

Antifungal stewardship in the UK: where are we now?

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Background: Antifungal stewardship (AFS) is the judicious use of today's antifungal agents with the aim of improving patient outcomes and preserving their future effectiveness. Antifungal resistance (AFR) is increasing globally, with more patients at risk of Invasive Fungal Disease (IFD), highlighting the urgent need to standardize AFS practices in the UK. The aim of this position paper is to understand the current AFS landscape in the UK.

Methods: A virtual panel discussion was held from September to October 2023 on an online platform followed by a virtual meeting with nine healthcare professionals from across the UK selected for their expertise on IFD management and AFS. The discussion was structured across four topics: current AFS landscape, key elements of an AFS programme, diagnostics and diagnostic stewardship, and unmet needs in education and training. A thematic analysis was carried out. The results represent the collated and summarized views from these activities.

Results and discussion: Participants reported barriers to implementing AFS and its integration within antimicrobial stewardship (AMS) programmes in the UK. The primary challenge identified was a lack of resources, including funding and staff time. Sub-optimal fungal diagnostics and limited mycology expertise was reported as a barrier to AFS, clinical IFD and AFR surveillance. Approaches to combatting these challenges may include investing in formal mycology networks to serve as centres of clinical expertise and diagnostic hubs.

Conclusion: National standards for AFS services and associated outcome metrics need to be established to set a benchmark for centres to improve AFS.

Introduction

Invasive fungal diseases (IFD) are increasing globally, with recent estimates suggesting an annual incidence of 6.5 million invasive fungal infections and 3.8 million deaths.¹ This increase is largely due to a rising number of at-risk patients, such as those receiving immunosuppressive treatment for cancer and auto-immune conditions. Additionally, new at-risk populations are emerging such as patients with chronic conditions requiring immunomodulation and intensive care unit (ICU) patients with severe viral pulmonary infections.² The most frequently seen IFDs in the UK are

invasive candidiasis and invasive aspergillosis, both of which have high crude mortality rates of 40%–55% and 50%–80%, respectively.³ Antifungal resistance (AFR) is also increasingly being reported globally, with previously sensitive species developing resistance such as azole-resistant *Aspergillus fumigatus* and fluconazole resistant *Candida parapsilosis*.⁴ Additionally, fungal species are emerging that are intrinsically resistant to antifungals e.g. *Candida auris*, which is commonly fluconazole resistant and can further evolve echinocandin and polyene resistance and *Trichophyton indotineae*, which is causing terbinafine resistant dermatophytosis globally.^{4,5} Although data on AFR are relatively

limited both in the UK and globally, data on the incidence and resistance rates of candidaemia are most widely available. In England, the 2023–24 English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report demonstrated that the incidence of candidaemia in the UK has been increasing since 2019, as has resistance to fluconazole in *C. albicans*, *N. glabratus* (formerly *C. glabrata*) and *C. parapsilosis*, the top three species causing candidaemia in England. The incidence of *Candida auris* increased significantly in 2023 due to two ongoing hospital outbreaks but invasive cases currently remain relatively rare, although reporting is not yet mandatory.⁶ Other countries with mandatory reporting show worsening spread of *C. auris*—and in South Africa, *C. auris* is now the third most common pathogen causing candidaemia.⁷

Antimicrobial stewardship (AMS) is a systematic approach to educate and support healthcare professionals to follow evidence-based guidelines for the optimal prescribing and administering antimicrobials with the aim of improving patient outcomes while preserving the future effectiveness of antimicrobial agents.⁸ Proposed core elements of AMS focus on engaging hospital leadership, setting out accountability and responsibilities, ensuring available expertise on infection management, education and training, and highlighting actions for responsible use, surveillance and feedback.⁹ Antifungal stewardship (AFS) is the judicious use of today's antifungal agents of which only four classes are available to treat IFDs: the azoles, polyenes, echinocandins and pyrimidine analogues. In practice, while AFS complements AMS it also has unique challenges that differentiate it from AMS, which is historically antibiotic centred. These challenges relate to the diagnosis of IFD in at-risk hosts, the appropriate deployment and management of antifungal drugs and the prevention of AFR.¹⁰

