



Global Guidelines and Initiatives from the European Confederation of Medical Mycology to improve Patient Care and Research Worldwide New Leadership is about Working Together

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Global guidelines and initiatives from the European Confederation of Medical Mycology to improve patient care and research worldwide: New leadership is about working together

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Summary

Invasive mycoses present a global challenge with expansion into new hosts, emergence of new pathogens, and development of multidrug resistance. In parallel, new antifungal agents and advanced laboratory diagnostic systems are being developed. In response to these evolving challenges, the European Confederation of Medical Mycology (ECMM) is committed to providing international expertise, guidance, and leadership with the key objectives of improving diagnosis, treatment, outcome, and survival of persons with invasive fungal diseases. Representing 25 affiliated National Medical Mycology Societies, the ECMM has developed several major ways to achieving these critical objectives: (a) tasking specific medical mycology working groups; (b) founding the ECMM Academy and Fellow program (FECMM); (c) expanding the goals of ECMM beyond the European region; (d) implementing the ECMM Excellence Centre Initiative in Europe; and (e) the ECMM Global Guidelines and Neglected Orphan Disease Guidance Initiatives focusing on mucormycosis, rare mould diseases, rare yeast diseases, and endemic mycoses. We believe that these important initiatives and other strategies of the ECMM will advance the field of medical mycology and improve the outcome of patients with invasive mycoses worldwide.

KEYWORDS

aspergillosis, *Aspergillus*, *Candida*, epidemiology, guideline, low resource, mucormycoses, recommendation

1 | BACKGROUND

Since 2013, the Leading International Fungal Education (LIFE) portal has facilitated an estimation of the global burden of serious fungal diseases. By the end of 2017, burden of fungal disease estimates was published for 57 countries and presented in public for another 18 (<https://www.gaffi.org>). The 2017 global estimates indicated that more than 10 000 000 cases of fungal asthma, ~3 000 000 cases of chronic pulmonary aspergillosis, ~1 000 000 cases of fungal keratitis, ~700 000 cases of invasive candidiasis, ~500 000 cases of *Pneumocystis jirovecii* pneumonia, ~250 000 cases of invasive aspergillosis, ~223 100 cases of cryptococcal meningitis complicating HIV/AIDS, and ~100 000 cases of disseminated histoplasmosis occur annually.¹ A more conservative overview of the burden of fungal infections worldwide has been derived from FungiScope®, a worldwide operating registry (Figure 1). Overall, the majority of fungal infections, in particular the majority of AIDS-related mycoses,² endemic mycoses, subcutaneous mycoses, and fungal keratitis, are found in low- and middle-income countries (LMIC), where the expertise and resources to manage these problems are limited.³ Further, in contrast to some national guidelines focusing on specific regions only,⁴ the vast majority of international guidelines on fungal infections for the management of fungal infections do not focus on providing specific recommendations for LMIC.⁵

In recent years, new groups of patients at risk of developing invasive fungal diseases (IFD) have been identified.⁶ Invasive

aspergillosis is frequently seen in critically ill patients with influenza.^{7,8} Biological therapies, such as tumour necrosis factor- α inhibitors, and new small molecule kinase inhibitors, such as ibrutinib and idelalisib increase the risk of IFD.⁹⁻¹¹ To further complicate the management of fungal infections, emergence of antifungal resistance in *Candida* and *Aspergillus* spp., driven by widespread agricultural use of antifungal compounds, has become increasingly apparent.¹² First described in Japan in 2009, *Candida auris* has become a global multidrug-resistant pathogen with the ability to persist in the inanimate environment, thus perpetuating the risk of further spread of the organisms.¹³⁻¹⁵ New medically important fungal pathogens continue to be reported, as exemplified by *Lomentospora prolificans*, or *Emergomyces* spp. that cause disseminating IFD in severely immunosuppressed persons.¹⁶⁻²⁰ Moreover, new antifungal agents have recently become available or are being developed that warrant up-to-date guidance on optimal treatment of IFDs.²¹⁻²³ Finally, the increasing availability of new nucleic acid amplification assays, blood culture detection systems, lateral flow devices, as well as matrix-assisted laser desorption time of flight (MALDI-TOF) mass spectrometry for detection of medically important fungi and laboratory diagnosis of invasive mycoses warrants guidance in their use in clinical practice.²⁴⁻²⁷

To respond adequately to these tasks, international societies of medical mycology have joined forces with a goal of improving diagnosis, treatment, prevention, and survival of persons with invasive fungal infections worldwide. Here, we highlight some of the most important outreach initiatives, spearheaded by the European Confederation of

