The current state of laboratory mycology and access to antifungal treatment in Europe: a European Confederation of Medical Mycology survey

Jon Salmanton-García, Martin Hoenigl, Jean-Pierre Gangneux, Esther Segal, Ana Alastruey-Izquierdo, Sevtap Arikan Akdagli, Katrien Lagrou, Volkan Özenci, Antonio Vena, Oliver A Cornely

Access to the appropriate tools is crucial for early diagnosis and clinical management of invasive fungal infections. This Review aims to describe the invasive fungal infection diagnostic capacity of Europe to better understand the status and the most pressing aspects that need improvement. To our knowledge, this is the first time that the mycological diagnostic capability and access to antifungal treatments of institutions has been evaluated at a pan-European level. Between Nov 1, 2021, and Jan 31, 2022, 388 institutions in Europe self-assessed their invasive fungal infection management capability. Of the 388 participating institutions from 45 countries, 383 (99%) had access to cultures, 375 (97%) to microscopy, 363 (94%) to antigen-detection assays, 329 (85%) to molecular tests (mostly PCR), and 324 (84%) to antibody tests for diagnosis and management. With the exception of microscopy, there were considerable differences in access to techniques among countries according to their gross domestic product. At least one triazole was available in 363 (94%) of the institutions, one echinocandin in 346 (89%), and liposomal amphotericin B in 301 (78%), with country gross domestic product-based differences. Differences were also observed in the access to therapeutic drug monitoring. Although Europe is well prepared to manage invasive fungal infections, some institutions do not have access to certain diagnostic tools and antifungal drugs, despite most being considered essential by WHO. These limitations need to be overcome to ensure that all patients receive the best diagnostic and therapeutic management.

Introduction

The prevalence of invasive fungal infections continues to increase in Europe and worldwide.[1] Europe is home to large populations at risk for invasive fungal infections, including haematological and oncological patients, patients requiring intensive medical care, recipients of solid organ transplants, and older populations.[2] The prevalence of invasive fungal infection is increasing in the intensive care unit (ICU) population, including people with respiratory viral infections, particularly influenza and COVID-19. In addition, the popularisation of travelling to areas with endemic mycoses[3] (eg, Latin America, Africa, and southeast Asia) and climate change[4] (ie, increased temperatures and tropicalisation) can facilitate the emergence of cases of mycoses previously restricted to equatorial areas, such as *Cryptococcus* spp, *Histoplasma* spp, or multi-resistant *Candida auris*.[5–8]

With almost 800 million inhabitants[9] and located in the northern hemisphere, Europe presents a wide diversity in terms of environmental climates,[10] access to health care,[11] and citizen income.[12] Four European countries are located within the top ten of the highest-income countries in the International Monetary Fund list of 2021, with an average gross domestic product (GDP) of greater than US$62 000.[13] However, there are also countries within Europe with lower average GDP, closer to those of countries in Africa or Asia. These discrepancies might jeopardise the access to appropriate mycological diagnoses and treatments and, therefore, result in increased death. Moreover, cases of invasive fungal infections due to strains with intrinsic or acquired resistance to available antifungals have been described.[8,14,15] This resistance increases the need to make specialised diagnostic tools more widely available for better management of such infections.

Hence, as part of a continued effort from the European Confederation of Medical Mycology (ECMM),[16–18] this Review aims to describe the invasive fungal infection diagnostic capacity of Europe to better understand the current situation and the most pressing issues that need improvement. Similar studies have been performed before, although restricted to national experiences.[19,20] To the best of our knowledge, this is the first time that the mycological diagnostic capability and access to antifungal treatments of institutions has been evaluated at a pan-European level.

Procedure

Data were collected via an online electronic case report form between November, 2021, and January, 2022. Before analysis, the answers from each participant were validated to ensure data coherence and completeness. The queries covered different categories; namely, institution profile, perceptions on invasive fungal infections in the respective institution, microscopy, culture and fungal identification, serology, antigen-detection, molecular assays, and therapeutic drug monitoring. In most categories, participants had to reply dichotomously to whether or not the respective technique was available in their places of work. Participants could specify availability onsite or through an outsourced institution for serology, antigen-detection molecular tests, and therapeutic drug monitoring (if accessible). The incidence of invasive fungal infections in general,

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Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD) (J Salmanton-García PhD, Prof O A Cornely MD), **Clinical Trials Centre Cologne** (Prof O A Cornely), **Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology** (J Salmanton-García, Prof O A Cornely), **Centre for Molecular Medicine Cologne (CMMC)** (Prof O A Cornely), **Faculty of Medicine and University Hospital Cologne** (J Salmanton-García, Prof O A Cornely), **University of Cologne, Cologne, Germany; Division of Infectious Diseases, ECMM Center of Excellence for Medical Mycology, Medical University of Graz, Graz, Austria** (Prof M Hoenigl MD); **Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, San Diego, La Jolla, CA, USA** (Prof M Hoenigl); **CHU de Rennes, INSERM, Institut de Recherche en Santé, Environnement et Travail, (UMR_S 1085), University of Rennes, Rennes, France** (Prof J-P Gangneux PhD); **Department of Clinical Microbiology and Immunology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel** (Prof E Segal PhD); **Mycology Reference Laboratory, Spanish National Centre for Microbiology, Instituto de Salud Carlos III, Madrid, Spain** (A Alastruey-Izquierdo PhD); **Hacettepe University Faculty of Medicine, Department of**

Medical Microbiology, Ankara, Türkiye (S Arikan Akdagli MD); **Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium** (Prof K Lagrou PharmD); **Department of Laboratory Medicine, Center of Excellence for Medical Mycology, and National Reference Center for Mycosis, UZ Leuven, Leuven, Belgium** (Prof K Lagrou); **Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden** (Prof V Özenci PhD); **Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden** (Prof V Özenci); **Department of Health Sciences, University of Genoa, Genoa, Italy** (A Vena PhD); **Infectious Diseases Unit, San Martino Policlinico Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy** (A Vena)

Correspondence to: Dr Jon Salmanton-García, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), University of Cologne, Cologne 50931, Germany
jon.salmanton-garcia@uk-koeln.de

For the **case report form** see www.clinicalsurveys.net/uc/IFI_management_capacity/

See **Online** for appendix

For more on **International Society of Human and Animal Mycology** see https://www.isham.org/

For more on **ECMM** see https://www.ecmm.info

and specifically of mucormycosis, could be answered with a Lickert scale, ranging from 1 (very low) to 5 (very high; appendix p 2).

