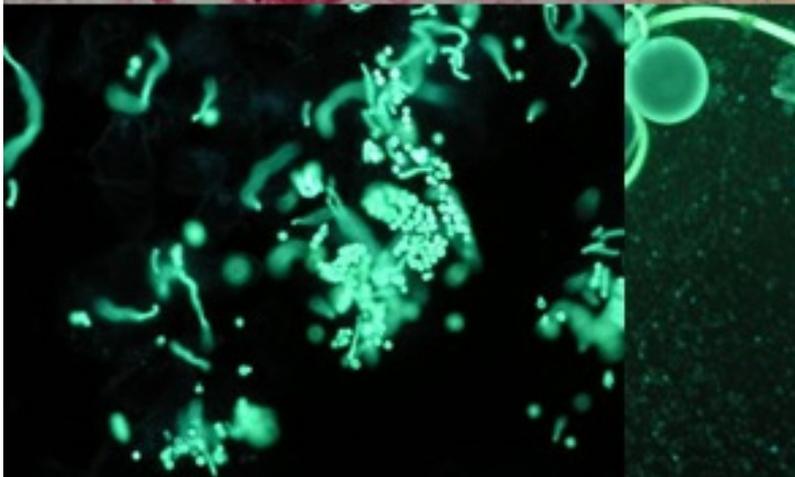
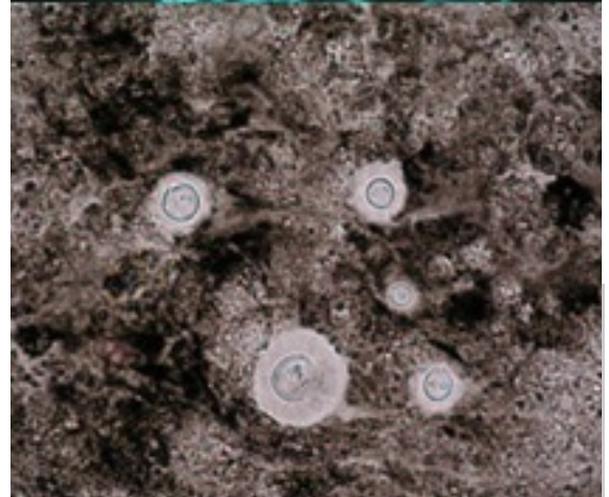
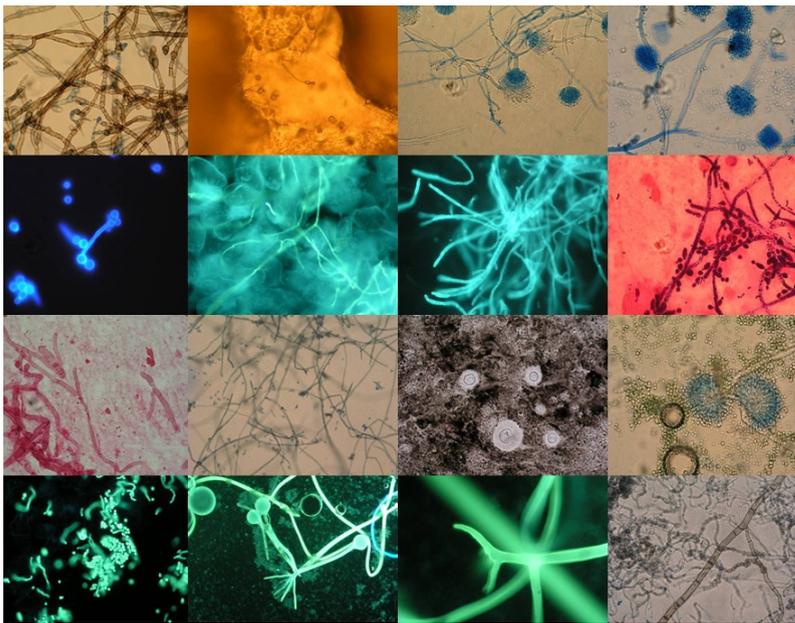


Fungal Diseases in the UK

The current provision of support for diagnosis and treatment:
assessment and proposed network solution





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Report of a working group of the Health Protection Agency Advisory Committee for Fungal Infection and Superficial Parasites

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Front cover picture: assorted fungi kindly supplied by Dr RP Hobson,
Mycology Reference Centre, Leeds