In 2017, a survey of 47 NHS Trusts in England showed that only 11% had a dedicated AFS programme.¹¹ In the same year, a survey of mycology laboratory testing capabilities for systemic fungal pathogens in the UK showed that the provision of fungal diagnostics was below accepted best practice.¹² In 2019, NHSE recognized the need for national AFS improvements with the inclusion of AFS within the Commissioning for Quality and Innovation (CQUIN) scheme. CQUINs support improvements in the quality of services and the creation of new, improved patterns of care by making a proportion of healthcare providers; income conditional on demonstrating improvements in quality and innovation. This CQUIN aimed to improve AFS across the NHS in England, have greater standardization in the use of antifungals, perform a diagnostic gap analysis and optimize use of generic products wherever clinically appropriate to ensure best value.¹³ Unfortunately, this programme was prematurely paused in 2020 due to the pressures of the COVID-19 pandemic on the NHS. The pandemic significantly impacted all AMS activities in the UK. One qualitative survey sent out to AMS leads across the NHS showed 65% of respondents perceived that COVID-19 had a negative impact on routine AMS activities, such as AMS ward rounds, multidisciplinary team (MDT)/AMS meetings, quality improvement, audits and education/training.¹⁴ Although no AFS specific data were reported in this study, a multicentre retrospective study from France showed an increase in antifungal consumption during the pandemic, where emerging secondary IFD and immense clinical pressure, in particularly ICU beds and

staffing, probably affected any AFS measures.¹⁵ COVID-associated Pulmonary Aspergillosis has been reported in ~10% of critically ill patients with COVID-19 and in 2021 COVID-associated mucormycosis surged in India, with >4000 cases reported over 4 months. An increased incidence of candidiasis in COVID-19 patients on ICU has also been reported.¹⁶ During the pandemic and since, reported cases of *Candida auris* have risen globally.^{17,18}

In 2022, the WHO published its first Fungal Priority Pathogen List. This list aims to raise public awareness of fungal disease and AFR and to drive global action. A major driver in determining pathogen priority was the potential for AFR.² The increase in AFR globally, compounded with increasing populations at risk of IFD, highlights the urgent need to standardize AFS practices in the UK. The aim of this panel discussion was to understand the current challenges to implementing AFS in the UK and identify opportunities to address them. This position paper illustrates the opinion of participants on the current landscape of AFS in the UK.

Materials and methods

A virtual panel discussion was held over an 8-week period between 4 September 2023 and 23 October 2023. See Figure 1.

Nine participants were selected in total, one participant did not take part in the text-based discussion but attended the virtual meeting. Three publications were given to each advisor as pre-reads.^{11,19,20} Participants were selected by Pfizer Ltd, based on their clinical expertise in the diagnosis and management of IFD, AMS and leadership of AFS initiatives at their respective hospitals, as well as to represent multiple specialities and disciplines relevant to AFS (infectious diseases, clinical and laboratory microbiology, pharmacy, haemato-oncology and intensive care) from across the UK.

Results and discussion

Participants opinion of antifungal stewardship in the UK in 2023

Participants unanimously agreed that since 2017, when only 43% of Trusts included AFS as part of their AMS programmes,¹¹ there has been limited positive development within the AFS landscape in the UK. A key reason cited was the impact of the COVID-19 pandemic on the NHS.⁹ Participants reported that prior to the pandemic there was increased interest in AFS in England because of the AFS CQUIN, with some Trusts investing in dedicated staff and in-house or locally accessible fungal diagnostics. The COVID-19 pandemic caused widespread workforce pressures and, in many centres, resulted in redeployment of AFS and AMS Teams, halting activities such as AFS ward rounds and MDTs.¹⁴ Several participants reported these activities have been largely re-established in their centres but agreed this is variable and often dependant on having a local driver to re-implement AFS. Despite the de-prioritization of AFS activities in 2020, it was suggested that the emergence of IFDs in COVID-19 patients improved awareness of IFDs in the ICU setting and resulted in clinicians becoming more confident in requesting fungal diagnostic tests.