Institutions in European sovereign states, de facto independent countries, and self-governing dependencies and regions were contacted by email and asked to participate.[21] Mass emailing was targeted not only to close collaborators of the authors, but also members of scientific societies, such as the International Society of Human and Animal Mycology and the ECMM. Online scientific repositories (ClinicalTrials.gov, EU Clinical Trials Register, Google Scholar, PubMed, and ScienceDirect) and journals in mycology were screened for a larger list of potential participants. Additionally, online advertisements were launched in the social networks LinkedIn and Twitter.

Participating institutions were classified according to their country GDP per capita to analyse whether there were statistically significant differences between European countries in the availability of antifungals and diagnostic tests. Three cutoffs were established, dividing the continent in countries and regions with a GDP greater than $45 000, GDP between $30 000 and $45 000, and GDP less than $30 000, according to the International Monetary Fund for 2021.[13]

Furthermore, participating institutions were assessed to place them in one of the ECMM excellence categories: blue, silver, gold, or diamond (appendix p 6).[22] The sole intention of this classification was to determine which accreditation levels these institutions could achieve in case of application.

Data are presented as frequencies and percentages. Proportions were laid out in contingency tables and compared with Fisher's Exact test (variables with at least one cell with expected value <5) and χ^2 test (variables with all cells with expected value >5), as appropriate. P values less than 0·05 were considered statistically significant. SPSS, version 27.0, was used for statistical analyses.

Results

Between Nov 1, 2021, and Jan 31, 2022, 388 institutions in Europe self-assessed their capabilitiy to manage invasive fungal infections. At least one institute from every sovereign state with more than 100 000 inhabitants participated, with the exception of Luxembourg (figure 1). Almost half of the answers (185 [48%] of 388) were from six countries accounting for 49% of the total WHO European population;[9] namely, France (n=44, 11%), Germany (n=40, 10%), Italy (n=38, 10%), Spain (n=38,

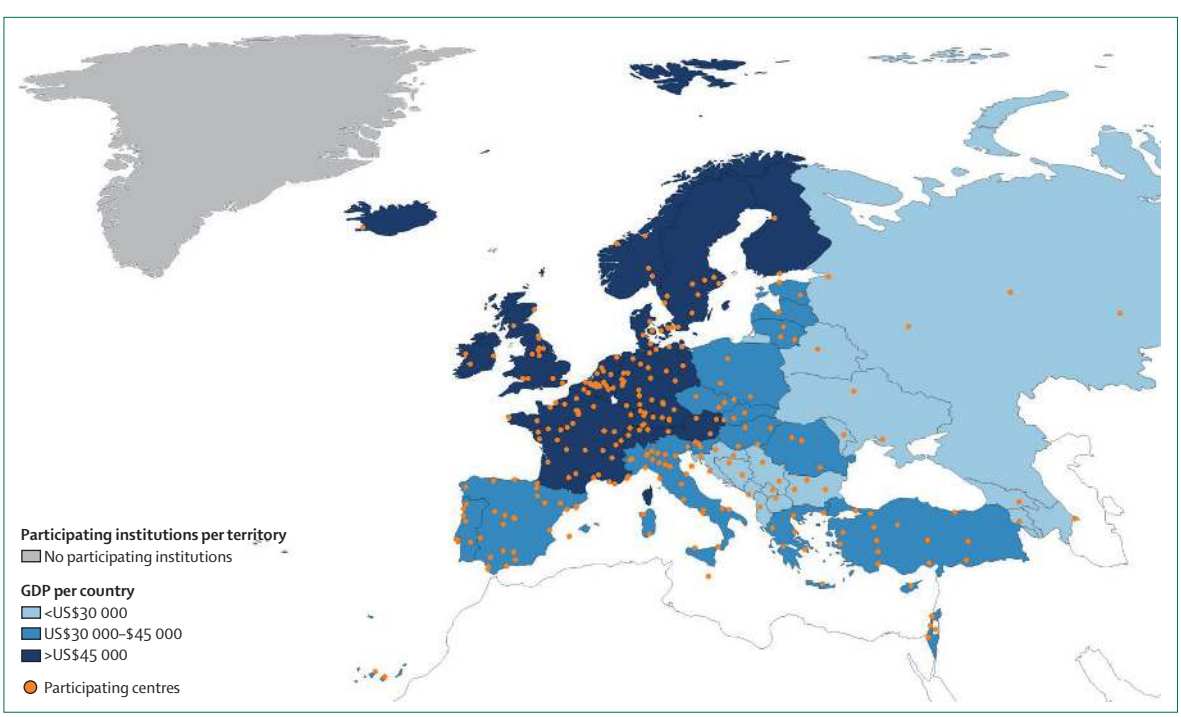

Figure 1: **Map of participating institutions per country**
Number of institutions per country with a GDP greater than US$45 000: Austria (n=4), Belgium (n=15), Denmark (n=7), Finland (n=2), France (n=44), Germany (n=40), Iceland (n=1), Ireland (n=8), Malta (n=1), Netherlands (n=7), Norway (n=4), Sweden (n=9), Switzerland (n=6), and UK (n=19). Number of institutions per country with a GDP US$30 000–$45 000: Cyprus (n=1), Czech Republic (n=6), Estonia (n=5), Greece (n=10), Hungary (n=4), Israel (n=6), Italy (n=38), Latvia (n=2), Lithuania (n=3), Poland (n=4), Portugal (n=12), Romania (n=5), Slovakia (n=5), Slovenia (n=3), Spain (n=38), and Türkiye (n=25). Number of institutions per country with a GDP less than US$30 000: Albania (n=1), Armenia (n=2), Azerbaijan (n=2), Belarus (n=2), Bosnia and Herzegovina (n=2), Bulgaria (n=4), Croatia (n=10), Georgia (n=2), Kosovo (n=1), Moldova (n=1), Montenegro (n=1), North Macedonia (n=1), Russia (n=13), Serbia (n=9), and Ukraine (n=3). In case there is more than one participating institution from the same city, a single point is pictured. GDP=gross domestic product.