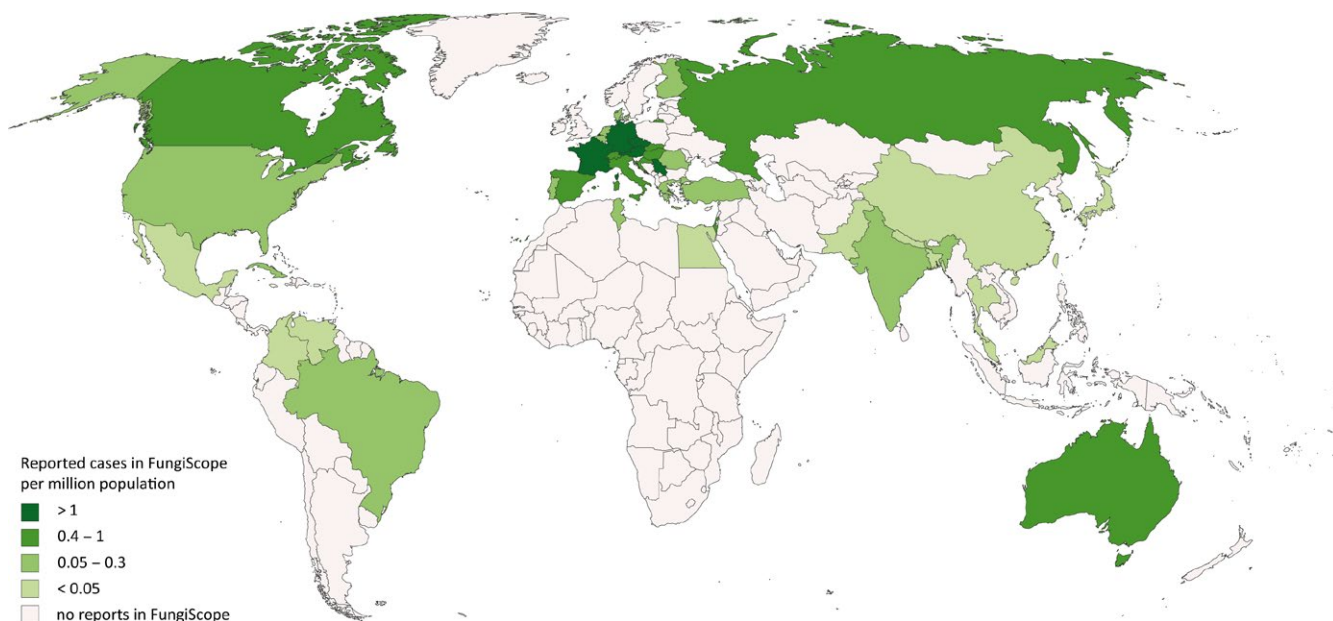


FIGURE 1 Cases Documented in FungiScope® from 2003 to June 2018 (per million inhabitants). In FungiScope® (online registry for rare invasive fungal diseases), clinical data are collected to study the clinical course. Reported cases are shown relative to the population per country. Population numbers were selected from <http://www.worldometer.info/>

Medical Mycology (ECMM <http://www.ecmm.info/>),²⁸ in close cooperation with the International Society for Human and Animal Mycology (ISHAM <https://isham.org/>): the ECMM Academy, the global ECMM laboratory and clinical Excellence Centre initiative, and the ECMM worldwide guideline initiative ("One World, One Guideline").

2 | ECMM: HISTORY, MISSION, AND WORKING GROUPS

The ECMM serves as a confederating organisation for National Medical Mycology Societies throughout Europe. The ECMM was founded in 1993 at the Institut Pasteur in Paris, France, and the first Executive Committee (Board) included Bertrand Dupont, France, as President, David Warnock, UK as General Secretary and Lars Edebo, Sweden as Treasurer. Ever since, the ultimate ambition of the ECMM is the "support to science and research, the international coordination of scientific and clinical activities, the organisation of mycological conventions and of training programmes." Its basic aims are to advocate scientific exchange, to facilitate communication among mycologists, to create study groups for the standardisation of diagnosis, to study the epidemiology of mycoses, and to coordinate multicentre drug trials.²⁸

Currently, the ECMM includes 25 affiliated National Medical Mycology Societies across Europe with a Council consisting of the representatives of the National Societies, who elect the Board. The Board is active for 3 years and can be re-elected for an additional term of 3 years. The Council meets at least once a year, generally during mycological conferences. The ECMM held 8 yearly scientific conferences in different European countries since its foundation. As of 2003, ECMM has held the Trends in Medical

Mycology (TIMM) Congress in different European countries every 2 years, organised jointly with the European Organization for Research and Treatment of Cancer (EORTC). The 9th TIMM Congress will be held in Nice, France, in October 2019. In between TIMM Congresses, ECMM holds educational symposia. The latest Symposium on "Ecology and Mycology: from the Environment to the Patient's Bed" was held in Tel Aviv, Israel, in February 2016.

The ECMM brings together working groups that were initiated independently and seek to profit from the vivid and continuously growing network of scientists and physicians within the ECMM. During the last council meeting in Amsterdam (ISHAM 2018), eleven working groups were presented by council members. These are: "Fungal respiratory infections in cystic fibrosis," "ECMM *Candida* III," "Aspergillus Resistance Surveillance," "Exploration of fungal contamination in the sand and water around the Mediterranean Sea and other water bodies of ECMM countries," "Next Generation Sequencing for mycobiota analysis," "Epidemiological survey on zygomycosis in Europe," "Pseudallescheria/Scedosporium infections," "FungiScope®-Global Rare Invasive Fungal Infection Registry,"²⁹⁻³¹ "Immunologic Markers for Diagnosis and Treatment Monitoring in Invasive Mold Infection," "Chronic disseminated candidiasis in haematological malignancies" and "Chronic Pulmonary Aspergillosis – CPA-net."

