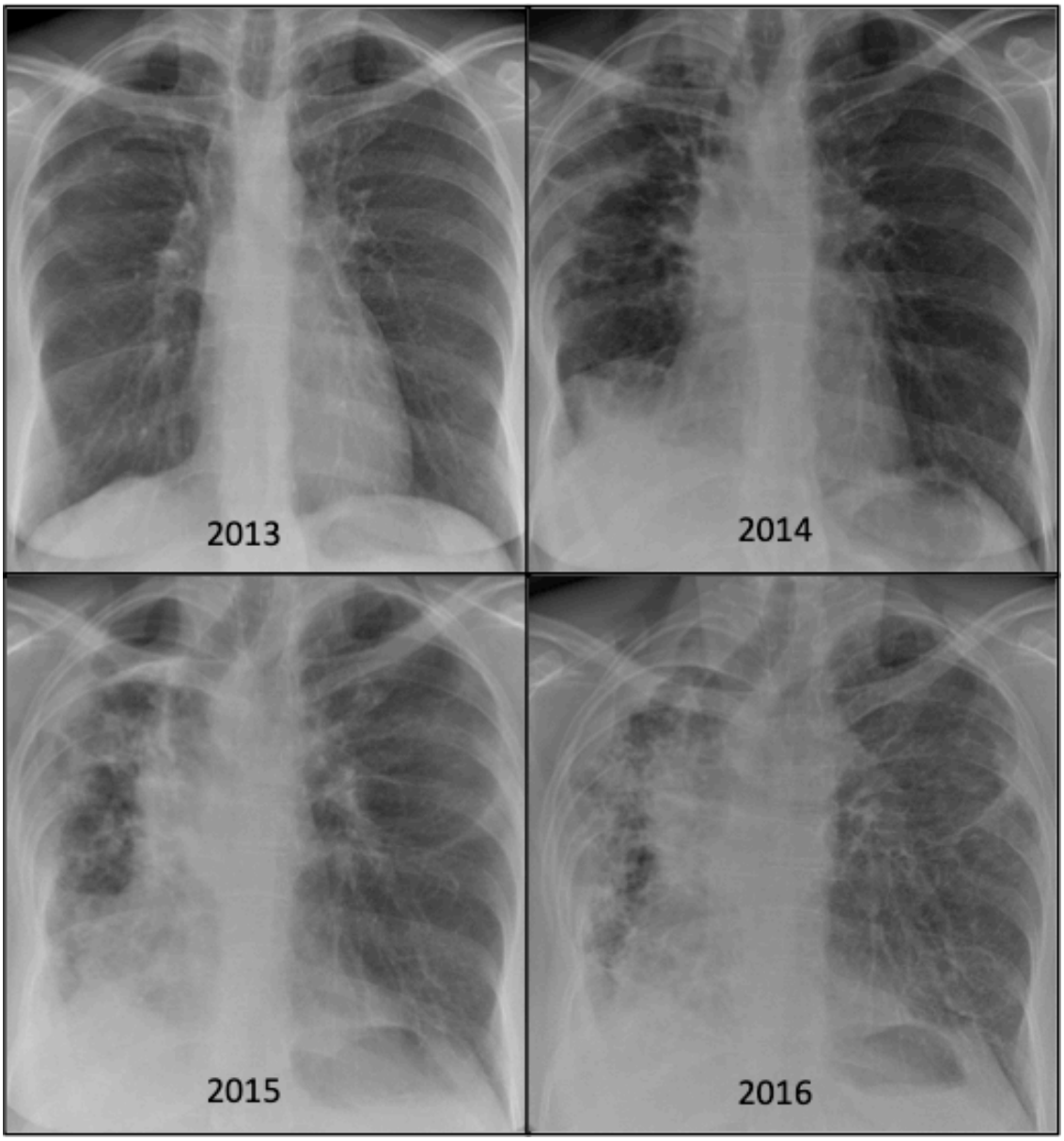
NHS National Commissioning Group - Highly Specialised Services

Chronic Pulmonary Aspergillosis National Service

The National Aspergillosis Centre

Annual Report 2018-2019



A European Centre of Excellence in Medical Mycology

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Previous NAC annual reports can be accessed here: https://aspergillosis.org/nac-reports/

Cover figure shows the asymptomatic progression of CPA over 3.5 years in a patient seen in secondary care, but without any new diagnosis being considered because of a lack of symptoms. On presentation her Aspergillus IgG antibody was >800 mg/L (normal <40).

1 General Overview and highlights

This report covers the tenth full year of this National Aspergillosis Centre (NAC), commissioned as a Highly Specialised Service within the NHS. A total of 131 new patients with CPA (out of a total of 367 with some form of aspergillosis) were seen from April 2018 to March 2019. At the end of March 2018, 521 patients from England and Scotland were on service with an additional 22 patients from Wales, Northern Ireland and Isle of Man. In the year 65 patients died and 33 were discharged from service. This represents a 6.1% growth (15.3% growth in prior year). Waiting times were on average 8 weeks (9 weeks in 20117/18) with 11 patients waiting for up to 6 months due to illness or rescheduling of appointments. Twelve patients referred in 2018/19 died in the same year.

Overall drug expenditure is similar to the previous year with a slight growth consistent with growth in patient numbers. Most oral voriconazole, posaconazole and isavuconazole is prescribed through Hospital at Home and delivered to patients' homes. Admission and OPAT days for IV micafungin or liposomal amphotericin B therapy were similar, with a slight rise in the number treated at their local hospital and reimbursed by the NAC. Azole antifungal resistance is the primary reason for IV antifungal use.

Posaconazole and isavuconazole was used in those intolerant or failing itraconazole and voriconazole as a trial of therapy. Posaconazole was successful in 15 of 36 (42%) and isavuconazole in 7 of 15 (47%) trialled, with outcomes pending on a further 10 patients.

The NHS Mycology Reference Centre (MRCM), provides the high level diagnostic mycology service for the NAC and is now independently UKAS ISO/IEC 15189:2012 acccredited. The laboratory is the largest mycology laborarory in Europe with a strong performance in turnaround time, critical results reporting in 1 hour, external EQA, linked clinical audits, publications and national and international representation. The MRCM has been at the forefront of diagnostic developments for aspergillosis in the last 8 years, with pyrosequencing to determine azole resistance, high volume sputum culture the latest developments.

