availability
Amphotericin B deoxycholate*	41.9% (n = 13)
Amphotericin B lipid complex (ABLC)	35.5% (n = 11)
Liposomal amphotericin B*	54.8% (n = 17)
Other lipid formulations of amphotericin B	16.1% (n = 5)
At least one amphotericin B formulation	83.9% (n = 26)
Anidulafungin	67.7% (n = 21)
Caspofungin	71.0% (n = 22)
Micafungin	64.5% (n = 20)
Fluconazole*	93.5% (n = 29)
Itraconazole*	77.4% (n = 24)
Voriconazole*	87.1% (n = 27)
Posaconazole	64.5% (n = 20)
Isavuconazole	22.6% (n = 7)
Flucytosine*	29.0% (n = 9)
Terbinafine	32.2% (n = 10)

*Part of WHO Model List of Essential Medicines. For Amphotericin B, WHO considers sodium deoxycholate *or* liposomal complex as an essential medicine.[19]

33,000 annually.[3] Although Europe is not a main area of endemic mycoses, migration, travel, and increase of immunocompromised population with the advance of oncologic therapies, for example, maintain the burden of invasive fungal diseases.[17]

To tackle this problem, an important step would be making relevant fungal infections (such as azole-resistant *Aspergillus spp.* and *Candida auris* infections) notifiable diseases, building more active surveillance systems, monitoring and avoiding possible breakthrough infections.[18] Furthermore, there is a need to improve infection control practices, considering that health-care-associated invasive fungal diseases are also an important cause of morbimortality. Educating health workers facing invasive fungal diseases according to the best evidence available is also an important strategy. Initiatives such as ECMM Expert Consult provide tools to help capacitating and empowering institutions worldwide.[11] Improving access to rapid diagnostic methods, such as molecular tests (which were available for only half of institutions), would also strengthen infection control practices in the region.

This survey has some limitations, including the small number of responders. Once the survey was released online through ISHAM and ECMM websites, our data is also restricted to institutions which were aware of these societies. However, this is the first attempt to document the strengths and limitations of the region, regarding the capacity of diagnosis and treatment of fungal infections. Future studies are needed to compare diagnostic capabilities between different regions of Europe to identify areas of highest need. Surveys like these are important to understand the gaps and point towards the fungal infections as a global health issue, identifying the necessity of multidisciplinary actions from stakeholders and policy makers.

Declaration of interest

ACP has received research grants, given paid talks and consulted for Pfizer, Gilead, MSD, United Medical, Teva, and IMMY, not related to this study. DRF has received research support, payment for lectures and consulting fees from United Medical, Gilead, Astellas, MSD, IMMY and Pfizer, not related to this work.

In the last 5 years, DF has received payment for research grants, lectures, advisory boards, and/or travel reimbursements, not related to this study, from Pfizer, GSK, Gilead, MSD and United Medical.

MH has received grants or contracts from NIH, MSD, Gilead, Astellas and Pfizer, not related to this study. MH is also president of the ECMM, unpaid position.

OAC reports grants or contracts from Amplyx, Basilea, BMBF, Cidara, DZIF, EU-DG RTD (101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; Consulting fees from Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Noxxon, Octapharma, PSI, Scynexis, Seres; Honoraria for lectures from Abbott, Al-Jazeera Pharmaceuticals, Astellas, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Pfizer; Payment for expert testimony from Cidara; Participation on a Data Safety Monitoring Board or Advisory Board from Actelion, Allecra, Cidara, Entasis, IQVIA, Jannsen, MedPace, Paratek, PSI, Shionogi; A patent at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); Other interests from DGHO, DGI, ECMM, ISHAM, MSG-ERC, Wiley.

JPG has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead and Pfizer, not related to this study.

DES reports grants or contracts from Abbvie, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Dr. Reddy's, Montavit, Noventure, Nutricia, and Reckitt Benckiser, support for attending meetings from Nestle, not related to this study.

JRP reports advisory panel, consultation or research grants with Pfizer, Scynexis, Cidara, Matinas, Appili, F2G, Astellas, and Minnetronix.

CD, AC, JFM, VAA, ES, MJE, and TM have no conflict of interest to declare.