Executive summary

The health burden of diseases caused by fungi is considerable. In 2002, almost 10,000 patients in England were estimated to have suffered a deep-organ fungal infection as a negative corollary to otherwise successful treatment for a serious illness; almost half of them died from their fungal disease. Fungal infections such as athlete's foot and vaginal thrush are ubiquitous throughout the population. The financial impact of all fungal diseases is reflected in a national expenditure on antifungal drugs exceeding £90M in 2002. This cost has been rising annually and could rise even further with the recent introduction of important new antifungal drugs. Specialised support services for fungal diseases are few and patchily distributed throughout the UK. A coherently administered network of medical microbiologists with a specialised interest in clinical fungi could dramatically improve diagnosis and optimise antifungal therapy, thus reducing morbidity, mortality and drug costs associated with fungal disease.

In England in 2004, there are only 3 specialised laboratories for fungal diseases, employing 6 Grade B and 1 Grade C Clinical Scientists; none is located in the capital. In Scotland there is one further specialised laboratory. The numbers of UK personnel specialised in fungal laboratory tests has been decreasing steadily since the early 1980s. Certain specialised tests (such as antifungal drug monitoring and antifungal susceptibility testing) impact directly on care, and it is recognised that increased hospital infection, deaths and additional expense accrue from poor therapy. In addition, much unnecessary therapy contributes to the £40M annual community drug expenditure on antifungal agents.

Developing programmes for susceptibility testing of fungi involved in invasive infections is specifically mentioned as part of the Health Protection Agency's (HPA) strategic goal to prevent and reduce the impact and consequences of infectious diseases.

A Working Group of the Advisory Committee for Fungal Infection and Superficial Parasites was convened to identify how the provision of support services for fungal diseases in the UK can be improved, with the effect of optimising antifungal therapy. The key recommendations are as follows:

Key recommendations

- **Each region should have access to a comprehensive fungal testing service. This service should involve a clinician with a major interest in fungal infection to assist in all aspects of diagnosis, treatment and surveillance.**
- **A UK-wide HPA network should be set up to co-ordinate development of the service via training, SOPs and national surveillance. Development of the service will be supported by the British Society for Medical Mycology, which is already established in the provision of mycology training and standards of care. Funding for England will be pursued through the HPA and Workforce Development Confederations. Funding for the rest of network would need to be pursued from other sources.**
- **The fungal surveillance system needs to be strengthened, and should include antifungal resistance. This process should be jointly led by the HPA Mycology Reference Laboratory (Bristol) and Communicable Disease Surveillance Centre (now part of the Centre for Infections) (London), capturing data from all laboratories undertaking sensitivity testing.**

Introduction

Invasive fungal infections are increasing in frequency in all western countries as a result of modern medicine and increased survival from otherwise lethal diseases (Cohen, 2000). While there is some world class expertise in fungal diseases in the UK in some locations, service provision at all levels (routine, specialist, reference laboratory services and clinical care) is tenuous and poorly distributed nationally. Major advances have been made in diagnosis and treatment over the last 10 years (fluorescent microscopy, antigen detection, PCR, CT scanning, validated susceptibility testing, therapeutic drug monitoring, 2 new antifungal agents), but very few are in routine practice in the UK, except for usage of the new (expensive) drugs.

This paper sets out the current situation in England, analyses the deficits and identifies areas in which major improvements could be made, at minimal cost. Provision for fungal disease services in the rest of the UK is not notably different from that in England.

The burden of fungal diseases in England

Fungal diseases can be divided into three broad groups:

- Invasive life-threatening infections, especially those due to *Candida* and *Aspergillus* spp.
- Superficial infections such as thrush, athletes foot, scalp ringworm, nail infections etc.
- Allergic fungal disease of the sinuses or chest

Our understanding of the overall burden of fungal infections in the UK is very limited as there are no infectious disease surveillance programmes specific to fungal infections currently in existence. However, some data are available from surveillance activities designed to capture a range of infectious disease diagnoses. As these programmes were not designed to specifically capture data on the incidence of fungal infections, they each have their limitations.