Amongst the 71 papers and book chapters published in calendar year 2018 (see Appendix 5) (81 were published in 2017), there were several areas of direct relevance to patients with CPA and aspergillosis: 1) European guidelines for the diagnosis, prophylaxis and management of all forms of chronic and invasive aspergillosis, 2) Diagnosis recommendations of CPA in low and middle income countries, 3) A major audit of 200 patients with CPA from the NAC and their 12 month outcomes, 4) Summary of posaconazole for CPA, given as n-of-1 trials as per the NAC service specification, 5) A human genetic variant (ZNF77) allowing a high *Aspergillus* load in the airway, 6) Neutrophil defects allowing ABPA to develop, 7) Common occurrence of cystic fibrosis carrier status (10%) in ABPA.

Patient support, educational and outreach activities continue to grow especially with social media use. A remarkable 100,000-130,000 individual computers accessed The Aspergillus Website and Patients' website per month, 5,000 to 8,000 people daily, primarily from USA, UK, India, France and China. Live and recorded monthly online events held by the NAC are hosted within Facebook communities with >500 viewers each month. A Medical Alert card is available for patients. Public awareness efforts on aspergillosis continue as probably thousands remain undiagnosed.

2 Activity

2.1 Referrals, inpatient stays and caseload

The total referrals, inpatient stays, procedures, death and caseload in 2018/19 (Table 1) were as follows:

Activity Measure / Currency	M01 Apr	M02 May	M03 Jun	M04 Jul	M05 Aug	M06 Sep	M07 Oct	M08 Nov	M09 Dec	M10 Jan	M11 Feb	M12 Mar	YTD Actual
New Patients Testing	27	27	27	29	28	28	36	44	28	42	29	22	367
Outpatient - Follow-Up Attendances	12	14	8	9	15	9	8	16	12	10	14	4	131
Caseload - Band 1	147	150	151	142	152	137	124	124	114	115	105	151	1,612
Caseload - Band 2	149	150	146	146	148	147	146	149	153	153	153	157	157
Caseload - Band 3	306	310	320	320	324	332	336	330	333	330	333	332	332
Occupied Bed Days	24	23	24	25	26	25	25	24	24	25	25	28	28
Inpatient Discharges	87	98	114	50	115	25	26	10	51	16	95	7	694
IV Homecare (OPAT)	4	9	4	5	9	2	4	2	3	4	6	1	53
Surgical Resection	0	21	33	26	115	17	15	13	0	74	28	76	418
Embolisations	0	0	2	0	1	0	0	0	0	0	0	0	3
Patient Death	2	1	1	0	7	0	0	1	1	0	0	0	13
Discharge from Service	6	5	3	3	2	3	4	9	6	13	6	5	65
	2	3	4	4	2	3	4	3	3	1	2	2	33

* The NCG fund patients from England and Scotland only
# Appendix 1 shows the Banding criteria used

Of the 367 new aspergillosis referrals from England and Scotland during the year 2018/19 (369 the prior year), 131 (35.7%) had CPA, a slightly increased proportion compared with prior years. Among the outpatient referrals, the mean time from referral to being seen was 8 weeks (Appendix 2), including 12 patients who rescheduled their appointments or were too unwell to attend which is reflected in their the long wait times of 4-6 months. There were 2 transitions from another form of aspergillosis into CPA, 10 patients whose diagnosis took weeks to confirm and 1 from the TB service. There were 3 admissions and 3 patients who were referred for an opinion first.

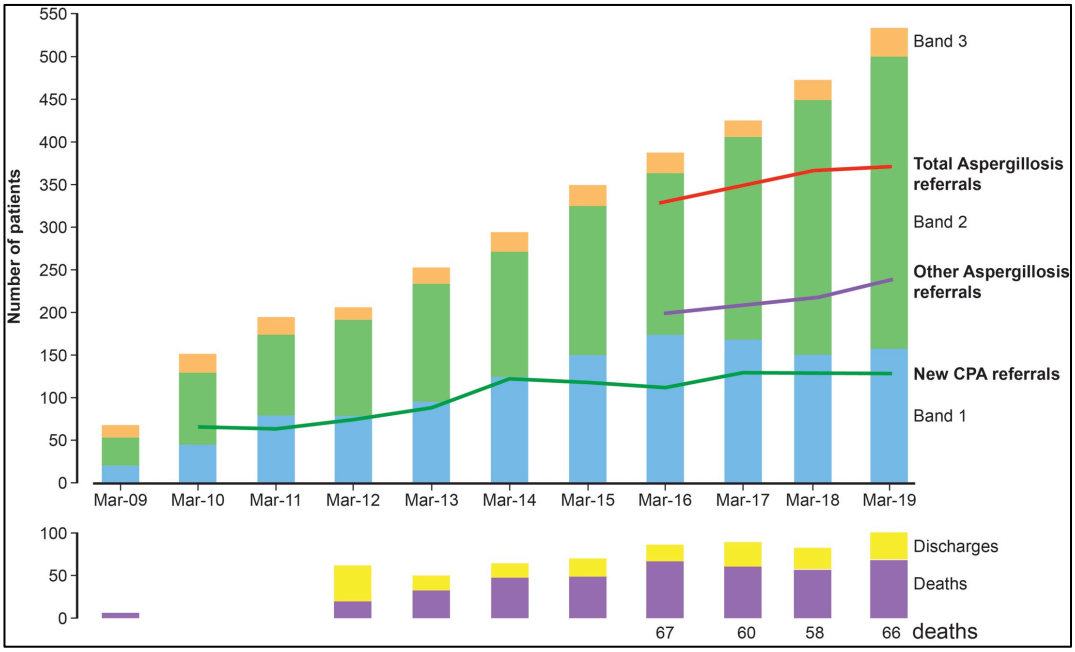
Appendix 2 shows the area of residence, date of referral and date of appointment. These numbers include 1 referral from Northern Ireland, 3 from Scotland, 1 from Wales, 1 from Portugal and 1 from Greece. There were three direct admissions and one ward referral at Wythenshawe Hospital from another team. Overall 12 of 131 (9.2%) referred patients died within the year. The residence of each referral and all patients under review are shown in the heatmaps in Appendix 3.

Many new patients with aspergillosis do not have CPA but are seen by the same medical and nursing team (Figure 1). These other forms of aspergillosis include allergic bronchopulmonary aspergillosis (ABPA), severe asthma with fungal sensitisation (SAFS), invasive aspergillosis, *Aspergillus* bronchitis, Aspergillus nodules and fungal rhinosinusitis, otitis, onychomycosis, building sickness syndrome and primary community acquired *Aspergillus* pneumonia.