10%), Türkiye (n=25, 6%), and the UK (n=19, 5%). An equal number of institutions (n=167, 43% each) participated from countries with a GDP per capita of greater than $45 000 or between $30 000 and $45 000. The remaining 54 (14%) institutions were in countries with a GDP of less than $30 000 (table 1).

The survey was answered mainly by clinical microbiologists and laboratory professionals (n=184, 47%), and by attending physicians (n=92, 24%). Most participants were affiliated with either a university hospital (n=247, 64%) or a public hospital (n=140, 36%). Analysing the target patient groups, nine of ten institutions were admitting patients with solid cancer (n=355, 91%) or haematological cancer (n=341, 88%). Approximately 85% of the institutions were also treating patients with COVID-19 (n=333, 86%), diabetes (n=331, 85%), or patients needing parenteral nutrition (n=330, 85%). All institutions except one (0·3%) had access to a microbiology laboratory, and 368 (95%) of these had a microbiology laboratory onsite. Out of these 368 institutions, 225 (61%) always performed mycological diagnostic procedures onsite, 45 (37%) performed these procedures partly onsite and partly outsourced, and 13 (3%) always outsourced the procedures (table 1).

Participants were asked about their perception of invasive fungal infections in their respective institutions. For more than half of the participants, the incidence of invasive fungal infections was low (n=129, 33%) or very low (n=72, 19%) in their institutions. Moderate incidence was reported by approximately one-third of participants (n=133, 34%), whereas 52 (13%) reported a high or a very high incidence, mainly in France (n=9, 2%), Italy, and Spain (n=6, 2% each). When asked to list the most relevant pathogens at their institutions, most participants stated *Candida* spp (n=366, 94%), followed by *Aspergillus* spp (n=345, 89%). Conversely, Mucorales were of special relevance for 88 (23%) institutions, whereas *Fusarium* spp was relevant for 84 (22%), and *Histoplasma* spp for 16 (4%; table 1).

Microscopy techniques were available in 375 (97%) institutions. When invasive fungal infection was suspected, microscopy was the method of choice for most institutions (n=290, 75%), and was used sometimes or rarely in 40 (10%) institutions. China or India ink were the most widely available staining dyes (present in 303 [78%] institutions), followed by potassium hydroxide (n=223, 57%), Giemsa stain (n=210, 54%), calcofluor white (n=180, 46%), and silver stain (n=147, 38%). The availability of calcofluor white was mainly reported from countries with a GDP of greater than $45 000 (p<0·0001; table 2).

383 (99%) institutions had access to culture media, with 343 (88%) capable of performing blood cultures when fungaemia was suspected; this capability was more common in countries with a GDP of greater than $30 000 (p<0·0001). Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) was the most frequently available method for species identification (n=287, 74%; 31% in countries with a GDP of <$30 000 [p<0·0001]). Automated identification (n=230, 59%), biochemical tests (n=208, 54%), and DNA

	All countries (total n=388)	Country division by GDP per capita		
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)
Participant				
Director	25 (6%)	1 (2%)	12 (7%)	12 (7%)
Infection control practitioner	4 (1%)	4 (7%)	0	0
Professor	67 (17%)	14 (26%)	24 (14%)	29 (17%)
Attending physician	50 (13%)	14 (26%)	21 (13%)	15 (9%)
Attending physician, infectious diseases specialist	42 (11%)	2 (4%)	24 (14%)	16 (10%)
Laboratory professional	83 (21%)	5 (9%)	36 (22%)	42 (25%)
Not reported	16 (4%)	5 (9%)	5 (3%)	6 (34%)
Clinical microbiologist	101 (26%)	9 (17%)	45 (27%)	47 (28%)
Type of institution				
Day hospital	20 (5%)	1 (2%)	10 (6%)	9 (5%)
Dialysis clinic	11 (3%)	0	7 (4%)	4 (2%)
Federal institute or research hospital	33 (9%)	13 (24%)	13 (8%)	7 (4%)
Oncology clinic	27 (7%)	6 (11%)	13 (8%)	8 (5%)
Private hospital	10 (3%)	2 (4%)	5 (3%)	3 (2%)
Private laboratory	5 (1%)	1 (2%)	2 (1%)	2 (1%)
Public hospital	140 (36%)	11 (20%)	68 (41%)	61 (37%)
University hospital	247 (64%)	24 (44%)	106 (63%)	117 (70%)
Other	27 (7%)	12 (22%)	7 (4%)	8 (5%)
Target patients				
COVID-19	333 (86%)	25 (46%)	149 (89%)	159 (95%)
Diabetes	331 (85%)	27 (50%)	147 (88%)	157 (94%)
Haematology	341 (88%)	38 (70%)	146 (87%)	157 (94%)
HIV/AIDS	295 (76%)	19 (35%)	125 (75%)	151 (90%)
Neonatal ICU	260 (67%)	18 (33%)	116 (69%)	126 (75%)
Oncology	355 (91%)	38 (70%)	154 (92%)	163 (98%)
Parenteral nutrition	330 (85%)	30 (56%)	145 (87%)	155 (93%)
Solid organ transplantation	251 (65%)	17 (31%)	112 (67%)	122 (73%)
Stem cell transplantation	263 (68%)	26 (48·%)	114 (68%)	123 (74%)
Microbiology laboratory service	387 (99%)	53 (98%)	167 (100%)	167 (100%)
Onsite	368 (95%)	47 (87%)	162 (97%)	159 (95%)
Outsourced	19 (5%)	6 (11%)	5 (3%)	8 (5%)
Mycological diagnostic procedures performed	370 (95%)	48 (89%)	160 (96%)	162 (97%)
Always in our institution	225 (58%)	28 (52%)	104 (62%)	93 (56%)
Part in our institution, part outsourced	145 (37%)	20 (37%)	56 (34%)	69 (41%)
Fully outsourced	13 (3%)	3 (6%)	6 (4%)	4 (2%)
Invasive fungal infection incidence				
Very low	72 (19%)	15 (28%)	32 (19%)	25 (15%)
Low	129 (33%)	18 (33%)	61 (37%)	50 (30%)
Moderate	133 (34%)	13 (24%)	52 (31%)	68 (41%)
High	40 (10%)	5 (9%)	18 (11%)	17 (10%)
Very high	12 (3%)	3 (6%)	3 (2%)	6 (4%)