When asked to consider whether AFS programmes should be independent of AMS programmes, participants believed that it is

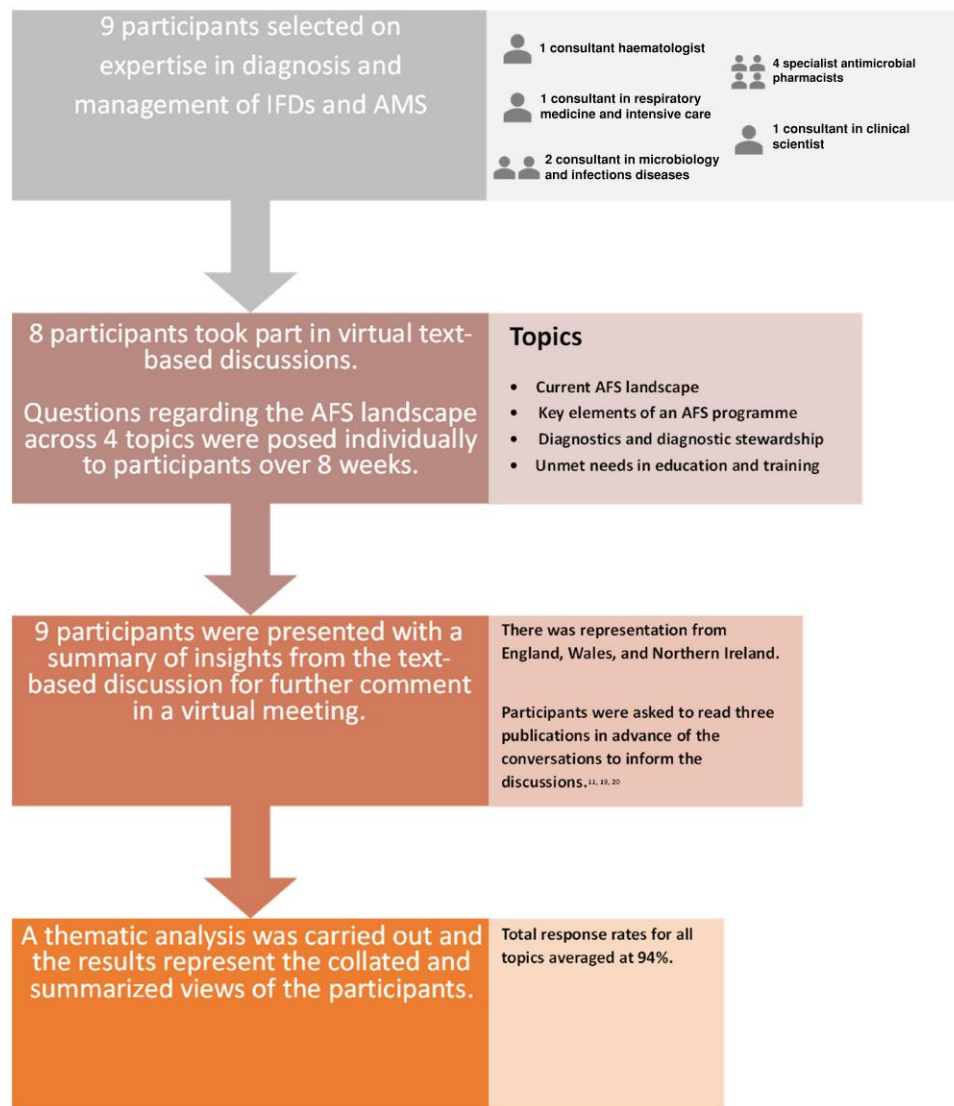


Figure 1. Participants and methods.