There has a modest rise in Band 1 numbers from 149 patients to 157 but a much greater rise in Band 2 patient numbers from 301 to 332 (see Banding criteria at Appendix 1). There was a slight rise in Band 3 from 23 to 29 patients. The principal reasons for these shifts are: substantial problems with antifungal resistance, concern about a high rate of resistance with itraconazole and earlier use of voriconazole in those with extensive disease and large aspergillomas. These shifts include 65 deaths (58 the previous year and 60 the year before that) and 33 discharges from service (26 the previous year). At the end of March 2019, 521 patients from England and Scotland were on service with an additional 18 patients from Wales, two from Northern Ireland and two from the Isle of Man. This

represents a 6.1% growth (15.3% growth in prior year). Three patients were presumptively cured with surgery and 13 underwent bronchial artery embolization (11 last year), some because of poorly controlled disease attributable to azole resistance.

Figure 1. CPA patients on service at the end of each year from 2009/10 to 2018/19 with new aspergillosis referrals (2016-2019) and. Patient discharges and deaths per year are also shown.



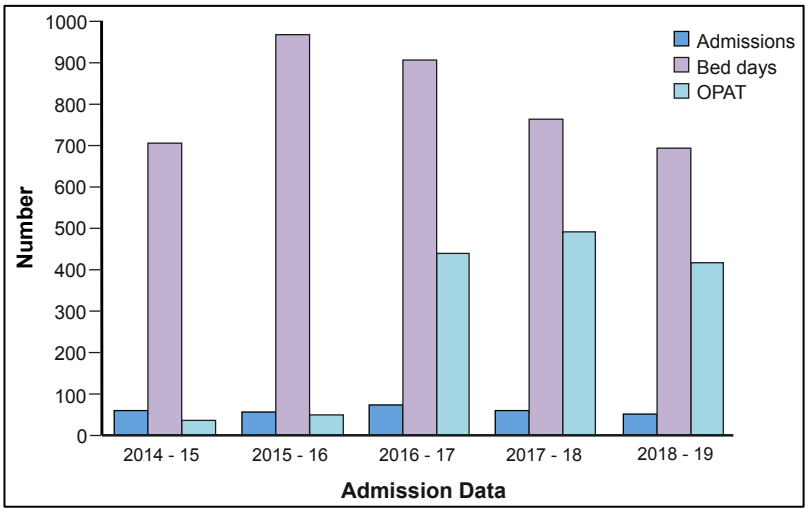
Admission days were slightly lower than the prior year at 694 (764 the prior year), but with many days of home IV therapy (OPAT) – 418 IV days. OPAT at other hospitals closer to home is not included in the figures, but is considerable. We also recommended admission locally and directly reimburse intravenous antifungal therapy for a number of patients who live a long way from Manchester.

2.2 OPAT for NAC

The outpatient parenteral antimicrobial therapy (OPAT) team provides intravenous therapy for patients deemed suitable to receive their therapy in the community. During the financial year 2018-19 the following number of patients referred from the National Aspergillosis Centre were treated by the OPAT service:

- 15 CPA patients in total
- Bed days saved: 364
- All treated with IV Micafungin
- 0 re-admissions to acute care

Figure 2. Number of admissions, bed days and OPAT days at Wythenshawe by year from 2014-15.



3 Clinical service developments and personnel (Director Prof David Denning)

The NAC has completed its tenth year of operations. The major shifts and improvements in practice and capacity are as follows:

3.1. Clinical and administrative personnel

The following staff were appointed or redeployed to contribute to the NAC:
Professor David Denning, Professor of Infectious Diseases in Global Health (3 clinical PAs)
Dr Pippa Newton, Consultant in Infectious Diseases (6 PAs) (until February 2019)
Dr Chris Kosmidis, Consultant in Infectious Diseases (5 PAs)
Dr Paschalis Vergidis, Consultant in Infectious Diseases (5 PAs)
Dr Rohit Bazaz, Consultant in Infectious Diseases (5 PAs) (from September 2017)
Dr Giorgio Calisti, Consultant in Infectious Diseases (5 PAs) (from December 2017)
Dr Ibrahim Hassan, Consultant in Microbiology (1 PA)
Dr Riina Richardson, Consultant in Medical Mycology (4 PAs)
Mrs Christine Harris, NAC manager (100%)
Dr Stephen Hopping, Educational Fellow (50%)
Ms Deborah Kennedy, Specialist Nurse (40%)
Mrs Jenny White, Specialist Nurse (60%)
Ms Judith Ford, Specialist Nurse (50%) (from June 2018)
Ms Smitha James, Specialist Nurse (50%) (from September 2018)
Ms Francesca Woolnough, Specialist Nurse (50%) (from July 2018)
Mrs Carol Toner, Band 2 Nursing assistant (100%)
Mr Philip Langridge, Senior Specialist Physiotherapist (50%)
Miss Reyenna Sheehan, Specialist Physiotherapist (20%) (until June 2018)
Ms Mairead Hughes (50%) (from November 2018)
Ms Fiona Lynch, Senior Pharmacist (40%) (from October 2018)
Dr Rowena Mills, Clinical Fellow (100%) (until February 2018)
Dr Firas Maghrabi, Clinical Research Fellow (100%)
Dr Akan Otu, Clinical Fellow (100%) (from December 2017)
Dr Ed Monk, Clinical Fellow (100%) (from February 2018 – January 2019)
Dr Andrew Wright-Taylor, CT2 in Infectious Diseases (50%)

Dr Graham Atherton, Senior Clinical Information Architect (Patient engagement) (40%)
Dr Helen Findon (Website for Patients) (40%)
Dr Beth Bradshaw (Medical Writer and Web Manager) (100%)
Mr Marcin Walczak, EPR and Clinical Database Manager (100%)
Ms Alison Pearce – Team Leader (50%)
Mrs Jen Rostron (50%)
Ms Alex Parton (50%)
Medical Secretary (50%) – vacant
Mrs Megan Hildrop Clerical Assistant (25%)

3.2 National Aspergillosis multidisciplinary team meetings (MDT's)
The National Aspergillosis Centre hold a variety of MDT's to improve the management and care of our patients.