(Table 1 continues on next page)

	All countries (total n=388)	Country division by GDP per capita		
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)
(Continued from previous page)				
Incidence of mucormycosis				
Very low	266 (69%)	34 (63%)	123 (74%)	109 (65%)
Low	68 (18%)	7 (13%)	30 (18%)	31 (19%)
Moderate	25 (6%)	7 (13%)	4 (2%)	14 (8%)
High	9 (2%)	0	2 (1%)	7 (4%)
Very high	2 (1%)	0	1 (1%)	1 (1%)
Most important pathogens				
Aspergillus spp	345 (89%)	44 (81%)	145 (87%)	156 (93%)
Candida spp	366 (94%)	50 (93%)	156 (93%)	160 (96%)
Cryptococcus spp	88 (23%)	15 (28%)	35 (21%)	38 (23%)
Fusarium spp	84 (22%)	14 (26%)	34 (20%)	36 (22%)
Histoplasma spp	16 (4%)	1 (2%)	5 (3%)	10 (6%)
Mucorales	116 (30%)	17 (31%)	41 (25%)	58 (35%)

GDP=gross domestic product. ICU=intensive care unit.

Table 1: **Baseline characteristics of participating institutions in Europe**

sequencing (n=187, 48%) were other relevant tools that were available. Automated identification (p<0·0001) and biochemical tests (p=0·010) were more common in countries with a GDP of less than $45 000, whereas DNA sequencing was more common in countries with a GDP of greater than $45 000 (p<0·0001; table 2).

Antifungal susceptibility tests were available for both moulds and yeasts in 247 (64%) institutions, whereas only for yeasts in 113 (29%). All countries had a similar proportion of institutions with access to antifungal susceptibility test technologies (p=0·13), although the gradient strip test (p=0·022) was mostly reported from countries with a GDP of $30 000–$45 000 (n=102, 61%) and more than $45 000 (n=106, 63%). VITEK (p<0·0001) was more commonly reported from countries with a GDP of less than $45 000 (GDP $30 000–$45 000 n=80, 48%; GDP <$30 000 n=23, 43%; table 2). Antifungal susceptibility tests were not available in 25 (6%) of the institutions.

Serological antibody detection was frequently performed onsite (n=324, 84%), with differences between countries (p=0·030), mainly for *Aspergillus* spp (overall n=304, 78%; p=0·037) and *Candida* spp (overall n=239, 62%; p=0·0018). Regarding the tests for *Histoplasma* spp (overall n=177, 46%; p<0·0001) and *Paracoccidioides* spp (overall n=133, 34%; p<0·001), the differences in the geographical distribution according to the country GDP were clearer (table 2).

Countries with a GDP of $30 000–$45 000 and greater than $45 000 had greater availability of antigen-detection tests (p=0·010); although, overall, 363 (94%) institutions had at least one antigen assay available. *Aspergillus* galactomannan and other enzymatic immunoassay-based antigen-detection systems (EIAs) were performed in 340 (88%) institutions, whereas lateral flow assays (LFAs) were used in 129 (33%) institutions and lateral flow devices (LFDs) were used in 94 (24%) institutions, all without significant differences among countries (EIAs p=0·061, LFAs p=0·87, and LFDs p=0·92). There were statistically significant differences in the availability of antigen tests for *Candida* (overall n=195, 50%; p=0·047), *Histoplasma* (overall n=133, 34%; p<0·0001), *Cryptococcus* (LFA; p<0·0001), and for β-D-glucan tests (overall n=236, 61%; p<0·0001), which were accessible mainly in countries with a GDP greater than $45 000 (table 2). Molecular tests were frequently available across Europe (n=329, 85%), with differences between countries for PCR targeting *Aspergillus* spp (p<0·0001), *Candida* spp (p=0·027), Mucorales (p<0·0001), and *Pneumocystis* spp (p<0·0001; table 2).

Triazoles (n=363, 94%), echinocandins (n=346, 89%), and amphotericin B systemic formulations (87%) were the most commonly available classes of antifungals. Allylamines (terbinafine; n=202, 52%) or pyrimidine analogues (flucytosine; n=193, 50%) were both available in half of the institutions. All triazoles (isavuconazole [p<0·0001], itraconazole [p=0·0044], posaconazole [p<0·0001], and voriconazole [p=0·0084]), except for fluconazole (p=0·093), were more often available in countries with a GDP of greater than $30 000 than in those with a lower GDP. The same pattern was observed for echinocandins that were more often available in countries with a GDP greater than $30 000 compared with countries with a lower GDP ([p<0·0001], anidulafungin [p<0·0001], caspofungin [p<0·0001], and micafungin [p<0·0001]) and amphotericin B lipid-based formulations (amphotericin B lipid complex [p<0·0001] and liposomal amphotericin B [p<0·0001]; table 3). The access to therapeutic drug monitoring of azoles was unevenly distributed between countries as well (overall [p<0·0001], itraconazole [p<0·0001], posaconazole [p<0·0001], and voriconazole [p<0·0001]) and is presented in figure 2.

Overall, 207 (52%) institutions would fulfil ECMM criteria for placement in the blue excellence category. These minimum standards were achieved in 18 (33%) countries with a GDP of less than $30 000, 89 (53%) with a GDP of $30 000–$45 000, and 100 (60%) with a GDP of greater than $45 000 (p=0·0030).

Discussion

Our Review evaluates the diagnostic and therapeutic capacity for the management of invasive fungal infections at a pan-European level. The study succeeded in collecting data from at least one institution from every European sovereign state with more than 100 000 inhabitants, except for Luxembourg.