Invasive fungal infections

The only source of national surveillance data for invasive fungal infections are derived from routine microbiology laboratory reports made to CDSC (now Centre for Infections) via regional Health Protection Agency units. As these data are derived from microbiological diagnoses, their robustness is dependent on the diagnostic laboratory's capacity to make the diagnosis, as well as their consistency and quality of reporting. These data are likely to be of most value for invasive candidosis, owing to its relative ease of microbiological diagnosis. A review of reports made between 1990 and 1999 identified substantial increases in invasive candidosis over this period, from 6.8 to 13.7 per million population in England and Wales (Lamagni *et al.*, 2003). Invasive candidosis was the most commonly reported invasive

mycosis during this review period. Since 2002, reports of candidaemia are published each year in the CDR Weekly, and show further year-on-year rises in numbers of diagnoses, a total of 1148 being reported for England, Wales and Northern Ireland in 2002 (HPA, 2003).

Another approach to quantifying the burden of fungal infections is to estimate likely numbers of cases from studies measuring incidence in a specified time, place and patient group and applying this to defined populations of patient groups. What follows are estimates of the burden of disease in the UK (Denning, pers comm. 2003). If the patient groups below in table 1 were to be summed, this would give 5466 cases of invasive candidosis/candidaemia and 4120 cases of invasive aspergillosis, although there may be overlaps between these groups.

Table 1: Invasive fungal infection - estimated number of cases, 2002

Patient group	Number of patients	Invasive candidosis/ candidaemia risk estimates**	Expected number invasive candidosis/ candidaemia	Invasive aspergillosis risk estimates®	Expected number invasive aspergillosis
AlloBMTx	793	4%	32	10%	79
Solid organ Tx	2953	5%	148	1.9%	56
Leukaemia	16269	3%	488	6%	976
Solid tumour (neutropenic)	28955	3%	869	2%	579
Advanced cancer	131678	1%	1316	1.5%#	1975
ICU	210130	1%	2101	0.2%	420
Burns	378	5.6%	21	1.9%	7
Renal dialysis	24536	0.2%	490	0.02%	5
HIV/AIDS	661	0.2%	1	4%	26

** no estimate for surgical patients, but some are in ICU, or have advanced cancer

@ no inclusion of most chronic chest, steroid-treated patients, an increasing group

the literature figure is 6%, but felt to be autopsy selection bias, so reduced by 75%.

Mortality statistics, based on information provided on deaths certificates, are a further potential source of national data on fungal infections. However, at present the only routinely available mortality statistics are based on underlying cause of death, and are therefore of limited use in enumerating the role opportunistic pathogens, such as fungi, in patients' deaths.

Invasive mycoses have been shown in many studies to be associated with relatively high levels of mortality. Invasive candidosis has an overall mortality of approximately 30% (Kibbler, 2003), a reduction from 55% in the early 1990's (Wey, 1988). Of this approximately half is attributable mortality, the remainder a function of co-morbidity. Survivors are usually completely cured, although ~5-10% suffer complications such as unilateral or bilateral blindness, bone infections or surgical complications related to treatment.

Invasive aspergillosis has a high mortality (~60%), higher if the diagnosis is delayed (von Eiff *et al.*, 1995), and in highly immunocompromised patients. Survivors have limited sequelae, unless they get brain infection. Because the treatments are suboptimal, and tissue damage often extensive, delay in treatment of the underlying disease (notably anti-leukaemia therapy) is

delayed, leading to higher relapse rates, and subsequent additional costs (Lewis *et al.*, 2003) and death.

Three factors impact on these figures: underlying disease, speed of diagnosis and optimisation of therapy. Some patients are so ill by the time they develop invasive fungal infection that no drug will make an impact. However, a large percentage of deaths (possibly 66%) might be prevented, with early accurate diagnosis and optimisation of therapy.

Superficial fungal infections

Although superficial fungal infections are rarely life-threatening they are associated with considerable inconvenience and discomfort. Persistent or recurrent vaginal thrush causes much misery and constitutes a significant burden to the NHS owing to the sheer numbers of individuals affected. Statistical returns from genitourinary medicine (GUM) clinics alone recorded over 77,000 attendances for genital candidosis in England in 2002 (HPA, 2003). Skin problems generally have a high impact on patients because of appearance, and there is an increasing trend to treat infected nails, primarily for cosmetic reasons but also for cogent medical reasons (Roberts, 1999). Athlete's foot is another common cause of minor discomfort, and occasionally leads to lower leg skin infections (cellulitis) which requires hospital admission. Approximately 3% of hospital admissions in general medicine are for cellulitis (Anonymous, 2003), each requiring an average of 10 days in hospital (Cox *et al.*, 1998).