3 | ECMM ACADEMY

Oliver Cornely, the former president of the ECMM and Martin Hoenigl, the current president of the ECMM launched the ECMM Academy, by electing the first fellows of the ECMM (FECMM) in September 2016. The mission of the ECMM Academy is to recognise scientists for outstanding contributions to medical mycology and provide mycological

expertise in the service of science and the public (<https://www.ecmm.info/news/academy-european-confederation-medical-mycology-big-success-europe-abroad/>).²⁸ The working body of the Academy is the ECMM Academy Committee that consists of a chair (currently Katrien Lagrou, Belgium) and four regular members who are not at the same time members of the ECMM board. They are responsible for reviewing applications, and organising FECMM inauguration and activities. FECMM are elected through a highly selective peer-reviewed process and are based on their records of scientific achievement and original contributions, which have advanced clinical mycology. The designation is available for a wide range of professionals, from laboratory-based scientists to clinicians (<https://www.ecmm.info/FECMM>). With the goal of the ECMM to strengthen and further expand its network beyond the European region, important modifications were implemented to make this network more attractive, more accessible to experts outside Europe. First, starting in 2019, the international scientific committee for the biennial TIMM conference was expanded to include three members from outside Europe. For the 9th TIMM in Nice (October 11–14, 2019), FECMM from Australia, Canada, and the USA were added. This is an essential step in further establishing TIMM as a key global clinical mycology conference. Second, all FECMM—as well as additional experts—are centrally involved in the new “Global Clinical and Microbiological Guidance on Diagnosis and Management of Invasive Fungal Infections” initiative which has been launched early 2018 as further pointed out. Third, to increase its outreach to non-ECMM countries, particularly LMICs, the academy membership fees have recently been substantially decreased for non-ECMM countries with Gross National Income (GNI) per capita converted to international dollars using purchasing power parity (PPP) rates between 10 000 and 20 000 (source data derived from <http://data.worldbank.org/indicator/NY.GNP.PCAP.PP.CD>), to meet the fees that were previously applicable

only to countries with a GNI PPP < 10 000. These changes led to an increased number of qualified applications from countries with GNI PPP rates between 10 000 and 20 000; the ECMM Academy was recently expanded with new FECMM members from Brazil, Iran, and Lebanon and as of mid-July 2018 counts 64 FECMM from 29 countries in total (Figure 2). Furthermore, fees for FECMM from all other high-income non-ECMM member countries have been adjusted accordingly.

FECMM members are encouraged to use their FECMM title in the corresponding author contact (or the author byline) to increase the visibility of their status and this initiative. In return, publications of FECMM will be promoted via the ECMM Twitter account (ie, @EurConfMedMycol) and the homepage.³²

4 | ECMM EXCELLENCE CENTRE (EC) INITIATIVE

An ECMM EC is an institution designated by the ECMM Board to form part of an international collaborative network. In line with the ECMM policy and strategy, an ECMM EC participates in the strengthening of country resources, in terms of information, services, research, and training, in support of national health development.²⁸

An ECMM EC designation provides institutions with enhanced visibility and recognition by national authorities, calling public attention to the health issues on which they work. It opens up improved opportunities to exchange information and develop technical cooperation with other institutions, in particular at international level, and to mobilise additional resources from funding partners.

Any centre, which fulfils the ECMM-related requirements, is encouraged to apply for a designation. Centres will only be designated as ECMM EC after careful onsite auditing. At least one centre per country is