Author's contributions

CD Writing – Original Draft, Visualization; DRF Writing – Original Draft, Visualization; MH Conceptualization, Methodology, Writing – Review & Editing; OAC Conceptualization, Methodology, Writing – Review & Editing; AC Conceptualization, Methodology, Writing – Review & Editing; JPG Writing – Review & Editing; ES Writing – Review & Editing; MJE Writing – Review & Editing; TM Writing – Review & Editing; JFM Writing – Review & Editing; JRP Writing – Review & Editing; VAA Writing – Review & Editing; MM Writing – Review & Editing; DES Writing – Review and Editing; ACP Writing – Original Draft, Review & Editing, Supervision.

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References

1. Chrdle A, Mallátová N, Vašáková M, Haber J, Denning DW. Burden of serious fungal infections in the Czech Republic. *Mycoses*. 2015; 58: 6–14.
2. Klimko N, Kozlova Y, Khostelidi S et al. The burden of serious fungal diseases in Russia. *Mycoses*. 2015; 58: 58–62.
3. Sinkó J, Sulyok M, Denning DW. Burden of serious fungal diseases in Hungary. *Mycoses*. 2015; 58: 29–33.

4. Arsenijević VA, Denning DW. Estimated burden of serious fungal diseases in Serbia. *J Fungi*. 2018; 4: 1–13.
5. Osmanov A, Denning DW. Burden of serious fungal infections in Ukraine. *Mycoses*. 2015; 58: 94–100.
6. Mareș M, Moroti-Constantinescu VR, Denning DW. The burden of fungal diseases in Romania. *J Fungi*. 2018; 4: 1–7.
7. Cornely OA, Alastruey-Izquierdo A, Arenz D et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis*. 2019; 19: e405–e421.
8. Hoenigl M, Salmanton-García J, Walsh TJ et al. Global guideline for the diagnosis and management of rare mold infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiolo. *Lancet Infect Dis*. 2021; 21: e246–e257.
9. Chen SCA, Perfect J, Colombo AL et al. Global guideline for the diagnosis and management of rare yeast infections: an initiative of the ECMM in cooperation with ISHAM and ASM. *Lancet Infect Dis*. 2021; 21: e375–e386.
10. Scholz N. *Addressing Health Inequalities in the European Union*; 2020. doi:10.2861/567478.
11. Koehler P, Denis B, Denning DW et al. European confederation of medical mycology expert consult—An ECMM excellence center initiative. *Mycoses*. 2020; 63: 566–572.
12. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. *Lancet Infect Dis*. 2017; 17: e383–e392.
13. Rajasingham R, Smith RM, Park BJ et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis*. 2017; 17: 873–881.
14. Driemeyer C, Falci DR, Oladele RO et al. The current state of clinical mycology in Africa: a European Confederation of Medical Mycology and International Society for Human and Animal Mycology survey. *The Lancet Microbe*. 2022; 5247: 1–7.
15. Falci DR, Pasqualotto AC. Clinical mycology in Latin America and the Caribbean: a snapshot of diagnostic and therapeutic capabilities. *Mycoses*. 2019; 62: 368–373.
16. World Health Organization EC for DP and C. *HIV/AIDS Surveillance in Europe*. Vol 5. 2020. doi:10.2900/073965.
17. Benedict K, Richardson M, Vallabhaneni S, Jackson BR, Chiller T. Emerging issues, challenges, and changing epidemiology of fungal disease outbreaks. *Lancet Infect Dis*. 2017; 17: e403–e411.
18. Ider BE, Adams J, Morton A, Whitby M, Clements A. Infection control systems in transition: the challenges for post-Soviet Bloc countries. *J Hosp Infect*. 2012; 80: 277–287.
19. OMS. World Health Organization Model List of Essential Medicines. *Mental and Holistic Health: Some International Perspectives*. 2019; 21: 119–134. https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1.

5. CONCLUSÕES

Nossa pesquisa demonstra que há um longo caminho a percorrer no enfretamento das infecções fúngicas. Existem deficiências importantes na disponibilidade de testes diagnósticos, especialmente nas tecnologias mais recentes - como MALDI-ToF, métodos moleculares e não baseados em cultura. Além disso, o acesso ao tratamento adequado é restrito, com falta de medicamentos essenciais em muitos países, principalmente no continente africano.