NCG/ID MDT – The NAC team meets every Thursday to discuss problems that arise with patients and their management, and overview all new cases of azole resistance, including pyrosequencing requests and results. The issues range from medication, in-patient stays, referrals, care in the community, GP and hospital physician enquires etc. The team discuss and decide what action should be taken. This is an important forum for antifungal and antimicrobial stewardship.

Surgical MDT – arranged when sufficient cases are listed for discussion (approximately quarterly). To discuss cases that may be suitable for surgical resection. Scans and results are reviewed with several of the cardiothoracic surgeons and our team. If patients are suitable they are referred to the cardiothoracic surgeons for further discussion and the patient is informed.

Radiology MDT – Every Thursday with consultant radiologists and respirarory physicians to discuss difficult CTs, embolisation etc.

3.3. External opinions
There have been at least weekly requests for opinions, without referral. This reflects several factors, including travel distance, fragile patients, concern about RTT breaches, a focussed question only (such as duration of therapy) and complexity. These require registration of the patient at MFT to import images and a detailed clinical response, usually without any additional laboratory data, but a suggestion to request it.

3.4 Antifungal therapy at a distance
Healthcare at Home continue to deliver high cost antifungal medicine and voriconazole to patients at home, reducing some clinic visits and improving service to patients.

An increasing number of patients are receiving intravenous antifungal therapy close to home. Sometimes this is arranged through our OPAT team and delivered at home or on a day case unit locally, and sometimes as inpatients with NAC guidance. All these local courses of therapy are reimbursed to the prescribing unit from NAC. This is one of the reasons why our admission days are relatively low for the increasing volume of work.

3.5 Postal bloods and sputum
The postal blood and sputum service works well for following up antifungal drug levels between clinics, and getting much higher quality and volume samples. As *Aspergillus* PCR on sputum is barely available elsewhere in the country, sample delivery to the MCRM in the post is an important component of care. PCR is more sensitive than culture and can be used as a proxy for detecting resistance and

clinical failure. Some of these samples end up undergoing pyrosequencing to detect resistance. An increasing number of high volume cultures to improve the culture yield for susceptibility testing come in through postal packs. Significant results and new cases of azole resistance are discussed in the weekly MDT.

3.6 Use of validated scores to assess severity of disease and outcomes (QOL)
The St. George's Respiratory Questionnaire (SGRQ) is routinely and frequently used as a proxy measure of patients' well-being or quality of life. Together with the MRC dyspnoea scores, weights and Aspergillus IgG antibody levels, the 2018/19 data is presented in Appendix 4. The database has been rewritten and is now housed on a secure NHS server managed by the hospital, with remote login only possible via VPN secure system. There have been some issues with capturing all the new CPA patients partly because of confusion about outpatient codes.

3.7 N-of-1 trials of posaconazole or isavuconazole for third or fourth line antifungal therapy
We have now fully evaluated the new guidelines to use posaconazole on an individual trial basis, 'n-of-1' trials, and published this (Rodriguez-Goncer I et al, Section 7.1). We continue to use these n-of-1 trials for posaconazole and also now for isavuconazole. In the year April 2018 to March 2019, 36 patients were trialled on posaconazole (49 in 2017-18) and 15 on isavuconazole (21 in 2016-17). The outcomes are shown in the tables below. Posaconazole success was not statistically superior to isavuconazole success (p=0.11) in 2018-19.

Table 3: Trials of posaconazole and isavuconazole 2017-2018 at NAC

Outcomes	Posaconazole		Isavuconazole	
		%		%
Success	24	49.0	6	28.6
Failure	20	40.8	11	52.4
Death	5	10.2	4	19.0
Total	49	100.0	21	100.0

Table 4: Trials of posaconazole and isavuconazole 2018-2019 at NAC

Outcomes	Posaconazole		Isavuconazole	
		%		%
Success	15	41.7	7	46.7
Failure	19	52.8	8	53.3
Death	2	5.6	0	0.0
Total	36	100.0	15	100.0
Pending	7		3	

4 NHS Mycology Reference Centre, Manchester (Director Prof Malcolm Richardson)

4.1 Introduction

The NHS Mycology Reference Centre, Manchester (MRCM) has completed its eighth year of operations and has expanded in step with the evolution and continued growth of the NAC. It provides a specialist medical mycology reference

service to patients attending the NAC clinics, patients of Wythenshawe Hospital, Manchester University Foundation Trust (MFT), and other hospitals throughout the UK and specialist clinics in Europe. It is the only European Confederation of Medical Mycology (ECMM) Centre of Excellence in Clinical and Laboratory Mycology and Clinical Studies in the UK. There have been further developments and continued growth in its portfolio of tests and activities, and as well as contributing to over 30 publications, and major contributions to the University of Manchester PhD programmes in Medical Mycology. In 2018 the laboratory became a member of the Manchester University NHS Foundation Trust (MFT) Division of Laboratory Medicine. The MRCM is directed by Professor Malcolm Richardson, a Consultant Clinical Scientist in Medical Mycology. The Deputy Director of the MRCM is Dr Caroline Moore. Mrs Nichola Duddy is the MRCM Quality Manager and deputises for Dr Caroline Moore. Mrs Elaine Taylor is the Quality and Training Coordinator and deputises for Mrs Nichola Duddy. These senior staff of the MRCM work together as the MRCM quality management team. The Clinical Lead for the MRCM is Dr Riina Richardson who oversees the clinical interpretation of the laboratory's activities. The routine diagnostic activities of the laboratory are performed by eight Mycology Technologists, two Medical Laboratory Assistants, and supported by two clerical officers. A molecular mycology diagnostic and research team is lead by Dr Lily Novak-Frazer. The total workload is approximately 13,000 specimens per annum, resulting in approximately 26,000 tests per year.