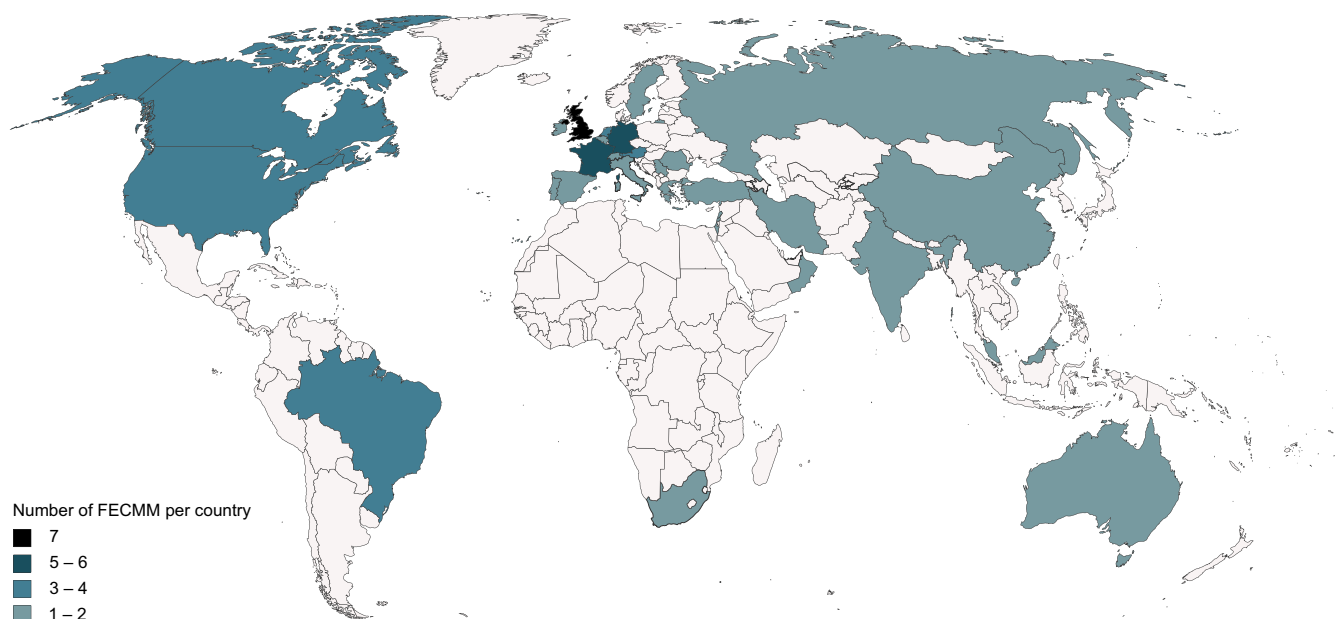


FIGURE 2 Fellows of the ECMM—Distribution by Country (mid-July 2018)

expected to fulfil the quality criteria and serve as a local ECMM EC for patients with IFD. An institution is designated initially for a term of 4 years the designation may be renewed for the same or a shorter period. ECMM provides a quality audit plan, as an important tool for the inspectors.

The EC designation recognises both the collaboration with ECMM and the designated institution and provides a formal framework for future joint activities. It is a time-limited, renewable agreement of collaboration between ECMM and ECMM EC.

Excellence centres are encouraged to display the label "European Medical Mycology Center" in letterheads, websites, presentations, etc. If centres decide to use the designation, it is mandatory to combine it with the ECMM logo. However, the initiative clearly reaches beyond Europe, and this was recently emphasised by the appointment of two FECMM from non-European countries (Australia and Brazil) as members of the ECMM EC committee, which has been established as a separate committee within ECMM.

The designation differentiates ECMM EC by Silver, Gold and Diamond Status and ECMM Fungal Centers (without the term "Excellence") in Blue Status (Table 1). ECMM Fungal Centers with Blue Status have to fulfil minimum clinical and/or laboratory requirements and the status goes in hand with educational efforts offered by ECMM in collaboration with other worldwide acting mycology societies. The audit plan gives a detailed overview of the requirements needed. The audit takes place by collecting data on how laboratory diagnosis is performed and on how clinical management of IFD is effectively executed. As a basis of the laboratory audit, the best practice recommendations for the diagnosis of serious fungal diseases will be used.³³

Presently, five ECMM EC with diamond status and one with silver status (Zagreb, Croatia) are already implemented, and one EC (Houston, USA) is under evaluation (Figure 3).

4.1 | ECMM EC Study Coordinator

The ECMM has appointed an ECMM study coordinator who will coordinate within the ECs. The study coordinator Alexandre Alanio, France, is in charge of following the corresponding studies. His role is to help ECs to implement the studies locally (writing protocols, discussing the implementation of studies locally) and to act as a facilitator. Regular appointments at the different annual meetings (TIMM, ISHAM, ECCMID) will be organised to help the study coordinator follow the progress of the project (implementation, number of cases enrolled). The study coordinator will discuss on a regular basis (teleconference, Skype®) with one representative of each centre designated by the ECs for the corresponding study. Next to that, the study coordinator will help to collect the data, analyse the results, and write the manuscript.

5 | ECMM GLOBAL GUIDELINES INITIATIVE/ORPHAN DISEASE GUIDANCE

In the context of a growing population of immunocompromised patients at risk of opportunistic infections, the prevalence of IFD, including infections due to *Candida*, *Aspergillus*, and emerging and

TABLE 1 Definitions and requirements for the various types of ECMM ECs

Blue Status
ECMM Centers fulfilling minimum requirements in diagnosis and management of invasive fungal infections. This status is an ECMM Fungal enter, possibly a candidate for a future ECMM Excellence Center.
Silver Status^a
Excellence in either clinical microbiology or infectious diseases.
Gold Status
Excellence in both mycological fields of clinical microbiology and infectious diseases.
Diamond Status
Gold Status and participation in ECMM endorsed clinical or epidemiological studies.