Em relação a classificação dos centros respondedores, ressaltamos as diferenças entre os continentes. No África, apenas 12.5% dos centros estaria apto a categoria inicial da classificação, Blue Status, estando cada um localizado em um dos países a seguir: Camarões, Nigéria, Quênia, Sudão e Uganda. Já no Leste Europeu, 48,4% estaria apto ao Blue Status caso se candidatasse, estando localizados nos países Rússia (n = 5), Grécia (n = 4), Croácia (n = 1), República Tcheca (n = 1), Hungria (n = 1), Sérvia (n = 1), Eslováquia (n = 1) e Eslovênia (n = 1).

6. CONSIDERAÇÕES FINAIS

Embora focado no continente africano e no leste europeu, nosso trabalho foi realizado em parceria com pesquisadores do mundo todo, engajados com a finalidade de superar inequidades em saúde e também de suprir déficits epidemiológicos que balizem ações em saúde pública e global. Consideramos essencial a parceria estabelecida com a ECMM e o ISHAM, que possibilitou atingir um maior número de pesquisadores e também de ampliar a divulgação dos resultados.

Uma ação fundamental é tornar as infecções fúngicas invasivas uma doença de notificação compulsória**,** construindo sistemas de vigilância mais ativos, monitorando e evitando possíveis infecções. Dessa forma, seria possível obter mais dados de vida real que guiem investimentos e ações em saúde racionalmente.

Melhorar as práticas de controle de infecção é essencial, considerando que as doenças fúngicas invasivas associadas à assistência são também uma importante causa de morbimortalidade. Ademais, faz-se mandatório capacitar os profissionais de saúde de acordo com as melhores evidências disponíveis.

É preciso garantir o acesso aos serviços de saúde em suas três dimensões: cobertura, acessibilidade e disponibilidade de cuidados. Assim, não há ação individual suficiente e são necessários esforços de profissionais, pesquisadores, políticos e sociedade civil para que seja possível melhorar a capacidade diagnóstica e terapêutica no tratamento de pessoas com infecções fúngicas.

Após a conclusão e publicação do nosso trabalho, outras publicações vêm sendo realizadas com objetivos semelhantes, visando a adequadas medidas de recursos em saúde, de disponibilidade diagnóstica e de tratamento em diferentes partes do globo. O surgimento destes outros trabalhos corrobora a importância de estudos como este para o estabelecimento de políticas públicas e de um plano de ação comum entre os diferentes atores da sociedade civil para avanços em relação ao desafio global que são as doenças fúngicas.

7. BIOGRAFIA

Nasci em São Leopoldo em 1995 e iniciei os estudos em Medicina na Universidade Federal de Pelotas em 2014, também no Rio Grande do Sul, onde estudei por apenas um semestre, sendo em seguida aprovada na Universidade Federal de Ciências da Saúde de Porto Alegre em 2015.

Interessei-me pela pesquisa ainda no início no curso, sendo monitora de Metodologia Científica e bolsista de Iniciação Científica. Ao mesmo tempo, também estudei sobre saúde global, inequidades em saúde e determinação social do processo saúde doença. Fui monitora de Medicina Social e coordenei um programa de intercâmbio em parceria com a Universidade de Havana, em Cuba e no Brasil.

Devido aos projetos desenvolvidos durante a graduação, tive a oportunidade de conhecer alguns países, e gostaria de poder conhecer cada um dos que cito nesta dissertação.

APÊNDICE

Questionário aplicado através da plataforma Clinical Surveys.

Fragebogen

1 IFI Management Capacity Questionnaire

"Evaluation of the Diagnostic Capabilities of Mycology Laboratories"

2 Institution Profile

Your position

- ○ Director
- ○ Infection Control Practitioner
- ○ Professor
- ○ Attending Physician
- ○ Attending Physician - Infectious Diseases Specialist
- ○ Laboratory Professional
- ○ Other

Contact information

non-mandatory information

Your Name

Your E-mail Address

Institution

Institute, Department

Location of your institution

Please provide names in English.