important to link AFS with AMS, but that AFS must retain its identity within AMS, rather than be engulfed by it. Participants reported that there are many barriers to both implementing AFS and its integration within AMS programmes. The primary challenge identified by participants was a lack of resources, both financial and staff time, echoing the responses to a 2017 survey of NHS Trusts.¹¹ Showing the value of AFS is challenging and without data to demonstrate its positive impact it is difficult to make a case for greater resource allocation. Participants highlighted that most antifungals in use are now generic and as a result there are fewer financial incentives to implement AFS. It was reported that focus is increasingly on patient throughput and services that facilitate earlier hospital discharge or admission avoidance such as OPAT and virtual wards. Recent CQUINs support this, with one 2021–22 CQUIN centred around IV to oral switching of antimicrobials.²¹ This highlights the imperative for Trusts to be able to demonstrate that AFS strategies optimize patient care and healthcare resource use.

Participants observed that there is a lack of staff expertise in IFD and antifungal management in the UK. Low numbers of specialist mycology laboratory and clinical staff and lack of expertise, even among specialists in infection, makes implementing AFS difficult. Participants also highlighted the importance of having more than one mycology or AFS champion within a Trust to ensure the sustainability of AFS programmes. Participants reported that there is a paucity of on-site or nearby laboratories with sufficient mycological diagnostic and antifungal therapeutic drug monitoring (TDM) capacity at UK Trusts. A lack of joined-up services across the UK, frequently results in samples needing to be sent off-site to larger laboratories or reference centres leading to long turnaround times. It was suggested that the centralization of many laboratories, and a public–private provider divide may be partly responsible for this. This variability in access to fungal diagnostics and mycology expertise across the UK may lead to inequitable access for patients to a diagnosis and appropriate treatment in a reasonable timeframe.

Key elements of an AFS programme

Core activities and members of an AFS team

Participants proposed that core activities for AFS teams in the UK should be at a minimum providing clinical support and expertise on IFD management (including starting/stopping and choice of antifungal, advice on drug-drug interactions (DDIs), TDM and appropriate diagnostics) facilitated via virtual or in-person ward rounds on at least a weekly basis. The creation, implementation and regular updating of guidelines, providing training and education on AFS and IFD management, and carrying out clinical audit were also suggested as core activities of any AFS team.

There was agreement among participants that the minimum core members of the AFS team are a microbiology/infectious disease consultant and a specialist AMS pharmacist. The core members of the AFS MDT would ideally also include a healthcare scientist with fungal diagnostic expertise, a radiologist, a data analyst and a member of the specialist clinical team looking after the patient, who are essential for providing clinical context and without whose buy-in meaningful decisions would not be possible. See Figure 2.

The role of the infection prevention and control team in AFS was considered to be primarily related to outbreak management (e.g. *C. auris*), as well as a potential role in collecting surveillance and resistance data.

One participant highlighted that a potential limitation of AFS programmes is that they tend to focus on those already being treated with an antifungal, missing high risk patients where IFI is not being considered due to lack of expertise. This highlights the need for clinical teams to be educated on the risk factors for fungal disease in their patient cohort.

Guidelines

Participants unanimously agreed that in their experience there were barriers to implementing local antifungal guidelines. The primary barriers reported by participants were again a lack of resources, particularly time available for guideline creation and implementation, as well as lack of staff with sufficient expertise. From a clinical perspective, antifungals are often started empirically and therefore it is challenging to make recommendations for when to cease antifungal treatment in the absence of timely diagnostics. Multiple participants highlighted the need for frequent users of the guideline (e.g. haematology and ICU) to be involved in guideline creation to ensure applicability and future adherence. It was reported that implementing guidelines for empiric therapy can be more challenging than for proven infection (a rarity for most IFD), particularly in settings where on-site diagnostics are unavailable, meaning patients can remain on empiric therapy for prolonged periods until results are available. As with AMS, behavioural change was reported as a challenge to implementing AFS guidelines.