Many superficial fungal infections are chronic or recurrent, so simple incidence figures are not the most useful means of understanding the burden of disease. Of all the superficial fungal infections, vaginal thrush, nail infections (onychomycosis) and scalp infections in children are the most common and problematic.

- Vaginal thrush occurs in about 75% of women (Ferrer, 2000) at some time in life, most commonly in pregnancy or after antibiotics. However about 30% of women of childbearing years get recurrent episodes and ~1% are almost continuously troubled by it — approximately 150,000 women in the UK.
- Onychomycosis is common in the general adult population, probably 5-25% rate depending on age, according to recent surveys (Pierard, 2001). This equates to >1,500,000 affected patients. Many people with discoloured or distorted toenails have other problems, but are treated empirically with antifungal therapy.

Scalp ringworm infection due to the anthropophilic species *Trichophyton tonsurans* is increasingly common in UK children, and readily passes amongst primary school children. There are studies that suggest a 12-47% carriage

rate in some London schools (Fuller *et al.*, 2003) and it is particularly common in children of Afro-Caribbean origin. Estimates vary because of localised outbreaks but there has been a substantial increase in the UK over the last 20 years (a laboratory-based survey recorded 27 cases in 1980 and 1227 in 2000; unpublished data, Mycology Reference Laboratory, Bristol).

Allergic fungal infection

While allergic fungal infection is probably commoner than realised (chronic sinusitis etc), estimates of caseload are unreliable, diagnostic tests are poorly developed, and response to antifungal therapy uncertain. Asthma and chronic rhinitis/sinusitis are extremely common and require substantial medical time in the community and in hospital practice. Significant developments are in progress in this area, and a major diagnostic need is foreseen. They will not be considered further in this document, although a significant change in practice is possible in the future in this segment of fungal disease.

Hospital stay

The occurrence of an invasive fungal infection usually increases the duration of the hospital stay, whether the patient survives or not. The additional length of stay for patients with candidaemia compared with matched controls is 14.7-36.3 (Hobson, 2003) days, usually in intensive care or high dependency units for much of the time. For invasive aspergillosis most patients require a long period of expensive in-patient therapy, but, because of the high mortality, many still die at the end of this (Dasbach *et al.*, 2001; Abbott *et al.*, 2002).

Antifungal expenditure

Antifungal drugs are generally expensive. Intravenous drugs are commonly used in intensive care units and in haematology, transplant and HIV patients, and in large hospitals with large units the annual expenditure can exceed £1m annually. In hospitals with active cancer/leukaemia units, antifungal expenditure exceeds all other categories.

In a country-wide study in the US, the mean additional costs of invasive aspergillosis was \$62,500 per patient, prior to the introduction of caspofungin or voriconazole (Dasbach *et al.*, 2001). The case finding identified 10,200 patients nationally in the US, therefore the estimate of cost nationally was \$633M.

Data from the US showed the estimated cost (1997 U.S.\$) of an episode of care for candidaemia is \$34,123 per Medicare patient and \$44,536 per private insurance patient in 1993 (Rentz *et al.*, 1998). The major cost associated with candidaemia is that of an increased hospital stay.

Standard amphotericin B causes renal impairment. This was the primary reason for the introduction of the lipid amphotericin B preparations (Abelcet, AmBisome and Amphocil). The direct and indirect costs of renal impairment

caused by amphotericin B have been assessed. In a large US study of 700 patients treated with conventional amphotericin B, renal failure developed in 30%, leading to a mortality rate of 54% versus 16% of those treated without amphotericin B (Harbarth *et al.*, 2002). Using multivariate analysis techniques, the additional length of stay was calculated as 8.2 days and additional adjusted cost as \$30,000 per case. Hence, the higher acquisition costs of lipid amphotericin B preparations appear worthwhile.

Costs of drugs

Intravenous antifungal drugs may be used for variable lengths of time. Typical usage is shown in table 2 below.