City

State

Country

Institution profile

Please select at least one of the following options.

- ☐ University Hospital
- ☐ Public Hospital
- ☐ Private Hospital
- ☐ Oncology Clinic
- ☐ Dialysis Clinic
- ☐ Day-Hospital
- ☐ Federal Institute / Research Hospital

Institution size - number of beds

If not applicable, please enter "0".

Overall

Adult intensive care beds

Pediatric/Neonatal intensive care beds

Does your institution take care of patients with any of the following conditions?

Please answer each question. Please select unknown in case of missing information.

Oncology	O Yes	O No	O Unknown
Hematology	O Yes	O No	O Unknown
HIV/AIDS	O Yes	O No	O Unknown
Stem cell transplantation	O Yes	O No	O Unknown
Solid organ transplantation	O Yes	O No	O Unknown
Neonatal Intensive Care Unit	O Yes	O No	O Unknown
Parenteral nutrition	O Yes	O No	O Unknown

Does your institution have a microbiology laboratory?

- ○ Yes, in place
- ○ Yes, outsourcing laboratory services
- ○ No

Where are diagnostic mycological procedure performed?

- ○ Always in our instituition
- ○ Part in our instituition / part outsourced
- ○ Totally outsourced
- ○ We do not have access to mycological diagnostic tools

3 Perceptions on invasive fungal disease in your institution

Please rate the incidence of invasive fungal infections in your institution from very low (1) to high (5)

- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Pathogens of highest importance Please mark all that apply.

- ☐ Aspergillus spp.
- ☐ Fusarium spp.
- ☐ Mucorales
- ☐ Candida spp.
- ☐ Cryptococcus spp.
- ☐ Histoplasma spp.

What is the approximate number of samples (per month) processed in your mycology laboratory?

If unknown, please leave it blank.

TOTAL number of samples	
BLOOD samples	
BAL (bronchoalveolar lavage) samples	
TISSUE (from biopsies) samples	
URINE samples	

Please indicate all available drugs for antifungal treatment in your instituition
Please answer each question. In case of missing information please select "unknown".

Itraconazole	O Yes	O No	O Unknown
Voriconazole	O Yes	O No	O Unknown
Posaconazole	O Yes	O No	O Unknown
Fluconazole	O Yes	O No	O Unknown
Isavuconazole	O Yes	O No	O Unknown
Amphotericin B deoxycholate	O Yes	O No	O Unknown
Amphotericin B lipid complex	O Yes	O No	O Unknown
Amphotericin B liposomal	O Yes	O No	O Unknown
Amphotericin B - other formulations	O Yes	O No	O Unknown
Micafungin	O Yes	O No	O Unknown
Anidulafungin	O Yes	O No	O Unknown
Caspofungin	O Yes	O No	O Unknown
Flucytosine (5-FC)	O Yes	O No	O Unknown
Terbinafine	O Yes	O No	O Unknown

4 Microscopy

Which methodologies are used in fungal microscopy?

Please answer each question. In case of missing information please select "unknown".

Potaissum hydroxide	O Yes	O No	O Unknown
Silver stain	O Yes	O No	O Unknown
Giemsa stain	O Yes	O No	O Unknown
India/China Ink	O Yes	O No	O Unknown
Calcofluor white	O Yes	O No	O Unknown
Others	O Yes	O No	O Unknown

How frequently is microscopy performed when a fungal disease is suspected? (e.g., in sterile clinical samples or BAL) from never (1) to always (5)

- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Do you have access to fluorescence dyes?

- ○ Yes
- ○ No

When cryptococcosis is suspected is direct examination in body fluids available?

- ○ Yes, India Ink
- ○ Yes, other dyes
- ○ No

When pneumocystosis is suspected is silver stain performed?

- ○ Yes
- ○ No

5 Culture and Fungal Identfication

Are automated blood cultures available in case of fungemia suspicion?

- ○ Yes
- ○ No

Please mark all methods used for fungal cultures

Please answer each question. In case of missing information please select "unknown".