Up until 2017, the MRCM was part of the Manchester Medical Microbiology Partnership (MMMP) which included Microbiology services at Wythenshawe Hospital and Manchester Royal Infirmary (the majority of services being provided by Public Health England). MMMP (including MRCM) had an Initial Assessment to ISO 15189 in 2015. Issues related to legal entity were raised and MRCM was disenfranchised from MMMP in 2017 and a separate application for ISO accreditation was made in October 2017. The MRCM was inspected by UKAS in May 2018 and granted ISO 15189 accreditation for scope in September 2018. The full scope of the MRCM's portfolio can be found here: www.ukas.com/wp-content/uploads/schedule_uploads/00007/10196%20Medical%20Single.pdf

This portfolio includes: two new investigations that benefit, in particular, NAC patients:

- Identification of triazole resistance in *Aspergillus fumigatus* by pyrosequencing using DNA extracted from sputum, bronchoalveolar lavage and bronchial washing determined by identifying polymorphisms in the gene cyp51A using the Qiagen Pyromark system, and validated by fungal culture data.
- Identification triazole resistance in *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus niger* by Sanger sequencing, the DNA sequence reads provided by Eurofins Genomics GmbH for analysis by MRCM staff to detect polymorphisms in the gene

4.2 Role and Functions

The key aims and objectives of the MRCM are to provide and maintain:

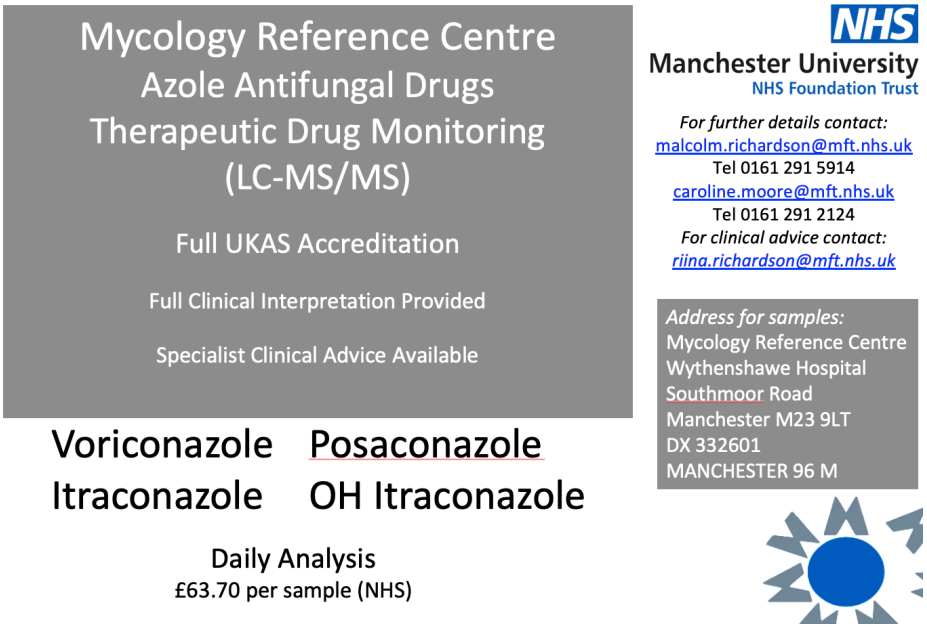
- An exemplary NHS reference mycology service for the UK and beyond,
- International, national and local leadership in medical mycology diagnostic services, and training,

- A service, which is comprehensive, interpretative, accredited and appropriate to user needs, and supports antifungal stewardship.
- Education and training for all staff, including participation on national and international courses, that is appropriate and relevant to the departmental goals,
- A safe, appropriate and comfortable working environment which is inspirational and motivating that empowers a team environment,
- To maintain UKAS ISO 15189 Accreditation,
- Maintain a research programme in-house at the MRCM in collaboration with the NAC and support others undertaking mycology research within the Manchester Fungal Infection Group, within industry, and playing an integral part in clinical trials,
- To maintain an excellent and close working relationship with Wythenshawe Hospital Infectious Diseases, NAC, microbiology, pathology and with other departments within the Trust, and colleagues in other hospitals and Universities.

4.3 Workload, review and testing developments

Approximately 50% of the MRCM workload is sent from the NAC and Infectious Diseases (Wythenshawe Hospital) clinics and wards. In consultation with clinical colleagues, the MRCM reviews its scope of work and responds to demands for new diagnostic tests and procedures. A particular forum for reviewing the diagnostic procedures and clinical relevance is the weekly Infectious Diseases/National Aspergillosis Centre/OPAT MDT. Analytical issues are also discussed at the fortnightly Wythenshawe Hospital Microbiology Action Group meetings and the monthly Infectious Diseases Speciality meetings. The scope of the tests carried out and sample requirements are detailed in the MFT-Wythenshawe Hospital Pathology Handbook: https://mft.nhs.uk/wythenshawe/services/pathology/. The Pathology Handbook is regularly reviewed. All of these reviews and document revisions lead to improvement and patient benefit.

In collaboration with the MFT Department of Biochemistry a business case was submitted to MFT. A successful outcome of this application enables us to provide a nationwide antifungal therapeutic drug monitoring service using LC-MS/MS. See Figure 3 below:



The MRCM continues to monitor indoor environments (dwellings, schools, workplaces and hospitals) for pathogenic and allergenic moulds and will in due course apply for UKAS/ISO accreditation for this activity.

4.4 Turnaround times - published and % achieved

Turnaround times for results are continually monitored:

- Yeast ID: phenotypic 2-5 days, molecular sequencing 14 days, **achieved 71.8% of yeast ID reported in 5 days or less**
- Mould ID: phenotypic 2-7 days, molecular sequencing 14 days, **not determined**
- Yeast sensitivity testing: 1-5 days, **achieved 90%**
- Mould sensitivity testing: 3-7 days, **achieved 95.8%** [This is the figure for ≤7 days. Many results are reported in 2 days, many isolates from NAC patients grow slowly]
- Cryptococcus antigen: same day, **achieved 94.8%**
- *Aspergillus* galactomannan: 2 days, **achieved 99.9%**
- 1-3-β-D-glucan: 3 days, **achieved 99.8%**
- *Aspergillus* PCR: 7 days, **achieved 97.6%**
- DNA extraction and molecular sequencing: 14 days, **not determined**
- Flucytosine levels: 1 day, **achieved 91.7%**
- Azole levels: 1-2 days, **achieved 78.4%**

4.4.1 Royal College of Pathologists KPIs

- Diagnostic advice available 08.00 to 22.00 (phone/email)
- Clinical advice available 24/7/52 (phone/email)
- 100% of critical results reported within one hour:

The objective of the critical results communication KPI is to have a rate of 100% of all critical results communicated appropriately within one hour of the result becoming available. Table 2 shows a summary of critical results communication performance.