^aFor Silver Status (laboratory or clinical), two-thirds of the practice recommendations according to the audit plan should be implemented.

often drug-resistant moulds, such as Mucorales, is on the rise. Despite these developments, most IFD meet the definition of orphan diseases²⁸ and resources remain more limited than in other areas of medicine. Whilst new diagnostic and therapeutic options are now available to tackle IFD, cutting-edge guidance for their correct utilisation in a range of clinical settings is urgently needed.

On that background, ECMM has set out an unprecedented orphan disease guidance initiative involving all disciplines involved in diagnosis and treatment of IFD. Utilising the global network of the ECMM Academy and the ECMM Excellence Centers, clinicians, microbiologists, and other medical professionals from around the world contribute expertise. The rationale for the "Global Clinical and Microbiological Guidance on Diagnosis and Management of Invasive Fungal Infections" is to unify the medical mycology community, by creating guidelines that are applicable worldwide, "One World – One Guideline." The ECMM emphasises an inclusive approach and whilst currently partnering primarily with ESCMID will have the additional goal of integrating with other societies from other continents.

Guidelines on individual fungal diseases are being created in parallel, intensively leveraging online resources including shared folders, video and teleconferences and YouTube® tutorials, due to the fact that face-to-face meetings in the context of worldwide contribution are not feasible, and to ensure short timelines to guideline completion. Each guideline contains a relatively large pool of 30–80 contributors, and 2–4 coordinators. Contributors are trained via a training video (<https://www.ecmm.info/guidelines/>) on the guideline process.

A central point is that all United Nations regions (<https://unstats.un.org/unsd/methodology/m49/>) are represented in each of the guidelines (minimum 1 contributor if disease is present in the region, additional contributors per region depending on number of publications originating from that region). As work on these guidelines takes place in parallel and to ensure timely processing, guideline contributors mostly participate in one guideline at a time. Similarly, the initiative also aims towards an equal distribution of guideline conveners between UN

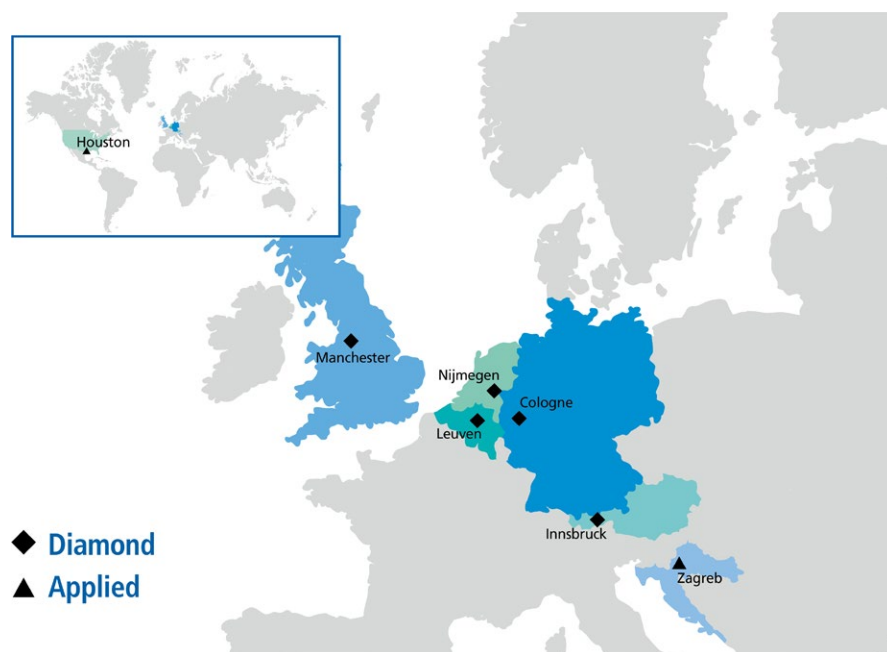


FIGURE 3 ECMM Excellence Centers—Distribution by Country (July 2018)

regions. In early 2018, the work on the first four guidelines (mucormycosis, rare mould diseases, rare yeast diseases, and endemic mycoses) has started in parallel and out of a total of 14 guideline coordinators (ie, the responsible coordinators and leading authors of the guideline) two are from Europe, three each from Asia and Latin America, four from the USA, one each from Oceania and Africa. All four guidelines are aimed to be published in 2019. Figure 4 maps the worldwide distribution of guideline coordinators and guideline contributors.

A second key element is the inclusion of all specialties essential in the management of IFD. The guidelines therefore aim to include each an equal number of contributors who are specialised in infectious diseases and clinical microbiology, but also contributors specialised in intensive care medicine, haematology, anatomical pathology, paediatrics, pharmacology, radiology, and surgery.

5.1 | Systematic approach

The guideline follows the structure and definitions of the ESCMID Guideline on candidiasis and the ESCMID/ECMM guidelines on rare IFD, which are in accordance with the GRADE and AGREE systems.^{34,35} The fact that most IFD are orphan diseases necessitated some adaptation, however. Formal meta-analyses will not be conducted for the guidelines on mucormycosis, rare mould diseases, rare yeast diseases, and endemic mycoses, because prospective comparative clinical trials are very rare exceptions in these >40 different disease entities.