Table 2: Intravenous antifungal drugs - typical costs and usage

Agent	Route	Typical daily dose	Cost per day (£)	Typical duration (range)	Typical cost per course*	Year of license
Fluconazole (Pfizer)	IV	400mg	56	14 (5-21)	820	1991
Fluconazole (generic)	IV	400mg	36	14 (5-21)	503	2003
Caspofungin	IV	50mg	334	14 (5-21)	4676	2002
Abelcet	IV	5mg/kg	246	10 (5-30)	2464	1996
AmBisome	IV	3mg/kg	554	10 (5-30)	5538	1996
Amphocil	IV	3mg/kg	380	10 (5-30)	3801	1996
Amphotericin	IV	1mg/kg	7	5 (1-10)	37 [#]	1960's
Itraconazole	IV	400mg	72	14 (7-60)	1143	1992
Voriconazole	IV	4mg/kg	80	21 (7-60)	1688	2002
Flucytosine	IV	100mg/kg	86	10 (5-30)	860	1975

* includes loading doses

[#]Before usually transferring to other more expensive therapy as a result of toxicity

Oral drugs are less expensive, and used for much more variable lengths of time. For example vaginal thrush is treated with a single dose or 2 doses in most instances, but may be treated for 3-6 months in the few women with persistent problems. Thus computing cost per course is more difficult.

Table 3: Oral antifungal drugs - typical costs and usage

Agent	Indication	Dose and duration	Typical cost per course	Year of license
Fluconazole (Pfizer)	Vaginal thrush suppression	100mg, 6 months	£850	1991
Fluconazole (generic)	Vaginal thrush suppression	100mg, 6 months	£403	2003
Itraconazole	Scalp ringworm	200mg, 6 weeks	£43	1992
Terbinafine	Fingernail infection	250mg, 6 weeks	£134	1995
Terbinafine	Toenail infection	250mg, 3 months	£268	1995
Voriconazole	Chronic pulmonary aspergillosis	400mg, 12 months	£20,506	2002

Antifungal drugs are currently recorded in 4 categories – hospital prescription, gynaecological, dermatological and topical/OTC. This makes accurate data collection difficult. However the following data on prescription oral drugs (excluding therefore topicals and OTC usage) have been made available from the Department of Health (primary care) (see table 4).

Hospital sector

There are as yet no published or easily accessible data on the usage of antifungal drugs in the hospital sector, although the Department of Health's Pharmacy Initiative has indicated that such data will be available in future. In 1999, £30.3M was spent in the hospital sector. In the 12 months to September 2003 the hospital expenditure in the UK £52.5M, an increase of 73%, or 18% annually (IMS data). Over 50% of that market is in intravenous AmBisome®. Some oral usage derives from hospitals, particularly in genitourinary medicine and prophylaxis. This compares with US expenditure of \$700M only on injectable antifungal drugs.

Primary care

Table 4: Costs of antifungal drugs to primary care

Antifungal market : Community /England only **£000's @ Basic NHS price**

Source: Department of Health Prescription Cost analysis

		1997	1998	1999	2000	2001	2002
TOTAL	BNF 5.2	28195	29469	31675	33694	37113	40863
Amphotericin		61	58	76	54	60	59
Fluconazole		6128	6302	6331	6585	7029	7162
Griseofulvin		247	220	211	206	36	404
Itraconazole		4642	5317	5091	4894	4982	4190
Ketoconazole		101	93	95	90	88	86
Miconazole		3.8					
Nystatin		974	941	950	929	899	876
Terbinafine		16038	16538	18921	20935	24019	28086

The role of fungal testing laboratories

Although there is a wide range of tests conducted in mycology laboratories, there are a small number of critical tests. Most tests are diagnostic tests, and include culture, microscopy, antigen and antibody detection and, increasingly, molecular diagnostics. Other tests assist in treatment selection and to optimise therapy, including therapeutic drug monitoring. Some diagnostic testing can contribute to surveillance.

Some tests are critical to clinical management, and some of these have substantial potential to minimise antifungal expenditure. For example, making the correct diagnosis of invasive aspergillosis is associated with lower costs and better outcomes. It is assumed that basic culture tests are done in every microbiology laboratory and do not require specialised laboratories although there is clearly still a need to provide training in the optimal performance and application of these tests. Such tests include blood, sputum and nail cultures, for example. Specialised tests and their role in clinical management are described below. These tests are not suitable for routine laboratories, unless the laboratory is very large, with experienced personnel and servicing a very large population of critical care and immunocompromised patients. A rapid turnaround time is critical for good clinical decision-making.

Cryptococcal antigen

This is the best diagnostic test for the diagnosis of cryptococcal meningitis and other forms of cryptococcal disease. It can be done in a few hours, unlike culture which usually takes 2-4 days (and may take more than a week in some cases). Cryptococcal meningitis is fatal if not diagnosed promptly.