Table 2: Critical results reporting performance

	2018									2019		
Critical result (report in ≤60 mins)	**April**	**May**	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**
***Aspergillus* galactomannan (target 100%)**									100%			95%
Beta glucan (target 100%)									97.8%			89%
Cryptococcal antigen (target 100%)									40%			100%
Flucytosine drug levels (target 100%)									No tests performed			No tests performed

4.5 User engagement

User engagement activities provided by us in 2018/19 include:

- Training provided by laboratory staff to NAC nurses (as and when requested) to give them a better understanding of the tests performed on the samples they send us and the laboratory's role in the diagnostic process.
- Full week of training proved by laboratory and clinical staff to clinical microbiologist from Leeds (21-25 January 2019).
- Laboratory staff attend weekly MDT meetings where any issues can be raised/requests made by clinicians.
- MRCM represented at monthly infectious diseases speciality meeting which also includes NAC and OPAT. Laboratory issues are included on the agenda.
- User survey distributed in April 2018 for which few returns were received.
- Full week of training proved by laboratory and clinical staff to Paediatric Infectious Diseases Consultant from Wolverhampton (January/February 2019).

4.6 Reviews by external organisations

4.6.1 UKAS ISO/IEC 15189:2012 - Medical Laboratories inspection 1st-3rd May 2018

"Executive Summary and Recommendation:

This is the Initial Assessment for the Mycology Reference Centre Manchester (MRCM). Up until 2017, the laboratory was part of the Manchester Medical Microbiology Partnership (MMMP) which included Microbiology services at Wythenshawe Hospital and Manchester Royal Infirmary. MMMP (including MRCM) had an Initial Assessment to ISO 15189 in 2015. Issues related to legal entity were raised and MRCM split from MMMP in 2017 and a separate application for accreditation was made. Although this is an Initial Assessment for

MRCM, the outcomes of the clinical advisory service assessment for MMMP which relate to MRCM have been considered and included in this assessment.

Key Strengths:
- Competent and knowledgeable staff
- Well established document control system
- Excellent examination procedures
- International profile and recognition
- Continual improvement culture

Key Areas for Improvement
- Internal audit schedule and plan
- Traceability of calibrations

QA procedures (EQA and IQC) are extremely robust ensuring the attainment of the intended quality of results, there is continuous review of all quality control processes. Documentation provided gives confidence that assays are validated appropriately supported by well documented SOPs. Reagents and consumables are very well managed, there are regular checks throughout their use in routine testing. Quality system undergoes regular review and improvement action is evident as a result of on-going review. The assessment team were confident regarding the competence of the clinical and laboratory service.

Recommendation:
It is recommended that accreditation to ISO 15189:2012 is offered for the scope of testing defined in AC6 document received on 5/4/18. This is conditional on the following:
- Submission of evidence to clear the 21 findings by 3/8/18
- Satisfactory clearance of mandatory findings
- Approval of an independent UKAS decision maker."

All findings were satisfactorily cleared and UKAS granted ISO 15189 accreditation for scope in September 2018 (UKAS Medical 10196).

4.6.2 Participation in inter-laboratory comparison programmes

MRCM currently participates in the following EQA schemes:
- UK NEQAS for Antifungal assays (Flucytosine)
- UK NEQAS Antibody to fungal and related antigens (*Aspergillus fumigatus* precipitins)
- UK NEQAS for Antifungal susceptibility
- UK NEQAS for Mycology
- UK NEQAS for Fungal biomarkers (Galactomannan)
- UK NEQAS for Cryptococcal antigen detection
- QCMD Immunocompromised and associated diseases (*Aspergillus* PCR)

4.7 Audit, Research and Development

4.7.1 Clinical audits linked to MRCM

Table 3 shows a summary of clinical audits started, completed or published in 2018/19:

Table 3: MRCM clinical audits

Audit title	Date started	Date completed	Date presented to the team	Published	Action
Audit of safety of posaconazole tablet use in CPA clinics	June 2017	August 2018	April 2018	Journal of Antimicrobial Chemotherapy 2019	Team aware that a lower dose of posaconazole may be better tolerated
Audit of beta glucan in antifungal stewardship	May 2014	August 2016	Presented at the regional meeting in October 2017	Journal of Antimicrobial Chemotherapy 2018	Continue monitoring the use of BDG test (overuse, actions on results), no other actions required at this point
Audit on Respiratory input on ABPA and SAFS patients	November 2018	February 2019	Will be presented in May 2019		Remind the team of the need to record this in the notes
European audit of candidaemia management (Wythenshawe coordinating centre)	July 2018	In progress, due to complete end of June 2019			

Other audits with significant clinical input described in section 5.

4.7.2 Support of clinical trials

• Ongoing experience regarding sensitivity testing on *Aspergillus* isolates to include terbinafine, micafungin and new antifungals: isavuconazole, Ibrexafungerp, PC786 and Pulmatrix PUR1900.

• Provision of mycology services to national and international pharmaceutical companies who are developing new antifungal drugs: isavuconazole, Ibrexafungerp, PC786 and Pulmatrix PUR1900.

4.7.3 Recent research activities:

The MRCM is host to three University of Manchester PhD students and one MD student, as well as Medical Research Council funded researchers. Research themes include:

- Molecular analysis of settled dust from homes of CPA patients
- Effect of antifungal drugs on mixed fungal – bacterial biofilms
- Lateral flow technology for detection of fungal antibodies and antigens
- Aspergillus exposure in cystic fibrosis patients

4.8 Representation on national and international committees:

- UK Clinical Mycology Network: reference laboratory designation
- RCPath Microbiology SAC (Dr Riina Richardson)
- External Examiner, Royal College of Pathologists (Prof Malcolm Richardson)
- ISHAM: Professor Malcolm Richardson as immediate Past-President
- UK Institute of Buildings and Health: Malcolm Richardson as President
- PHE/NHS: Standards Unit. Microbiology Services (Dr Riina Richardson)
- EUCAST: European Union Committee for Antimicrobial Susceptibility Tests (Dr Caroline Moore)