Participants were also asked to give their opinion on whether there is a need for national antifungal guidelines in the UK. All agreed that international guidelines are useful, and some believed these are sufficient to negate the need for national guidelines. However, others proposed that a national action plan or executive summary may be beneficial to raise awareness of IFDs among UK healthcare professionals, collating key points

from across international guidelines into a single source for fungal pathogens most relevant to the UK. It was also suggested that guidelines with minimum recommendations for fungal diagnostic and TDM capabilities and minimum staffing for AFS roles for specific healthcare settings with at-risk groups would be of value. Participants highlighted that the British Society of Medical Mycology is currently updating its best practice guidelines for diagnostics and TDM which will help to fill this gap.

Surveillance and outcome metrics

The true burden of fungal disease needs to be demonstrated to incentivize investment in AFS. Participants were asked about barriers to carrying out surveillance on fungal infections, resistance and antifungal consumption. Carrying out clinical surveillance of fungal infections is challenging primarily due to sub-optimal diagnostics with limited proven definitive diagnoses, meaning often only a possible or probable diagnosis can be achieved. The use of biomarkers is increasingly critical to the diagnosis of IFD, and local availability of these tests is highly variable.

The lack of widespread laboratories with capacity to identify and speciate fungi, perform antifungal susceptibility testing (AST) and in the case of moulds lack of a cultured pathogen, and subsequent challenges with result reporting- were all barriers reported to IFD surveillance. To address this, it was suggested that certain priority fungal pathogens (e.g. *C. auris*) should be made notifiable to ensure sufficient surveillance of certain fungal diseases. A national registry or surveillance scheme for fungal diseases was also proposed. The challenges in carrying out IFD surveillance negatively affect the perception of the true IFD burden, which can hinder the need for change.

Resistance surveillance challenges reported overlapped with those affecting disease surveillance. The variability in access to AST in the UK was highlighted in a 2017 survey of mycology laboratory diagnostic capacity that showed only 55% of survey respondents performed susceptibility testing of yeasts on-site or at their centralized hub.¹² A lack of validated breakpoints and the need for a cultured fungal isolate to perform susceptibility testing on were highlighted as barriers. Participants suggested that mandatory reporting of resistant pathogens would support quicker responses to outbreaks and should also include private sector hospitals.

Antifungal consumption data was considered the most achievable metric to report on for AFS programmes, however, its usefulness is limited by the fact that it is not linked to clinical data to indicate whether the antifungals are being used for empiric, targeted or prophylactic treatment. There is also a lack of a clear meaningful denominator to compare across centres and assess trends over time.

AMS metrics are usually reported to senior management in NHS Trusts, however, the most important outcomes to measure for AFS are unclear. Participants unanimously agreed that patient outcomes should be measured in any AFS programmes with metrics such as length of hospital stay, adverse drug reactions and in-hospital mortality suggested. Other outcomes suggested were guideline adherence, trends in fungal epidemiology including resistance data (e.g. for invasive candidiasis), antifungal consumption per occupied bed days, number of DDIs identified and indication for antifungal use. Cost-effectiveness outcomes were