Aspergillus antigen

Recently introduced, the *Aspergillus* antigen test is capable of identifying neutropenic leukaemic patients with invasive aspergillosis several days earlier than clinical features and chest X-ray abnormalities appear. This requires a surveillance approach. This test can also be used in bronchoalveolar and cerebrospinal fluids. Early diagnosis has a major impact on survival. Knowing that the patient has aspergillosis and not another fungal infection or other diagnosis is critical in optimising therapy, and allows discontinuation of ineffective drugs.

Microscopy and culture of nail clippings

Fungal nail infections require therapy for 3-6 months. Often testing of the nail is not undertaken and therapy is prescribed empirically. If the diagnosis is incorrect, or if the fungus is not sensitive to the antifungal drug used, the therapeutic course is wasted and exposes the patient to unnecessary potential toxicity.

*Sensitivity testing of *Candida* spp. to fluconazole*

The majority of isolates of *Candida* are sensitive to fluconazole, but up to 15% may be resistant or of intermediate susceptibility. Many units faced with this rate of resistance will use either caspofungin or an amphotericin B preparation, rather than risk therapeutic failure with fluconazole. However fluconazole is much less expensive, is available orally and is associated with little toxicity so is a better choice in many patients, especially if they can take oral therapy. Widespread availability of rapid fluconazole sensitivity testing has the potential to save millions of pounds, and provide excellent care. However azole sensitivity testing is not straightforward and should be conducted by well-trained staff, undertaking many tests annually.

Identification and antifungal sensitivity testing of moulds

A wide range of filamentous fungi (moulds) cause invasive infection, even though most cases are due to *Aspergillus fumigatus*. Itraconazole resistance has been identified in *A. fumigatus* and amphotericin B resistance in *A. terreus*. Many other fungi are resistant to one or more antifungal agents. Susceptibility testing of moulds is challenging and in flux, but is becoming clinically useful. This should only be conducted at specialist centres.

Flucytosine therapeutic monitoring

Flucytosine is toxic to the liver and bone marrow at high concentrations. Flucytosine is excreted by the kidneys and is often given in combination with amphotericin B which can impair kidney function. Currently a third of levels assessed are in the toxic range. Monitoring is therefore crucial, especially in patients with renal impairment and in premature neonates.

Azole therapeutic monitoring

Itraconazole and voriconazole are compounds with substantial inter-patient variation in bioavailability. Both are also associated with numerous drug interactions. The bioavailability of oral itraconazole is poor, and a threshold for protection in prophylaxis or treatment has been defined. Voriconazole plasma concentrations are often very low in children and dose escalation is required for optimal therapy.

Table 5 below summarises the impact of these tests.

Table 5: Impact of fungal tests on choice of therapy, toxicity and costs

Test	Makes the diagnosis	Ensures appropriate therapy	Minimises toxicity	Saves money
Antigen tests	X	X		
Microscopy and culture of nail clippings	X		X	X
Fluconazole sensitivity testing		X	X	X
Mould ID and testing	X	X		X
Flucytosine assays		X	X	
Itraconazole assays		X		X
Voriconazole assays		X	X	X

Current provision of fungal testing

There are few laboratories undertaking all of these tests currently in England, principally in Bristol (the HPA Mycology Reference Laboratory), Leeds and Manchester. Flucytosine assays are undertaken in 13 laboratories nationally, and dermatological mycology in many laboratories. Likewise cryptococcal antigen testing is undertaken in many laboratories, particularly those servicing a large number of AIDS patients. Table 6 below shows where tests are currently performed.

Table 6: Laboratories where different fungal testing performed (at 2004)

Test	Bristol	Leeds	Manchester	London*	Some others
Cryptococcal antigen	X	X		X	X
Aspergillus antigen	X	X		X	X
Nail clippings	X	X	X	X	X
Fluconazole testing	X	X	X	X	X
Mould ID	X	X	X	X	X
Mould sensitivity testing	X		X		
Flucytosine assays	X		X		X
Itraconazole assays	X		X		
Voriconazole assays	X		X		

* Including the St John's Institute of Dermatology

Several HPA regions do not have these specialised services, and send all tests that are done to the 3 laboratories. This produces a problem of backlog and a slow turnaround time that greatly impacts on the value of doing the tests.