Selective agar (Chloramphenicol + Cycloheximide)	Yes	No	Unknown
Agar Niger	○ Yes	○ No	○ Unknown
Lactrimel Agar	○ Yes	○ No	○ Unknown
Potato Dextrose Agar	○ Yes	○ No	○ Unknown
Others	○ Yes	○ No	○ Unknown

Please select all available test for species identification

Please answer each question. In case of missing information please select "unknown".

Biochemical tests (classic mycology)	O Yes	O No	O Unknown
Mounting medium	O Yes	O No	O Unknown
Automated identification (i.e. VITEK, other commercial tests)	O Yes	O No	O Unknown
MALDI-TOF	O Yes	O No	O Unknown
DNA sequencing	O Yes	O No	O Unknown
Sabouraud	O Yes	O No	O Unknown
Sabouraud + Chloramphenicol	O Yes	O No	O Unknown
Sabouraud + Gentamicin	O Yes	O No	O Unknown
	O	O	O

Do you have access to antifungal susceptibility tests?

- O For yeasts
- O For moulds
- O For both
- O None

Which of the following technologies for suseptibility testing are available?

Please answer each question. In case of missing information please select "unknown".

Etest (previously known as Epsilometer test)	O Yes	O No	O Unknown
VITEK	O Yes	O No	O Unknown
Broth microdiluition, using CLSI standards	O Yes	O No	O Unknown
Broth microdiluition, using EUCAST standards	O Yes	O No	O Unknown

Please choose the answer that best matches the maximum identification capability (of yeasts) in your laboratory

- ○ Genus
- ○ Genus / species
- ○ Genus / species / complex
- ○ Genus / species / complex / cryptic species

Please choose the answer that best matches the maximum identification capability (of moulds) in your laboratory

- ○ Genus
- ○ Genus / species

6 Serology

Which of the following serology tests (antibody detection) are available?

Please answer each question. In case of missing information please select "unknown".

Aspergillus spp.	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Histoplasma spp.	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Paracoccidioides spp.	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Candida spp.	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown

7 Antigen Detection

Select all antigens that you can detect

Please answer each question. In case of missing information please select "unknown".

Aspergillus Galactomannan (immunoenzymatic sandwich microplate assay)	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Aspergillus Galactomannan (lateral flow assay)	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Aspergillus (lateral flow device)	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Cryptococcus (latex aggutination test)	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Cryptococcus (lateral flow assay)	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Histoplasma	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Beta-glucan	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Candida antigen	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown

8 Molecular Tests

Are any of the following molecular tests available?

Please answer each question. In case of missing information please select "unknown".

Candida PCR	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Aspergillus PCR	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Pneumocystis PCR	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
PCR for other fungi	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Other molecular tests	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown

9 Therapeutic Drug Monitoring (TDM)

Does your institution have access to therapeutic drug monitoring of antifungal agents?

Please answer each question. In case of missing information please select "unknown".

Itraconazole	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Voriconazole	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown
Posaconazole	○ Yes	○ No	○ Only at an outsourced laboratory	○ Unknown

10 Thank you for your participation

ANEXO

Parecer do Comitê de Ética da UFCSPA

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANÁLISE DE DIAGNÓSTICO LABORATORIAL EM MICOLOGIA EM PAÍSES EM DESENVOLVIMENTO: CONTINENTE AFRICANO, SUDESTE ASIÁTICO E LESTE EUROPEU

Pesquisador: ALESSANDRO COMARÚ PASQUALOTTO

Área Temática:

Versão: 2

CAAE: 40231920.0.0000.5345

Instituição Proponente: Universidade Federal de Ciências da Saúde de Porto Alegre

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.498.799

Apresentação do Projeto:

As micoses superficiais acometem cerca de um bilhão de pessoas em todo o mundo, estando em quarto lugar entre as causas gerais de infecções.