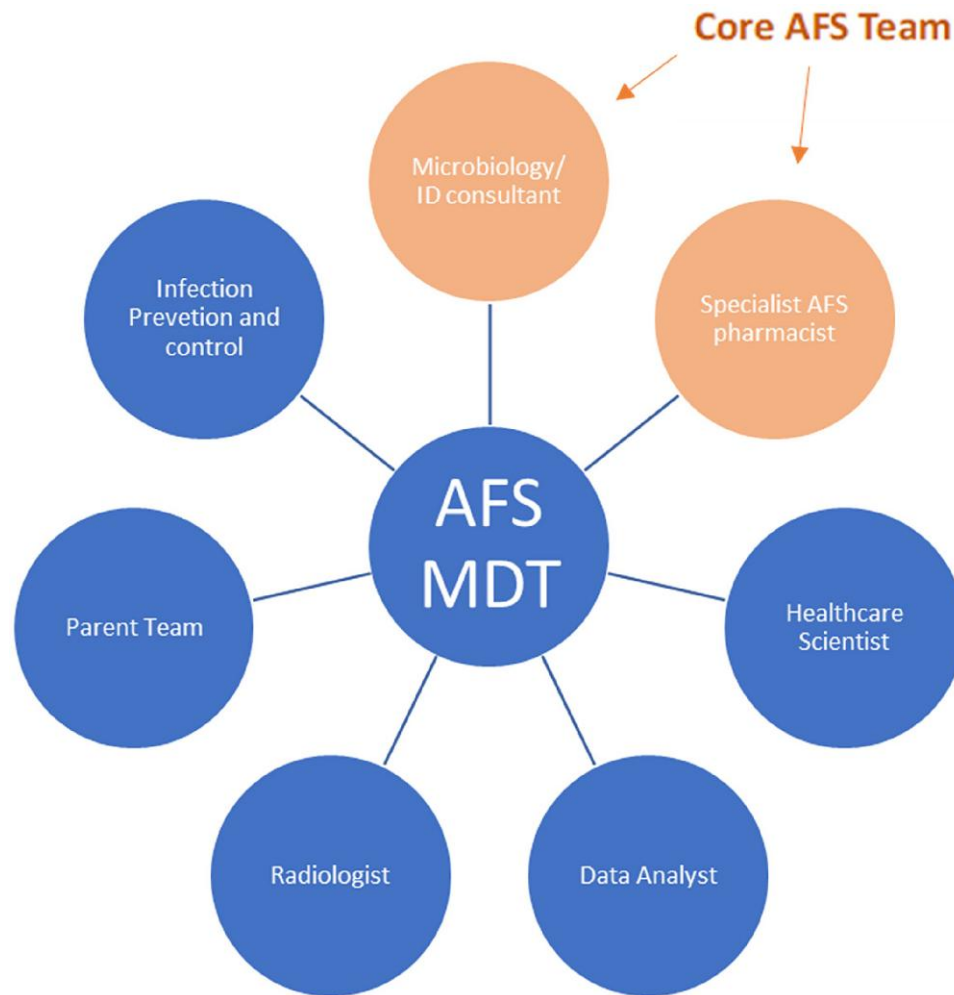


Figure 2. Proposed members of the core AFS team and AFS MDT. ID, infectious disease.

also highlighted as being very important at Trust level. Participants suggested outcome data at a national level could be reported to the UK Health Security Agency (UKHSA) and at a Trust level AFS data should be integrated into the annual AMS report. Ultimately, for Trusts to benchmark their AFS activities, national standards need to be set out.

Diagnosics—access and stewardship

The diagnosis of IFD is challenging with often only a probable or possible diagnosis achieved based on a combination of host, mycological and clinical criteria.²² Participants highlighted several barriers to the implementation of fungal diagnostics and stewardship. Key barriers raised included access to tests and (timely) results, cost, laboratory capacity, expertise and lack of high-quality evidence to support diagnostic approaches. Participants acknowledged that some samples can be difficult to obtain in specific patient groups (e.g. BAL in a thrombocytopenic haematology patients). It was also highlighted that most frontline conventional mycology is performed by routine microbiology laboratories following Standards for Microbiology

Investigations that may not be optimal for the recovery of fungi, although considerable efforts are underway to rectify these issues. Resource and financial implications were reported to be compounded by relatively low sample numbers and requests outside specialist centres. Access to timely results was unanimously reported to be hindered by a lack of on-site testing, centralization, and consolidation of laboratory services and private providers, as well as a paucity of reference facilities. Several participants cited turnaround times >7 days, which can greatly reduce the utility of the test result. Regional mycology networks serving as clinical diagnostic hubs may address some of these challenges.

Participants acknowledged that requirements around diagnostic capability vary according to population. Participants were asked what the minimum fungal diagnostic capabilities should be in the UK, based on a hospital setting, and their suggestions are outlined in Table 1.