The general principle behind the PICO (population, intervention, comparison, outcome) approach is rigorously applied, but in this set of ECMM guidelines, PICO comes in the form of streamlined tables (Table 2). Treatment strategies and diagnostic assays are both regarded as interventions, because they have the potential to alter a patient's course. The fixed sequence of the seven columns is predefined and follows the logic of the ECMM guideline approach of maximising transparency. First, a population is defined. Then, the

intention or objective is stated, followed by the intervention. For that logical sequence, the strength of recommendation and the quality of evidence are provided, followed by the references on which the recommendation is based. A comment may be added as appropriate.

5.2 | Definition of contributorship and authorship

Members of the group are experts involved in diagnosing or treating the IFD topic for which guidance is provided. Members have published on the topic in English language and such publications are listed in PubMed or Web of Science.

Authors are individuals who meet the requirements for authorship of the International Committee of Medical Journal Editors (<http://www.icmje.org/>). These criteria comprise four key elements: (a) Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; (b) Drafting the work or revising it critically for important intellectual content; (c) Final approval of the version to be published; (d) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

For the purpose of the specific process of the guidelines, we added criteria; (e) Responsiveness throughout the guideline process; (f) Training on the ECMM guideline process; and (g) Declaration of conflicts of interest (for authors and contributors). Contributors are individuals who do not meet all of the first six of the above requirements for authorship but have contributed significantly to the work.

5.3 | Grades of Recommendations, Assessment, Development, and Evaluation' (GRADE)

Every recommendation within the ECMM guidelines aims to indicate clearly the intention (eg, improved survival) and to describe the diagnostic or therapeutic option (intervention). Therefore, the guidelines

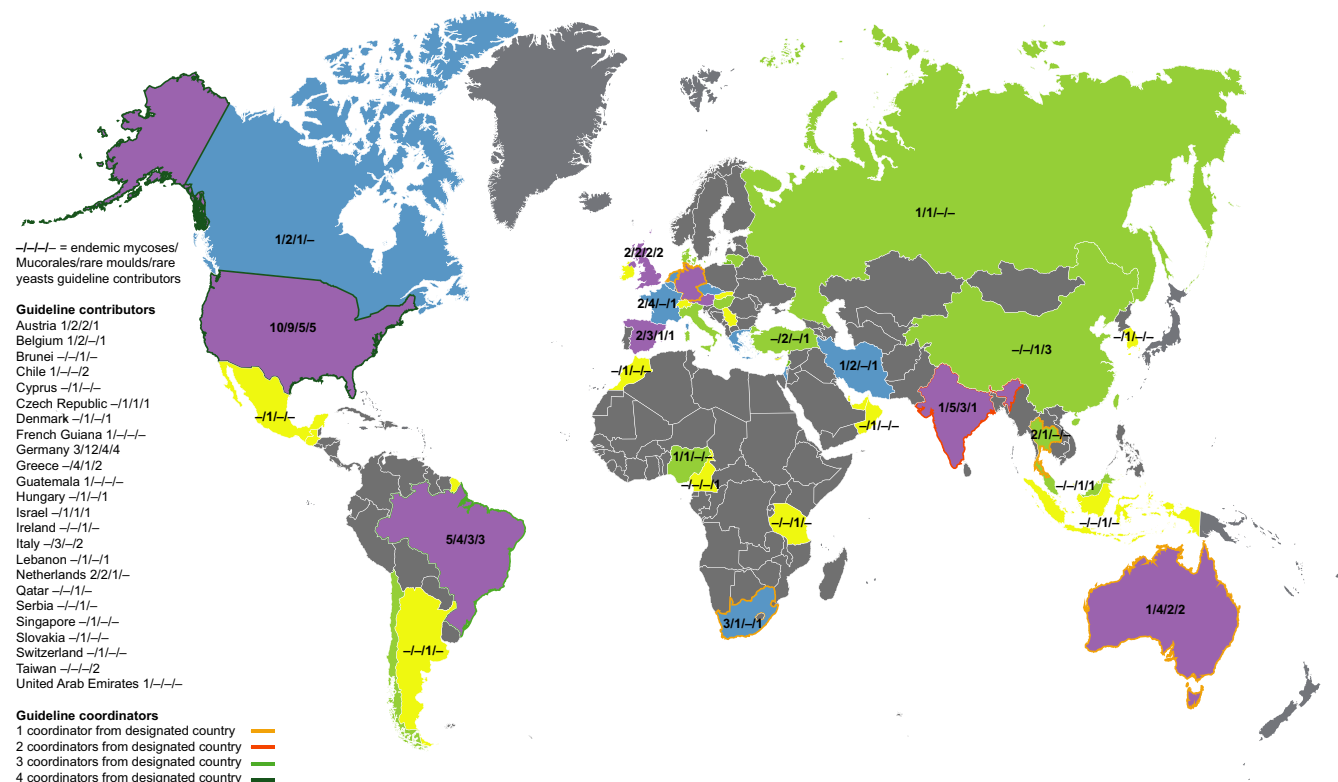


FIGURE 4 ECMM Guideline Initiative—Coordinators and Contributors by Country

TABLE 2 Examples for PICO tables used in ECMM guidelines: Applicability to diagnostic and therapeutic interventions