When asked about the self-perception of most relevant fungal pathogens in their respective institutions, there was consensus among the participants. *Candida* spp was the most relevant fungal pathogen, followed by *Aspergillus*

	All countries (total n=388)	Country division by GDP per capita			p value
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)	
Microscopy	375 (97%)	52 (96%)	162 (97%)	161 (96%)	0·93*
Staining dye					
Calcofluor white	180 (46%)	17 (31%)	64 (38%)	99 (59%)	<0·0001†
Giemsa stain	210 (54%)	30 (56%)	95 (57%)	85 (51%)	0·54†
China or India ink	303 (78%)	39 (72%)	137 (82%)	127 (76%)	0·22†
Potassium hydroxide	223 (57%)	25 (46%)	106 (63%)	92 (55%)	0·062†
Silver stain	147 (38%)	26 (48%)	63 (38%)	58 (35%)	0·21†
Others	191 (49%)	30 (56%)	79 (47%)	82 (49%)	..
Direct microscopy frequency when invasive fungal infection is suspected					
Never	17 (4%)	4 (7%)	7 (4%)	6 (4%)	..
Rarely	40 (10%)	7 (13%)	16 (10%)	17 (10%)	..
Sometimes	40 (10%)	3 (6%)	22 (13%)	15 (9%)	..
Often	70 (18%)	6 (11%)	38 (23%)	26 (16%)	..
Always	220 (57%)	34 (63%)	83 (50%)	103 (62%)	..
Direct examination in body fluids for suspected cryptococcosis	319 (82%)	38 (70%)	146 (87%)	135 (81%)	0·013†
Yes, India ink	259 (67%)	26 (48%)	122 (73%)	111 (66%)	..
Yes, other stains	60 (15%)	12 (22%)	24 (14%)	24 (14%)	..
Silver stain for suspected pneumocystosis	120 (31%)	22 (41%)	50 (30%)	48 (29%)	0·25†
Direct microscopy for suspected mucormycosis	211 (54%)	25 (46%)	87 (52%)	99 (59%)	0·19†
Culture and fungal identification	383 (99%)	51 (94%)	167 (100%)	165 (99%)	0·011*
Blood cultures for suspected fungemia	343 (88%)	36 (67%)	153 (92%)	154 (92%)	<0·0001†
Fungal culture media					
Niger seed agar (Bridseed agar)	46 (12%)	10 (19%)	23 (14%)	13 (8%)	0·064†
Candida chromogenic media	187 (48%)	20 (37%)	74 (44%)	93 (56%)	0·024†
Lactrimel agar	31 (8%)	3 (6%)	13 (8%)	15 (9%)	0·76*
Potato dextrose agar	148 (38%)	20 (37%)	73 (44%)	55 (33%)	0·13†
Sabouraud dextrose agar	293 (76%)	39 (72%)	132 (79%)	122 (73%)	0·39†
Sabouraud dextrose agar with chloramphenicol	245 (63%)	29 (54%)	111 (66%)	105 (63%)	0·24†
Sabouraud dextrose agar with gentamicin	175 (45%)	24 (44%)	74 (44%)	77 (46%)	0·95†
Selective agar (chloramphenicol with cycloheximide)	207 (53%)	21 (39%)	94 (56%)	92 (55%)	0·071†
Others	141 (36%)	13 (24%)	51 (31%)	77 (46%)	..
Available tests for species identification	372 (96%)	47 (87%)	164 (98%)	161 (96%)	0·0023*
Automated identification (ie, VITEK)	230 (59%)	39 (72%)	119 (71%)	72 (43%)	<0·0001†
Biochemical tests (conventional mycology)	208 (54%)	34 (63%)	99 (59%)	75 (45%)	0·010†
DNA sequencing	187 (48%)	13 (24%)	70 (42%)	104 (62%)	<0·0001†
MALDI-TOF MS	287 (74%)	17 (31%)	122 (73%)	148 (89%)	<0·0001†
Mounting medium	113 (29%)	12 (22%)	46 (28%)	55 (33%)	0·27†
Antifungal susceptibility tests	363 (94%)	50 (93%)	162 (97%)	154 (92%)	0·13*
Yeasts	113 (29%)	20 (37%)	53 (32%)	40 (24%)	..
Moulds	3 (1%)	2 (4%)	0	1 (1%)	..
Yeasts and moulds	247 (64%)	27 (50%)	109 (65%)	111 (66%)	..
Available antifungal susceptibility test technologies	363 (94%)	50 (93%)	162 (97%)	154 (92%)	0·13*
Broth microdilution, using CLSI standards	106 (27%)	15 (28%)	54 (32%)	37 (22%)	0·12†
Broth microdilution, using EUCAST standards	165 (43%)	22 (41%)	79 (47%)	64 (38%)	0·25†
Gradient strip tests	231 (60%)	23 (43%)	102 (61%)	106 (63%)	0·022†
VITEK	143 (37%)	23 (43%)	80 (48%)	40 (24%)	<0·0001†

(Table 2 continues on next page)