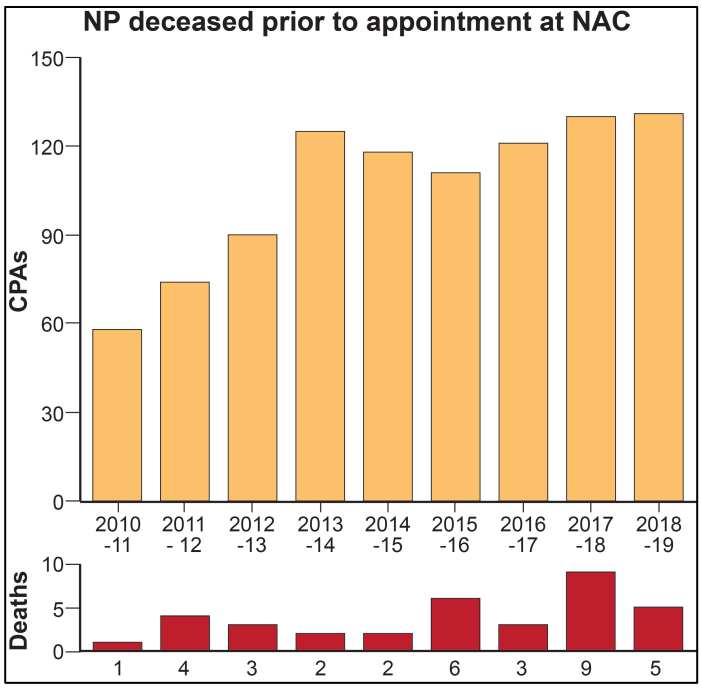
- UK NEQAS: Testing laboratory for microbiology/mycology identification and susceptibility schemes (Dr Caroline Moore)
- EUCAST: UK participating laboratory: Antifungal Fungal Susuceptibility Testing (Dr Caroline Moore)
- British Society for Antimicrobial Chemotherapy grants committee (Dr Riina Richardson)
- European Fungal PCR Initiative (FPCRI): UK test centre for Aspergillus, Candida, Pneumocystis, Mucorales and tissue (MRCM represented by Dr Riina Richardson and Dr Lily Novak-Frazer)
- ESPAUR: Public Health England surveillance programme for antimicrobial utilisation and resistance (Dr Caroline Moore, Prof Malcolm Richardson, Dr Riina Richardson). Their latest report here.
- BSMM: British Society for Medical Mycology Executive Committee (Dr Caroline Moore)
- ESCMID: European Society for Clinical Microbiology and Infectious Diseases Guidelines Group (Prof Richardson as co-author of Aspergillus, Candida, Mucorales, and rare moulds guidelines); and Candidosis, and Rare Yeasts diagnostic and treatment guidelines (Dr Riina Richardson)
- BASHH: British Society for Sexual Health: Candida vaginitis guidelines writing group (Dr Riina Richardson)
- Royal College of Paediatrics and Child Health (RCPCH): Working Group: Effects of Indoor Air Quality on Children and Young People's Health (Prof Malcolm Richardson as Member)

5 Clinical audits

5.1 Time to appointment and shared care

Among new referrals with a presumptive diagnosis of chronic pulmonary aspergillosis, the mean time from referral to being seen was 8 weeks (Appendix 2). There were 12 patients who rescheduled their appointments or were too unwell to attend and these patients had long wait times of 4-6 months (Appendix 2).

Figure 4: total CPA referrals seen and the number referred but not seen because of early death.



In the previous year, we had 9 patients who died after referral but before being seen. This number dropped to 5 for this reporting year. These patients are of great concern to NAC and have been the subject of a comprehensive audit to identify clinical characteristcs predictive of rapid death. Patients who die within the first 12 months of being seen at NAC are also included in the audit question.

5.2 Mortality audits

In 2017 the NAC instituted a monthly mortality review to carefully review the cause of death of patients not expected to die when they did. One of the consultants carefully reviews the notes to ascertain all the key facts and events leading up to the patient's death and this, together with a brief literature summary of the particular problem, is presented to the whole team for discussion and learning. All these mortality events are minuted.

5.3 Clinical and diagnostic audits

The following audits were undertaken in 2018/19:

Profiling Aspergillus fumigatus cyp51A polymorphisms by pyrosequencing reveals triazole resistance when susceptibility testing is not possible

Lily Novak-Frazer, Darin Hassan, Samuel Hill, Rikesh Masania, David W. Denning, Caroline Moore, Riina Rautemaa-Richardson, Malcolm Richardson

Background: The National Aspergillosis Centre (Manchester, UK) supports patients with chronic pulmonary and allergic bronchopulmonary aspergillosis. Many demonstrate culture-positive Aspergillus fumigatus using the high volume culture (HVC) procedure developed by our laboratory which improves fungal growth from respiratory samples thus allowing EUCAST susceptibility testing. However, culture positivity remains low (25-42%) even when elevated qPCR for Aspergillus spp. is demonstrated. Thus, there is a need to detect potential resistance markers directly in these PCR products. The mechanism of triazole-resistance is mainly attributable to acquired polymorphisms in 14-α-demethylase (cyp51A). We therefore developed a pyrosequencing assay to detect polymorphisms in cyp51A to ameliorate the detection of resistance.
Materials/methods: Patients who maintained therapeutic antifungal drug levels but whose samples were Aspergillus spp. qPCR-positive with negative or no HVC results were identified as potentially failing therapy. Their sputum or bronchoalveolar lavage (BAL) samples, already assayed for presence of Aspergillus spp. rDNA, underwent nested PCR amplification of A. fumigatus cyp51A to yield biotinylated products for subsequent pyrosequencing using the Qiagen Advanced PyroMark system. Positions G54, L98, Y121, P216-F219-M220 and T289 were included as well as possible insertions in the promoter region of cyp51A. Results were confirmed by Sanger sequencing.
Results: Seventy-one patient samples were analysed from March-November 2017. Of these there was insufficient specimen for HVC in 26 (37%) samples, 32 (45%) were culture negative and 13 (18%) yielded A. fumigatus. Of the culture-negative and insufficient specimens, 20 (34%) had cyp51A polymorphisms and 28 (48%) had none, while 10 (17%) failed to be amplified. We detected two samples with TR34 and/or L98H, potentially conferring pan-azole resistance, five with G54 (E, R or V) denoting possible itraconazole and posaconazole resistance, and thirteen with Y121F/T289A polymorphisms likely causing voriconazole resistance, the latter without the accompanying TR46 insertion. In HVC-positive samples, pyrosequencing results agreed with susceptibilities only half of the time, possibly due to amplification insensitivity, PCR inhibition or resistance due to non-cyp51A polymorphisms.
Conclusions: Pyrosequencing identified A. fumigatus cyp51A sequence information in 83% of patient samples when culture failed, including potential resistance markers. Resistance profiling is being assessed for its impact on improving patient care.