Challenges were also highlighted in relation to AST and TDM. As discussed, AST is rarely set up in local laboratories and often considered too specialist, with staff generally lacking the appropriate mycology expertise and training with generic healthcare

Table 1. Suggested mycology laboratory diagnostic capabilities and turnaround times by hospital settings for fungal disease, excluding dermatophyte infections

District general hospital (DGH)		Teaching hospital (TH)		Specialist centres (e.g. sizeable haematology-oncology population)	
Diagnostics	Turnaround times	Diagnostics	Turnaround times	Diagnostics	Turnaround times
<ul style="list-style-type: none"> • Microscopy • Culture/ID of very common fungi^a • Histology optimized for fungal recovery/ID • Access to ID and susceptibility testing and TDM via a referred service 	<ul style="list-style-type: none"> • Culture and Histology: in line with guidelines (with allowance for extended incubation) • Microscopy: 24 h in line with guidelines (with allowance for extended incubation) 	<ul style="list-style-type: none"> • As per DGH but also to include; • CrAg LFA • <i>Aspergillus</i> LFA • Simplified BDG testing (e.g. STAT) • Ability to ID common fungi^c • Access to further ID and susceptibility testing and TDM^b 	<ul style="list-style-type: none"> • CrAg LFA: 24 h • <i>Aspergillus</i> LFA:24 h • Simplified BDG testing (e.g. STAT):72 h 	<ul style="list-style-type: none"> • As per DGH and TH but also to include; • GM-EIA • BDG testing • <i>Aspergillus</i> PCR • Pneumocystis PCR • <i>Candida</i> PCR^b with support of reference laboratory • Local access to susceptibility for yeasts and moulds with support of reference laboratory • Access to TDM^b • Ability to locally ID some uncommon yeasts and common moulds with support of reference laboratory^{b,d} 	<ul style="list-style-type: none"> • GM-EIA: 48 h • BDG: 48 h • <i>Aspergillus</i> PCR: 48–72 h • Pneumocystis PCR: 48–72 h • <i>Candida</i> PCR: 48–72 h

ID, identification; CrAg, cryptococcal antigen; LFA, lateral flow assay; BDG, (1,3)- β -D-glucan; GM-EIA, Galactomannan enzyme immunoassay; PCR, polymerase chain reaction.

^aVery common fungi such as *C. albicans*, *C. glabrata*, *C. parapsilosis* and *Aspergillus* spp.

^bSend away service is minimal requirement.

^cCommon fungi may include very common fungi as before plus additional *Candida* species (e.g. *C. krusei*, *C. auris*), differentiate *Aspergillus* spp. (*A. fumigatus*, *A. flavus*, *A. niger*, etc.) and identify but not differentiate to a species level *Mucorales* spp., *Fusarium* spp., *Cryptococcus* spp. and *Scedosporium/Lomentospora*.

^dTo include common ID of fungi as above and additionally differentiate *Mucorales* spp., *Fusarium* spp., *Cryptococcus* spp. and *Scedosporium/Lomentospora* to a species level and presumptive identification of endemic fungi.

scientists only having a theoretical basic knowledge of the field. Participants suggested that susceptibility testing may only be performed when there is a lack of treatment response, leading to potential data bias. A significant barrier to TDM is the infrastructure required to set up a local service and subsequent time delays when samples must be sent away. This is compounded by limited awareness of when TDM is required. The establishment of regional fungal diagnostic hubs may address these delays. Additionally, embedding TDM guidance within an electronic prescribing system with prompts to support appropriate and timely requests was suggested to mitigate this.

Participants discussed the implementation of a diagnostic-driven or pre-emptive approach to antifungal management in the UK. A diagnostic-driven strategy has already been implemented at some centres both in the UK and globally whereby fungal biomarkers or computed tomography imaging are used to direct treatment, rather than commencing antifungals empirically. Participants acknowledged that there is sufficient evidence to support this approach in certain patient cohorts such as haemato-oncology patients.¹⁸ However, most participants cited the diagnostic challenges listed before as making a diagnostic-driven approach

unfeasible in most UK centres. For widespread implementation of a diagnostic-driven strategy across the UK there is a need for increased diagnostic capacity nationally and increased education on the importance of AFS and diagnostic stewardship.