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Any	Staging	CT cranial/sinus, thoracic, abdominal	B	III	Pagano Haematol 2004 Chamilos Clin Infect Dis 2005	Mucormycosis might be more acute and rapid than aspergillosis
Neutropenic, in presence of an outbreak	To prevent	Posaconazole 3 × 200 mg/d	C	III	Cornely NEJM 2007 Ullmann NEJM 2007 Pagano CID 2012	

follow the principles of GRADE (Table 3). For every recommendation, the following three questions are considered:

1. What do clinicians want (outcomes)? What is their intention?
2. Which option is better for patients? What intervention is needed to reach the desired outcome?
3. Review the chosen option whether it is truly better or not by adequate review of the literature.

5.4 | Appraisal of Guidelines, Research and Evaluation (AGREE)

A system for guideline development and indeed for systematically assessing the quality of guidelines is useful to enable comparison of different guidelines and to facilitate clinically and policy-driven decisions. The Appraisal of Guidelines, Research and Evaluation (AGREE) is an

internationally validated, rigorously developed tool used to evaluate independent domains of guideline development including: scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence.³⁶ Overall, consensus is that the AGREE items are useful in supporting the practical application of guidelines.³⁷ Table 4 outlines how the ECMM guidelines address each of those domains. The guideline methodology and procedures are also explained in a 30-minute video tutorial <https://www.youtube.com/watch?v=1silWTHWdgd>.

5.5 | Diagnostic/treatment flow charts for different settings with a particular focus on LMIC

The ECMM guideline initiative aims to create guidelines that are equally applicable to high-income countries and LMICs and to provide clear diagnostic and treatment pathways tailored to the resources available at each country. The simplest way of communicating the

TABLE 3 GRADE, SoR and QoE in ECMM guidelines

Strength of recommendation (SoR)	Definition
Grade A	Societies strongly support a recommendation for use
Grade B	Societies moderately support a recommendation for use
Grade C	Societies marginally support a recommendation for use
Grade D	Societies support a recommendation against use
Quality of evidence (QoE)	Definition
Level I	Evidence from at least 1 properly ^a designed randomised, controlled trial (orientated on the primary endpoint of the trial)
Level II	Evidence from at least 1 well-designed clinical trial (incl. secondary endpoints), without randomisation; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments Note: Every Level II evidence must have at least one added index.
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added index	Source of level II evidence
r	Meta-analysis or systematic review of RCT
t	Transferred evidence, ie, results from different patients' cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	For published abstract presented at an international symposium or meeting

^aPoor quality of planning, inconsistency of results, indirectness of evidence, etc. would lower the SoR.

essence of a set of recommendations to end-users is to develop a clinically relevant diagnostic and/or treatment algorithm. For each of the guideline documents, where applicable and possible, contributors have been asked to generate algorithms that can be used in both resource-rich and resource-limited settings.

6 | DISCUSSION OF IMPLICATIONS

Sharing knowledge on fungal infections is a common ambition of international societies of medical mycology (ECMM and ISHAM) and of the Global Action Fund for Fungal Infections (GAFFI). Annual congresses and specific meetings are friendly occasions to exchange ideas, and

scientific journals (>25 worldwide have mycology as thematic focus) facilitate the spread of scientific information and concepts in medical mycology. Development of new online tools to facilitate worldwide exchange and knowledge sharing, including educational videos, are now indispensable in our increasingly global world. By using these online resources, ambitious goals like worldwide guidelines suddenly become feasible, as communication and decision-making are transparent and quick, and is not restricted to planned, comparatively expensive in-person meetings, where a major challenge is to bring together experts from all regions around the globe to discuss matters.

The guidelines and other outreach initiatives presented above are cornerstones to improve skills and to connect scientists and physicians, giving them access to international data on the burden of fungal diseases and many other educational documents, to international networks of experts and excellence centres in mycology, and to global and consensual guidelines between various international bodies.

Follow-up indicators of these initiatives will combine individual education improvement of young doctors and scientists, the needs and answers to the population with innovative practices of diagnosis and treatment, increased reputation of medical mycology via international societies and scientific journals, but also institutional delivery mechanisms such as access to essential diagnostic tests and antifungal drugs.

In conclusion, this manuscript outlines the current vision and plan of operation of the ECMM regarding the discipline of Medical Mycology in respect to diagnosis and therapy of fungal infections. The planned guidelines will serve as updated and improved tools for diagnosis and therapy of the major mycoses, as well as for the rarer yeast and mould infections. The collected epidemiological data on incidence of the various mycoses in different geographical areas may foster awareness of local as well as of international governing organisations to the significance and relevance of fungal diseases. Together with other leading organisations in the field, the ECMM will continue to spearhead innovative initiatives that serve the long-term goal to reduce IFD-related morbidity and mortality.