Future improvements in diagnosis and monitoring of therapy

Molecular diagnosis

Major improvements in early diagnosis will probably come from the introduction of molecular diagnostic tests. Many academic laboratories have studied this area. Molecular diagnosis holds many benefits – speed of result, greater sensitivity, utility on unusual samples types where the current tests are not useful (histology specimens for example), and immediate species identification. Future developments may include the direct detection of resistance mutations.

Unlicensed tests for *Candida*, *Aspergillus* and *Pneumocystis* are available in the UK. A national group comprising representatives from all centres with an established interest in molecular diagnosis of invasive fungal infection has been collaborating on the optimal procedures for DNA extraction from blood and PCR detection to maximise sensitivity, and has made considerable headway. Tests are available on a research basis in Bristol, Cardiff, Glasgow, London and Manchester, but are not offered as services for lack of pump priming investment.

Drug assays

Therapeutic drug monitoring is evolving with the rapid deployment nationally of bench top mass spectrometry. Samples can be prepared in a few minutes and, after calibration, analysed in less than 10 minutes for levels of itraconazole and voriconazole. Flucytosine is more difficult to assay, but there are several acceptable methods for this including HPLC and bioassay. A close link between specialist mycology services and biochemistry/drug analytical services will be advantageous for optimal patient management, as the analysts are not very familiar with the clinical reality of these patients.

Five year action plan

First year objectives

1. With the assistance of the Inspector of Microbiology, implement a national action plan to designate regional centres of excellence in fungal disease and so establish a Clinical Mycology Network.
2. Establish a regional centre of excellence in London. The incidence of fungal infection is high but the service is lacking in this region.
3. With support from the Workforce Development Confederations, the Training Programme Steering Group to designate new training posts in the regional centres. Posts in other parts of the UK would need to be funded from other sources. Encourage appropriate candidates from these centres to embark on mycology training via the British Society for Medical Mycology Diploma course.
4. Prepare Standard Operating Procedures (SOPs) for the identification, susceptibility testing and reporting of fungal diseases and audit regional centres for current standards of practice in implementing these procedures

Second year objectives

1. Amend established reporting network (CoSurv) for the capture of antifungal susceptibility results.
2. Audit arrangements for provision of mycology diagnostic services in NHS hospitals and other clinical units.
3. Set up pilot research studies to examine the prevalence of dermatophyte infections and causative dermatophyte species in the primary care setting. Results to be compared with CDSC (now Centre for Infections) data on dermatophyte species reported.

Third year objectives

1. Audit/inspect implementation of standards of service at regional centres.
2. Review results of ongoing inter-laboratory survey of molecular diagnostic methods. Prepare SOPs if appropriate.
3. Build on the existing national surveillance scheme to develop a prospective sentinel based system allowing the capture of reports from regional and national reference centres

Fourth year objectives

1. Review workloads in fungal disease reference laboratories; these may have been reduced by the establishment of regional service centres, or increased because of the success of the network in encouraging a higher degree of specimen referral at all levels of patient care.
2. Introduce molecular diagnostic SOPs as routine tests, where appropriate, in reference laboratories.

3. Review first results of the expanded national surveillance scheme for fungal disease and feed-in to relevant expert committees as appropriate (e.g. SACAR).

Fifth year objectives

1. Audit and inspect full implementation of action plan; success of local, regional and reference service centres in operating SOPs for fungal diagnosis and susceptibility testing.
2. Assess nationwide impact of fungal service network on practice concerning diagnosis and management of fungal disease in primary, secondary and tertiary care settings using the BSMM standards of care.

Recommended service levels for fungal testing

There are many ways to configure services for mycology. Some tests require a high level of expertise (e.g. susceptibility testing and molecular diagnosis), others are infrequently requested and are best batched (e.g. fungal serology) and others require a high level of advice to clinicians (e.g. therapeutic drug monitoring). Below is the Committee's recommendation regarding partition of local, specialised and reference services. The divisions are somewhat artificial as some laboratories are well developed in some areas and not others, often because of a lack of resource and/or expertise. In almost all cases specialised laboratories will be on the same site as a local laboratory. All laboratories providing a mycology diagnostic service should be accredited by a national accreditation scheme such as CPA or ISO9000 and should work to national standards under the United Kingdom National External Quality Assessment Service.