Apresentam sintomas e gravidade bastante variáveis, representado, muitas vezes, um desafio diagnóstico. Nesse sentido, a micologia médica vem

aumentando sua relevância à medida que se desenvolvem novas tecnologias, permitindo diagnósticos em estágios iniciais e atuando de modo a

diminuir a morbimortalidade dos pacientes. No entanto, tais recursos ainda não estão disponíveis de maneira uniforme entre os países.Embora já

seja conhecida a capacidade diagnóstica e terapêutica em micologia médica em muitas regiões do globo, a realidade dos países em

desenvolvimento ainda não foi estudada em sua totalidade. Neste estudo transversal pretendemos classificar os laboratórios de micologia de países

do continente africano, do sudeste asiático e do leste europeu conforme as definições da Confederação Europeia de Micologia Médica (ECMM), algo

ainda inédito em relação a muitos desses países. Ainda, correlacionaremos as infecções fúngicas endêmicas em cada região com a disponibilidade

de terapia antifúngica nesses locais, características socioeconômicas e características climáticas de

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UF: RS **Município:** PORTO ALEGRE
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cada região. O estudo será feito através de um
questionário no sistema RedCap, com pesquisadores dos países destas regiões que tenham publicado sobre infecções fúngicas nos últimos 10 anos
(Pubmed).

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar a capacidade diagnóstica e terapêutica quanto a infecções fúngicas invasivas em países em desenvolvimento no continente africano, no
sudeste asiático e no leste europeu.

Objetivo Secundário:

Avaliar as infecções fúngicas mais prevalentes nos países destes continentes;Avaliar os métodos laboratoriais usados para diagnóstico das
infecções fúngicas nestes países;Avaliar o acesso às terapias antifúngicas nestes países;Definir as áreas endêmicas de infecções fúngicas de
acordo com características socioeconômicas de cada país ou região;Definir as áreas endêmicas de infecções fúngicas de acordo com características
climáticas de cada país ou região;Classificar os laboratórios de micologia destes países conforme as definições da Confederação Europeia de
Micologia Médica (ECMM).

Avaliação dos Riscos e Benefícios:

Riscos:

A probabilidade de ocorrer algum dano aos participantes neste estudo é mínima, uma vez que serão avaliados apenas os formulários enviados pelas
Instituições contatadas, sem qualquer intervenção. Este estudo será baseado na coleta de dados dos formulários enviados pelas Instituições. Todos
os cuidados para garantia de sigilo de dados pessoais/confidenciais serão realizados.

Benefícios:

O benefício do estudo se dá em nível populacional na medida em que o conhecimento epidemiológico da disponibilidade do diagnóstico laboratorial
em micologia contribuirá para uma melhor organização dos sistemas de saúde.

Comentários e Considerações sobre a Pesquisa:

A pesquisa apresenta relevância acadêmica, tem potencial de revelar conhecimentos que

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beneficiarão a população representada pelos participantes da pesquisa além de possuir interesse estratégico em termos de saúde pública.

Considerações sobre os Termos de apresentação obrigatória:

Os termos de apresentação obrigatória foram adequadamente anexados.

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

Projeto aprovado. O pesquisador deve retirar junto à secretaria do CEP o parecer de aprovação. Data de término do projeto: julho/2022.

Considerações Finais a critério do CEP:

De acordo com o parecer do Relator.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BASICAS_DO_PROJETO_1667328.pdf	14/12/2020 22:25:02		Aceito
Outros	tcud_candida.pdf	14/12/2020 22:23:19	CANDIDA DRIEMEYER	Aceito
Projeto Detalhado / Brochura Investigador	analise_de_diagnostico_laboratorial_em_micologia_em_paises_em_desenvolvimento.docx	14/12/2020 22:23:04	CANDIDA DRIEMEYER	Aceito
Solicitação registrada pelo CEP	termo_pasqualotto.pdf	14/12/2020 22:13:04	CANDIDA DRIEMEYER	Aceito
Outros	termo_de_compromisso.pdf	19/11/2020 17:42:50	CANDIDA DRIEMEYER	Aceito
Recurso Anexado pelo Pesquisador	anexo1.docx	19/11/2020 17:38:37	CANDIDA DRIEMEYER	Aceito
Outros	anuenciaufcspa.pdf	19/11/2020 17:25:12	CANDIDA DRIEMEYER	Aceito
Folha de Rosto	frdigitalizada.pdf	19/11/2020 17:19:13	CANDIDA DRIEMEYER	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não