Education

Education for clinicians is critical to improving AFS. Participants agreed that education on IFDs at an undergraduate level in medicine and pharmacy would introduce an awareness of mycology and AFS at an early stage. To increase the level of expertise within AMS teams, peer-to-peer training for clinicians and healthcare scientists with a specialist interest in infection such as AMS pharmacists and infectious disease trainees would be beneficial. This may include experts presenting and leading teaching rounds in established centres. The priority education topics for AFS suggested were fungal pathogens, monitoring parameters including TDM and diagnostic approaches and criteria.

Participants agreed that virtual educational materials are the most useful to educate HCPs on IFD and AFS. Both apps and on-line resources were highlighted as valuable formats to deliver

these materials. There are currently several online resources available to support healthcare professionals with implementing AFS programmes^{23–25} and there is some evidence to suggest that these free at point-of-access online educational solutions complement traditional educational methods.²⁶ Participants reported that the use of case studies for education is extremely valuable. Additionally online education in the form of interactive online materials and medical apps available via smartphone/multiple platforms to facilitate learning on-the-go are useful. One of the barriers highlighted was the individual clinician's interest in AFS. To increase engagement with AFS content, participants suggested resources could be CPD accredited and therefore integrated within a clinician's training.

Pooling expertise was considered important for supporting the management of complex patients. Useful methods reported included the setting up of regional networks, creating useful contact lists for clinical queries and virtual ward rounds led by expert personnel. Participants agreed that MDT-led approaches for complex patients provide great benefit, where they are currently in place, and the set-up of more, well organized and sufficiently funded regional networks would be of value. Pooling expertise by spotlighting centres where the AFS model is working effectively across teams was proposed as an approach to benchmark AFS activities within the NHS. Currently, no national education standards exist for AMS, including AFS: implementing accreditation that individuals or Trusts could work towards may support improved AFS practices in the UK.

Patient education was also highlighted as a gap. Across the UK there is a paucity of information for patients receiving antifungals either for treatment or prophylaxis. Participants advised they are not aware of any safety-netting materials for immunosuppressed patients at risk of developing an IFD when they are discharged home, e.g. advice to avoid building work or composting/gardening. Addressing this gap may improve patient and physician awareness of IFDs, encourage health advocacy and optimize AFS. It was suggested that counselling patients on their antifungal treatment plan, when it will be reviewed and potential switches available to them, would be an effective approach.

Conclusion

The findings from this panel discussion suggest that progress in the AFS landscape since 2017 in the UK has been limited. Lack of financial and staffing resources were reported as the main barriers to implementing AFS activities. Moreover, there is inadequate access to fungal diagnostic results within an acceptable timeframe. Mycology expertise is lacking even among laboratory and clinical infection specialists. Approaches to combatting these challenges may include setting up formal mycology networks across the country and linking them to regional diagnostic hubs to ensure all sites have access to mycology expertise and timely diagnostic results. The establishment of maximum acceptable turnaround times may support better practice. Making certain fungal pathogens notifiable would support AFR surveillance and outbreak management. Progress is being made, however, the ESPAUR fungal subgroup has recently been re-established in England and new BSMM guidelines on best practice for diagnosis and TDM are being revised. Additionally, UK Research and Innovation has recently awarded funding to eight new research

networks tackling AMR, of which one is focussed on fungal disease. Globally the Joint Programming Initiative on AMR (JPIAMR) is supporting an international Fungal Network for antifungal resistance surveillance as well as funding for other initiatives to detect and mitigate of AFR. Antifungal research and development, as well as data on surveillance and real-world usage to inform stewardship of new to market antifungal agents is imperative to combatting AFR. To this end, inclusion of antifungals within the UK Antimicrobial Registry (UKAR)²⁷ and proposals for the Antimicrobial Products Subscription Model²⁸ should be considered. For AFS to be sufficiently prioritized within the NHS, we recommend the establishment of national standards for AFS services and associated outcome metrics.

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