CONFLICTS OF INTEREST

M.H. has received untied research funding from Gilead and speaker's honoraria from MSD, Basilea and Gilead. J.P.G. has received research funding from Pfizer and speakers honoraria from MSD, Pfizer and Gilead. E.S. has no conflict. A.A. has received untied travel grant from MSD, Gilead and Astellas and honoraria from Pathoquest and Gilead. A.C. has received research funding from Pfizer and Merck through Asian Fungal Working Group and national mycological societies. S.C. has received untied educational grants from MSD Australia and Gilead Sciences Inc., Antifungal advisory boards of MSD Australia, Gilead Sciences Inc., Astellas. N.P.G. has received a travel grant from MSD South Africa and a speaker honorarium from Astellas. F.H. has no conflict. N.K. has been paid for talks on behalf of Astellas, Gilead, Merck and Pfizer. J.F.M. received grants from Astellas, Basilea, and Merck. He has been a consultant to Astellas, Basilea, Scynexis and Merck and has received speaker's fees from Merck, United Medical, TEVA and Gilead. A.C.P. has received research grants and/or given paid talks to Pfizer,

TABLE 4 Outline of how the ECMM guideline process addresses the domains of AGREE

1. Scope and purpose	All diseases and their corresponding patient groups are predefined and appropriately covered by the guideline.
2. Stakeholder involvement	Experts from all medical disciplines involved in diagnosis and treatment of IFDs are involved. The end-users are clearly defined by these guidelines. However, due to the nature of the guideline, meaning that the incidence rates are low and diversity of patient groups is wide, patients' views may not always be available. That said, patient views are being sought and integrated where available (eg, endemic mycoses).
3. Rigour of development	a. Definition of the rare and emerging fungi. b. Several manuscript parts will be prepared by individual writing (sub-)groups established with separate chairs and corresponding mandates. The entire guideline project is then reviewed by the whole guideline group. c. Predefined questions will be defined that need to be answered. d. Provision of alternative answers will be encouraged, all suggestions weighted by the body of evidence. e. Literature research will be performed in PubMed with predefined search algorithms including major scientific meetings. f. Slide kits will be prepared and circulated within the whole group for commentary. g. Presentation of the guidelines at scientific conferences intended for 2019/2020. h. Manuscript preparation including all valid commentary will be drafted and again circulated within the entire group for approval. i. Public consultation. j. An guideline update will be routinely conducted every 4-5 y. An earlier update will follow if new and striking changes are found in the body of evidence.
4. Clarity of presentation	a. All recommendations are specific and unambiguous. The major messages are provided in tables designed to be easily read and understood. b. Clear statements of the intention of each single recommendation and clarity regarding its intervention.
5. Applicability	a. One of the early criteria required by AGREE was the request to consider the potential cost implication by the application of the given recommendation. This is not really feasible in a global guideline because reimbursements differ within and between countries. Some guidelines only look at acquisition cost without considering outcomes analyses. Therefore this criterion cannot be considered for each recommendation. b. The guidelines will provide clear guidance to each clinician and microbiologist and recommend adaptation and individual modifications according to each hospital or country's epidemiology and abilities, without considering itself to be the whole truth of diagnosis or treatment. There will be emphasises on local differences in diagnosis and treatment paths.
6. Editorial independence	a. These guidelines are free of any pharmaceutical company influence. No member of pharmaceutical companies is involved or present during guideline discussions. b. All applicable costs are covered by ECMM, and potentially other scientific societies. Since mostly email, OneDrive, Skype, etc. are being used, there are no travel costs, and in general, costs are being kept low. c. The guideline will undergo public consultation and peer-review before its publication.

Gilead, MSD, and IMMY. D.S. has no conflicts. T.J.W. has served as a consultant to Astellas, ContraFect, Draai, iCo, Novartis, Pfizer, Methygene, SigmaTau, and Trius. K.L. has received research grants from Gilead, MSD and Pfizer; consultancy fees from Gilead, Pfizer, Abbott, MSD and SMB Laboratories Brussels; travel support from Pfizer, Gilead and MSD; speaker fees from Gilead, Roche, Abbott. C. L. has no conflicts. O.A.C. has received research grants from Actelion, Amplyx, Arsanis, Astellas, AstraZeneca, Basilea, Bayer, Cidara, F2G, Gilead, GSK, Leeds University, Matinas, Medicines Company, MedPace, Melinta, Merck/MSD, Miltenyi, Pfizer, Rempex, Roche, Sanofi Pasteur, Scynexis, Seres, is a consultant to Allegra Therapeutics, Actelion, Amplyx, Astellas, Basilea, Cidara, Da Volterra, F2G, IQVIA, Janssen, Matinas, Menarini, Merck/MSD, Paratek, PSI, Scynexis, Seres, Summit, Tetrphase, Vical, and received lecture honoraria from Astellas, Basilea, Gilead, Merck/MSD and Pfizer.

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