	All countries (total n=388)	Country division by GDP per capita			p value
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)	
(Continued from previous page)					
Maximum identification capability					
Yeasts	388 (100%)	54 (100%)	167 (100%)	167 (100%)	..
Genus	17 (4%)	8 (15%)	4 (2%)	5 (3%)	..
Genus and species	177 (46%)	31 (57%)	84 (50%)	62 (37%)	..
Moulds	388 (100%)	54 (100%)	167 (100%)	167 (100%)	..
Genus	67 (17%)	19 (35%)	26 (16%)	22 (13%)	..
Genus and species	321 (83%)	35 (65%)	141 (84%)	145 (87%)	..
Serology	324 (84%)	42 (78%)	133 (80%)	149 (89%)	0·030†
Aspergillus spp	304 (78%)	41 (76%)	122 (73%)	141 (84%)	0·037†
Onsite	208 (54%)	30 (56%)	83 (50%)	95 (57%)	..
Outsourced	96 (25%)	11 (20%)	39 (23%)	46 (28%)	
Candida spp	239 (62%)	37 (69%)	86 (51%)	116 (69%)	0·0018†
Onsite	138 (36%)	28 (52%)	50 (30%)	60 (36%)	..
Outsourced	101 (26%)	9 (17%)	36 (22%)	56 (34%)	..
Histoplasma spp	177 (46%)	13 (24%)	56 (34%)	108 (65%)	<0·0001†
Onsite	39 (10%)	4 (7%)	16 (10%)	19 (11%)	..
Outsourced	138 (36%)	9 (17%)	40 (24%)	89 (53%)	..
Paracoccidioides spp	133 (34%)	11 (20%)	42 (25%)	80 (48%)	<0·0001†
Onsite	13 (3%)	3 (6%)	6 (4%)	4 (2%)	..
Outsourced	120 (31%)	8 (15%)	36 (22%)	76 (46%)	..
Antigen-detection	363 (94%)	45 (83%)	160 (96%)	158 (95%)	0·010*
Aspergillus overall	351 (90%)	42 (78%)	154 (92%)	155 (93%)	0·0035†
Aspergillus LFD‡	94 (24%)	14 (26%)	41 (25%)	39 (23%)	0·92†
Onsite	53 (14%)	5 (9%)	26 (16%)	22 (13%)	..
Outsourced	41 (11%)	9 (17%)	15 (9%)	17 (10%)	..
Aspergillus galactomannan ELISA	340 (88%)	42 (78%)	148 (89%)	150 (90%)	0·061†
Onsite	258 (66%)	30 (56%)	115 (69%)	113 (68%)	..
Outsourced	82 (21%)	12 (22%)	33 (20%)	37 (22%)	..
Aspergillus galactomannan LFA§	129 (33%)	19 (35%)	53 (32%)	57 (34%)	0·87†
Onsite	80 (21%)	9 (17%)	33 (20%)	38 (23%)	..
Outsourced	49 (13%)	10 (19%)	20 (12%)	19 (11%)	..
Candida antigen	195 (50%)	29 (54%)	72 (43%)	94 (56%)	0·047†
Onsite	107 (28%)	18 (33%)	43 (26%)	46 (28%)	..
Outsourced	88 (23%)	11 (20%)	29 (17%)	48 (29%)	..
Cryptococcus overall	308 (79%)	32 (59%)	132 (79%)	144 (86%)	0·0001†
Cryptococcus LFA	188 (48%)	13 (24%)	71 (43%)	104 (62%)	<0·0001†
Onsite	138 (36%)	4 (7%)	53 (32%)	81 (49%)	..
Outsourced	50 (13%)	9 (17%)	18 (11%)	23 (14%)	..
Cryptococcus LAT	217 (56%)	29 (54%)	101 (60%)	87 (52%)	0·28†
Onsite	158 (41%)	16 (30%)	82 (49%)	60 (36%)	..
Outsourced	59 (15%)	13 (24%)	19 (11%)	27 (16%)	..
Histoplasma	133 (34%)	14 (26%)	41 (25%)	78 (47%)	<0·0001†
Onsite	28 (7%)	5 (9%)	10 (6%)	13 (8%)	..
Outsourced	105 (27%)	9 (17%)	31 (19%)	65 (39%)	..
β-glucan	236 (61%)	20 (37%)	91 (54%)	125 (75%)	<0·0001†
Onsite	123 (32%)	7 (13%)	53 (32%)	63 (38%)	..
Outsourced	113 (29%)	13 (24%)	38 (23%)	62 (37%)	..

(Table 2 continues on next page)

	All countries (total n=388)	Country division by GDP per capita			p value
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)	
(Continued from previous page)					
Molecular tests	329 (85%)	33 (61%)	138 (83%)	158 (95%)	<0·0001†
Aspergillus PCR	256 (66%)	25 (46%)	99 (59%)	132 (79%)	<0·0001†
Onsite	150 (39%)	14 (26%)	62 (37%)	74 (44%)	..
Outsourced	106 (27%)	11 (20%)	37 (22%)	58 (35%)	..
Candida PCR	210 (54%)	24 (44%)	83 (50%)	103 (62%)	0·027†
Onsite	100 (26%)	14 (26%)	51 (31%)	35 (21%)	..
Outsourced	110 (28%)	10 (19%)	32 (19%)	68 (41%)	..
Pneumocystis PCR	288 (74%)	24 (44%)	113 (68%)	151 (90%)	<0·0001†
Onsite	217 (56%)	16 (30%)	86 (51%)	115 (69%)	..
Outsourced	71 (18%)	8 (15%)	27 (16%)	36 (22%)	..
Mucorales PCR	182 (47%)	13 (24%)	59 (35%)	110 (66%)	<0·0001†
Onsite	76 (20%)	4 (7%)	24 (14%)	48 (29%)	..
Outsourced	106 (27%)	9 (17%)	35 (21%)	62 (37%)	..
Other molecular tests	185 (48%)	15 (28%)	64 (38%)	106 (63%)	..
Onsite	101 (26%)	8 (15%)	36 (22%)	57 (34%)	..
Outsourced	84 (22%)	7 (13%)	28 (17%)	49 (29%)	..

CLSI=Clinical and Laboratory Standards Institute. ELISA=enzyme-linked immunosorbent assay. EUCAST=European Committee on Antimicrobial Susceptibility Testing. GDP=gross domestic product. LAT=latex agglutination test. LFA=lateral flow assay. LFD=lateral flow device. MALDI-TOF MS=matrix-assisted laser desorption/ionisation–time-of-flight mass spectrometry. *Compared with Fisher's Exact test. †Compared with χ^2 test. ‡*Aspergillus*-specific LFD is a tool used in clinical microbiology to detect extracellular mannoprotein antigen secretion, which is only active when there is *Aspergillus* growing, by using the JF5 monoclonal antibody.[23] §*Aspergillus*-specific LFA is a tool capable of detecting galactomannan and has a shorter turnaround time as compared with ELISA.[23]

Table 2: **Comparison of available diagnostic techniques for mycological diagnosis in Europe**

spp, Mucorales, *Cryptococcus* spp, and *Fusarium* spp. This relevance matched the incidence of the diseases caused by these pathogens in 2009,[24] and with consideration of more recent invasive fungal infections clinical management guidelines.[25–36] However, in other continents, there was major concern for *Cryptococcus* spp (Africa [55·0%] and Latin America and the Caribbean [67·0%])[16,17] and *Histoplasma* spp (Africa [12·5%], Latin America and the Caribbean [48·0%], and Europe [4·1%]),[16,17] probably because of regional endemicity[37] or a larger number of uncontrolled HIV infections.[31]