1. Local laboratory services (every microbiology laboratory)
 - o Primary fungal cultures from blood, deep and superficial infections
 - o Identification of *Candida* spp. to species level and *Aspergillus* and common dermatophytes to genus level
 - o Microscopy on respiratory and other fluids for fungal elements and *Pneumocystis jiroveci* (*carinii*)
 - o Local clinical advice on common fungal problems
2. Local laboratory services (major microbiology laboratories in teaching centres or specialist cancer, AIDS or transplant hospitals)
 - o Services as for every local laboratory (as above)
 - o Cryptococcal antigen
 - o *Aspergillus* antigen, if a leukaemia centre
3. Regional laboratory services (undertaken by regional microbiology centres)

- Fungal serology (some undertaken by immunology labs)
- Identification of unusual fungi (not category 3 pathogens)
- Molecular diagnosis
- Susceptibility testing
- Therapeutic drug monitoring (azoles and flucytosine esp)
- Specialised clinical advice (clinical mycologist)
- Training centre
- Research agenda

4. Reference laboratory service

- All the functions of a specialised laboratory PLUS
- Identification of rare fungi (incl. category 3 pathogens) by conventional means
- Identification of rare fungi by sequencing
- Molecular diagnosis
- Focus for national standards and training in laboratory mycology
- Collection of national datasets
- Maintenance of the National Collection of Pathogenic Fungi
- Research agenda

Future considerations

Standards of care for fungal diseases

A paper from the British Society for Medical Mycology (BSMM), recommending standards of care for patients with invasive fungal infections was published in 2003 (Denning *et al.*, 2003). This publication, while not fully evidence-based should be regarded as a reasonable set of recommendations for optimised care of such patients. The document will be updated in future as further evidence becomes available. While it may be impractical to implement all the recommendations of this paper on a short time scale, the publication sets out criteria for hospital audits and inspections.

Training of specialists in fungal diseases

Over the past 20 years there has been a steady decline in the number of medical and scientific personnel with specialist training in fungal diseases. This loss of expertise needs to be addressed if England (and the rest of the UK) is to be left with levels of expertise appropriate to the country's needs. A new diploma distance-learning course in medical mycology, leading to the qualification of DipMedMyc, has been instituted by the BSMM in conjunction with University College, London. This course, which is undertaken on a part time basis over a period of 3 to 5 years, provides a means for training individuals as fungal specialists, particularly those already working as physicians, clinical scientists or biomedical scientists in infectious diseases and medical microbiology.

The BSMM also runs a biennial course in diagnostic mycology, which is highly regarded as an important training resource for medical laboratory personnel.

Since the BSMM is the sole national professional body representing fungal disease specialists of all types, the HPA should seek collaboration with this Society in developing any strategy for implementation of fungal disease networks. It should, however, be remembered that the remit of the BSMM covers the whole of the UK, not just England.

Although both Clinical Scientists and Biomedical Scientists (BMS) could potentially become specialists in fungal diseases the IBMS currently has no mycology training scheme and this requires strengthening if BMSs are going to be suitable for this role.

The Workforce Development Confederations are developing national strategies for managing the workforce issues in small specialties. The Yorkshire WDC has been identified as responsible for training in mycology on a national basis and it is anticipated that a coordinated network of training posts will be implemented in conjunction with this WDC.

There is also a need to train clinicians in aspects of mycology. At consultant level there are few with expertise nationally, and none devoted entirely to medical mycology problems. There are virtually no consultant dermatologists with this subject as their special interest in the country. Considerable expertise resides in the haematology community for certain problems. Exceptionally poor recruitment nationally into clinical studies of antifungal drugs, other than prophylaxis and empirical therapy, underlines the shortage of expertise. Trainees in the infection disciplines need to be encouraged to learn the subject well, and participation in the DipMedMyc or undertaking a research fellowship in the subject leading to a postgraduate degree should be the recognised routes forward to become expert. Laboratory training in the subject is a very important component of the training required, further emphasising the need to build the national infrastructure of mycology laboratories.

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Consultation

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Royal College of Physicians
Royal College of Pathologists
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HPA Communicable Disease Surveillance Centre
HPA Local and Regional Services
HPA Specialist and Reference Microbiology Division
Association of Medical Microbiologists
British Association of Dermatologists
British Association for Sexual Health and HIV
British Society for Antimicrobial Chemotherapy
British Society for Haematology
Hospital Infection Society
Intensive Care Society
Mycology Reference Centre, Leeds General Infirmary
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