Although the ruling of Europeans under the same institutions that encourages integration to a common government (ie, European Union and the Council of Europe) has been promoted for years,[38] GDP per capita differs substantially between countries.[13] In this survey, we describe how the availability of individual assays and thus, the invasive fungal infection management capacity correlates with GDP, limiting the compliance with available guidelines, and therefore affecting patient outcome.[27,29,30,32,33]

When managing invasive fungal infection, access to appropriate diagnostics is a prerequisite for achieving favourable outcomes. Since 2018, WHO has developed and updated a list of essential in vitro diagnostics, although for invasive fungal infection this list is still insufficient.[39] In this survey, regarding microscopy,

	All countries (total n=388)	Country division by GDP per capita			p value
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)	
Amphotericin B	337 (87%)	41 (76%)	148 (89%)	148 (89%)	0·040*
Deoxycholate	159 (41%)	25 (46%)	60 (36%)	74 (44%)	0·22*
Lipid complex	124 (32%)	27 (50%)	62 (37%)	35 (21%)	0·0001*
Liposomal	301 (78%)	26 (48%)	128 (77%)	147 (88%)	<0·0001*
Other formulations	65 (17%)	18 (33%)	22 (13%)	25 (15%)	..
Echinocandins	346 (89%)	39 (72%)	148 (89%)	159 (95%)	<0·0001*
Anidulafungin	251 (65%)	21 (39%)	127 (76%)	103 (62%)	<0·0001*
Caspofungin	335 (86%)	39 (72%)	141 (84%)	155 (93%)	0·0005*
Micafungin	254 (65%)	28 (52%)	124 (74%)	102 (61%)	0·0029*
Triazoles	363 (94%)	48 (89%)	155 (93%)	160 (96%)	0·17†
Fluconazole	362 (93%)	47 (87%)	155 (93%)	160 (96%)	0·093†
Isavuconazole	235 (61%)	11 (20%)	94 (56%)	130 (78%)	<0·0001*
Itraconazole	313 (81%)	37 (69%)	130 (78%)	146 (87%)	0·0044*
Posaconazole	300 (77%)	26 (48%)	128 (77%)	146 (87%)	<0·0001*
Voriconazole	346 (89%)	42 (78%)	149 (89%)	155 (93%)	0·0084*
Flucytosine	193 (50%)	11 (20%)	62 (37%)	120 (72%)	<0·0001*
Terbinafine	202 (52%)	12 (22%)	68 (41%)	122 (73%)	<0·0001*

GDP=gross domestic product. *Compared with χ^2 test. †Compared with Fisher's Exact test.

Table 3: **Comparison of available drugs for clinical management in European institutions**

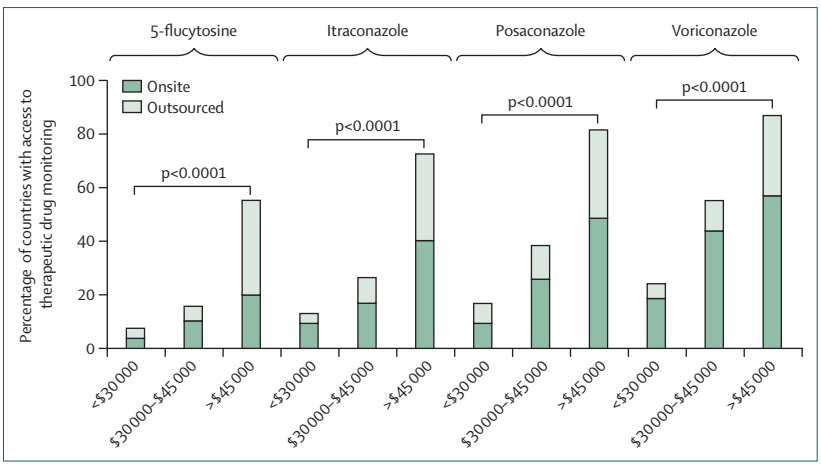

Figure 2: **Histogram of the access to therapeutic drug monitoring in analysed European institutions**
Currency is US$. χ^2 test used to obtain p value.

which was generally available at most institutions (97%), we observed restrictions in the access to calcofluor white stain, which was more accessible in countries with a GDP of greater than $45 000, probably related to its high cost.[40] This could be especially relevant for the diagnosis of aspergillosis or mucormycosis, for which this fluorescent dye is strongly recommended.[26,35]

Guidelines set by ECMM, ISHAM (International Society for Human and Animal Mycology), ASM (American Society for Microbiology), and MSG-ERC (Mycoses Study Group Education and Research Consortium) strongly recommend cultures for invasive fungal infection diagnosis.[25–30,32–36] Most of the European institutions (99%) could process isolates, which is 10 percentage points more than Asian institutions (89·2%),[41] and 20% more compared with Latin American and Caribbean institutions (78·0%).[17] Within Europe, we observed that the availability of tests for specific identification varied according to country GDP. This uneven distribution was especially relevant for access to MALDI-TOF MS. In regions with a GDP of less than $30 000, only 31% of the institutions had access to this technique, compared with 73% in countries with a GDP of between $30 000 and $45 000, and 89% when the GDP was greater than $45 000. Nevertheless, the availability of MALDI-TOF MS was reported to be much lower in African (17·5%),[16] Asian (12·3%),[41] and Latin American and Caribbean (20·0%) institutes.[17] The initial high cost of MALDI-TOF MS (between €100 000 and €200 000 for the instrument and software, which might change depending on different discounts based on variables such as purchase country, type of institution [academia *vs* industry], or year) makes MALDI-TOF MS unaffordable in many regions of the world, regardless of its post-installation cost-effectivity.[41–43]

The access to susceptibility testing is much higher in Europe (94%) as compared with surveys in Africa (62·5%),[16] Asia (58·9%),[41] or Latin America and the Caribbean (61·0%).[17] Considering the increasing number of reports of cases of invasive fungal infection due to strains resistant to various antifungals, either intrinsically or acquired, and to the continuous discovery of new pathogenic fungal species,[8,14,15] this puts Europe in a much better situation in the fight against antifungal resistance compared with other continents. However, it is still not an ideal situation because antifungal susceptibility testing for yeast is more frequently available than for moulds and there are still several European institutions that do not perform tests routinely.

The WHO list of essential systemic antifungal drugs comprises amphotericin B deoxycholate and liposomal formulation, anidulafungin, caspofungin, fluconazole, flucytosine, itraconazole, micafungin, and voriconazole.[44] There were statistically significant differences in the access to liposomal amphotericin B, itraconazole, voriconazole, and flucytosine. In all cases, there was a clear gradient between the availability of the drug and the GDP of the country of the respective institution. Limited availability also applied to other antifungals not included in the WHO list until 2021, such as all echinocandins,[45] or to the broad spectrum triazoles isavuconazole and posaconazole, and terbinafine, all of which are still not in the list. Isavuconazole and voriconazole are the recommended antifungals for invasive aspergillosis;[27,35] however, they were only available in 78% and 20% of institutions with a GDP of less than $30 000, respectively. Echinocandins, which are strongly recommended for the treatment of candidemia,[36] were available in only 72% of countries with the lowest GDP. Liposomal amphotericin B, isavuconazole, and posaconazole are the preferred options for mucormycosis;[26,29] however, in countries with a GDP of less than $30 000 these were available in 20–50% of the reporting institutions. These results show how access to important antifungals is associated with GDP.

Access to therapeutic drug monitoring also varied across Europe. Particularly for voriconazole, therapeutic drug monitoring is essential to provide an adequate antifungal dose and reduce drug-related adverse events.[27,29,30,32,33] Therapeutic drug monitoring availability was closely related to the GDP of the country in which each of the institutions was located.

This study has several limitations. First, there were no replies from the least populated countries and regions, which might be associated with several factors. It was more difficult to contact institutions from these countries and regions due to reduced research activity or a lack of international collaborations. Conversely, the lower number of inhabitants in these regions might suggest the scarcity of specialised health institutions within their borders or the automatic transfer of patients to other neighbouring countries with health-system agreements for severe diseases such as invasive fungal infections.[46,47] The second limitation could be associated with the number of institutions per country, which might be closely related to the traditional collaboration partnerships in the research environment. Third, the data for this

Search strategy and selection criteria

ClinicalTrials.gov, EU Clinical Trials Register, Google Scholar, PubMed, and ScienceDirect were searched for registrations and publications from Jan 1, 2015, to Jan 1, 2022, without language or trial or publication restrictions. A combination of terms such as "antifungal", "capacity", "case", "diagnosis", "diagnostic", "Europe", "fungal", "IFD", "IFI", "invasive fungal disease", "invasive fungal infection", "fungal disease", "fungal infection", "laboratory", "microbiology", "mycology", "mycoses", "patient", "report", and "[name of each of the European countries and territories]" was included in the search string. Average gross domestic product lists from the International Monetary Fund were used to distribute and classify the results of the participating institutions in three countries, enabling a comparison on the basis of economic situation for each country.

survey were collected during a pandemic, in which laboratory professionals, microbiologists, and infectious disease specialists might have had time restrictions to complete the survey. Fourth, the data from institutions with greater experience and capacity for invasive fungal infection diagnosis and treatment might not be extrapolated to non-major institutions. Last, further analysis of the specific problems of each of the countries is needed to better understand and make policies focused on specific needs.

Overall, we conclude that the general status of invasive fungal infection diagnostic capacity of Europe is at an acceptable level in many countries, but there are substantial differences based on GDP that need to be overcome so that every patient in Europe receives the best diagnostic and therapeutic management and, thus, the best possible outcome of invasive fungal infections.

Contributors

MH, J-PG, ES, and OAC contributed to study design. JS-G, MH, J-PG, ES, and OAC conceived the study idea. JS-G collected and validated the data, performed the statistical plan and analysis, and drafted the first version of the manuscript. All authors contributed to data interpretation, manuscript writing, and review of the manuscript.

Declaration of interests

JS-G received payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Gilead and Pfizer, outside of the submitted work. MH received grants or contracts from Gilead, Pfizer, Astellas, Euroimmune, MSD, Pulmocide, Scynexis, and F2G, outside of the submitted work. J-PG received grants or contracts from Pfizer, and consulting fees from Gilead and Pfizer, outside of the submitted work. AA-I received payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Gilead and Pfizer; received support for attending meetings and travel from Gilead; participated on a data safety monitoring board or advisory board for JPI-AMR; and had a leadership or fiduciary role in board, society, committee or advocacy groups that were either paid or unpaid, from WHO, European Society of Clinical Microbiology and Infectious Diseases, Fungal Infection Study Group, and Global Action For Fungal Infections, outside of the submitted work. KL received grants or contracts from Thermo Fisher Scientific and TECOmedical; consulting fees from Gilead, MSD, and MRM Health; and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Pfizer, Gilead, and FUJIFILM Wako, outside of the submitted work. SAA reports grants or contracts from Cidara; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Gilead; and support for attending meetings and travel from Astellas, outside of the submitted work. VÖ received grants or contracts from International Health Management Associates and Sentry, outside of the submitted work. OAC received grants or contracts from Amplyx, Basilea, Bundesministerium für Bildung und Forschung, Cidara, Deutsches Zentrum für Infektionsforschung, EU Directorate-General for Research and Innovation (grant: 101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from AbbVie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, Matinas, MedPace, Menarini, Molecular Partners, Mycoses Study Group Education and Research Consortium (MSG-ERC), Noxxon, Octapharma, Pardes, PSI, Scynexis, and Seres; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Abbott, Al-Jazeera Pharmaceuticals, Astellas, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck-MSD, Mylan, and Pfizer; payment for expert testimony from Cidara; patents planned, issued, or pending from the German Patent and Trademark Office; participation on a data safety monitoring board or advisory board for Actelion, Allecra, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, PSI, Pulmocide, and Shionogi; and other financial or non-financial interests from Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie, Deutsche Gesellschaft für Information und Wissen, European Confederation of Medical Mycology, International Society for Human and Animal Mycology, MSG-ERC, and Wiley, outside of the submitted work. ES and AV declare no competing interests.

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