Diversity of fungi in sputum samples from patients with chronic pulmonary aspergillosis and allergic bronchopulmonary aspergillosis

Alanah Proctor, Lily Novak-Frazer, Caroline Moore, Rikesh Masania, Ellen Hopwood, Riina Richardson, Malcolm Richardson

Background: The National Aspergillosis Centre (NAC) in Manchester has the largest cohort of patients with Chronic Pulmonary Aspergillosis (CPA) and allergic bronchopulmonary Aspergillosis (ABPA) in the UK. Sputum culture is a routine part of monitoring these patients. NAC is located within Wythenshawe Hospital which has a large respiratory department. In 2015, the Mycology Reference Centre Manchester (MRCM) switched to performing high-volume culture (HVC) for sputa as the *Aspergillus* recovery rate was found to be significantly higher compared to conventional culture. *Aspergillus fumigatus* is the most common mould identified by HVC but several other species have also been isolated and identified. Detection of non- *Aspergillus* species may be clinically important in patients with difficult to control disease and symptoms. On the other hand, co-infection with azole susceptible non- *Aspergillus* species and azole-resistant *Aspergillus* isolates can explain the partial clinical benefit of azole treatment in these patients.

Materials/methods: We reviewed the MRCM database of HVC results from December 2015 to November 2017 for non-*Aspergillus* isolates identified by sequencing, and correlated these against patient records for determination of clinical relevance.

Results: Seventeen non-*Aspergillus* isolates from 17 patients had been identified. This corresponds to 2% of the mould isolates identified by sequencing at the MRCM over the audit period. The underlying conditions in this cohort were a mixture of CPA (7), ABPA (2) and other clinical entities (10) including bronchiectasis, cough hypersensitivity, severe asthma and immunosuppression secondary to chemotherapy. Thirteen different fungal species were identified, with the most common being *Penicillium* and *Talaromyces* species. *Talaromyces columbinus* was identified in four samples and was the most common organism seen.

Conclusions: Although rare, a spectrum of non-*Aspergillus* moulds had been identified. The clinical relevance of these findings is unknown but it is well recognised that many environmental moulds can provoke an allergic response and exacerbate asthma. The use of HVC increases the detection of moulds and allows for susceptibility testing providing more information for clinicians making clinical decisions in difficult to manage patient populations.

***Aspergillus fumigatus* strains are adapted to the lung environment in a case of chronic pulmonary aspergillosis**

Gago S, Khateb A, Soto-Debran JC, Caroline Moore, Denning DW, Bowyer P

Objectives: The increasing global burden of chronic pulmonary aspergillosis (CPA) is a health concern. CPA is associated with greater morbidity and mortality than invasive aspergillosis. Moreover, because of the frequency of relapse, anti-fungal treatment is often long-term leading to negative side effects and the development of resistance. The aim of this study was to investigate in host adaptation of *Aspergillus fumigatus* in CPA.

Methods: Thirty *Aspergillus fumigatus* isolates were recovered from a CPA patient from 2008-2014. Whole genome sequencing was performed for 15 of the isolates to identify phylogenetic association between strains over time. An in vitro model using alveolar epithelial cells (A549) was used to describe fluctuations in the response of the lung epithelium to five of the *A. fumigatus* isolates recovered from the CPA patient compared to 3 *A. fumigatus* wild type strains (A1163, ATCC 90240 and ATCC 4664). A549 alveolar epithelial cells were exposed for 24 h to each of the strains and differences in epithelial cell detachment, fungal burdens and cytokine production (IL-8 and IFNγ) were evaluated. GraphPad Prism was used to interpret data and p values were calculated through One-way ANOVA test.

Results: *A.s fumigatus* strains isolated from the CPA patients were grouped into a common clade, although there was genetic variability within strains. Epithelial cell desquamation of A549 cells exposed to the *A. fumigatus*-CPA strains was 20 % higher than controls ($P < 0.0001$). In accordance with that observation, fungal burdens were 5-10 times higher in A549 cells challenged with *A. fumigatus* CPA strains than controls ($P < 0.05$). Moreover, IL-8 and IFNγ concentrations in cell supernatants from A549 cells challenged with *A. fumigatus*- CPA strains were lower than in those challenged with *A. fumigatus* control strains ($P < 0.01$).
Conclusions: *Aspergillus fumigatus* strains involved in a single case of CPA are phylogenetically associated. These strains were able to produce a higher percentage of epithelial cell damage than *A. fumigatus* strains used as controls. Therefore decreasing the ability of the epithelium to function as a physical barrier and, facilitating *A. fumigatus* growth and limiting the immune host response. Further research is needed to characterise the virulence properties of these strains.

Improved serological diagnosis of Chronic Pulmonary Aspergillosis in ImmunoCAP IgG negative patients using LD Bio Aspergillus ICT lateral flow assay
Elizabeth Hunter, bayu Wilopo, Malcolm D. Richardson, David W. Denning

Background: Prevalence of chronic pulmonary aspergillosis (CPA) is estimated at about 3 million cases worldwide. Serological detection of *Aspergillus*-specific IgG is a critical component in the diagnosis of CPA. In some cases however, false negative results by ImmunoCAP enzyme immunoassay (EIA) can make serological diagnosis of CPA difficult and requires increased diagnostic sensitivity. This study assessed the performance of two commercial assays to diagnose CPA in this specific patient population.
Materials/methods: Twenty-one (21) cases of clinically confirmed CPA were selected, for which the routine serological assay (ImmunoCAP, ThermoFisher) for *Aspergillus* IgG gave a consistently negative result over 1-3 years of patient assessment (≤ 50 mgA/L). *Aspergillus* IgG antibodies in patient sera were detected by lateral flow assay (*Aspergillus* ICT, LD Bio Diagnostics, France) or western blot assay (LD Bio Diagnostics, France), and compared to the routine diagnostic test – ImmunoCAP enzyme immunoassay (EIA) – used at the Mycology Reference Centre (Manchester).
Results: We determined sensitivities of 81.0% and 90.5% respectively for LD Bio western blot and LD Bio *Aspergillus* ICT, respectively, in serum samples from patients who have been assessed as negative for CPA by ImmunoCAP EIA (sensitivity = 0.0%). We also compared results from the Bordier Affinity Products ELISA for *Aspergillus* IgG and Microgen precipitin assay in a subset of this cohort and found poor sensitivities for these tests as well.
Conclusions: In select cases of CPA where ImmunoCAP EIA consistently fails to provide an accurate serological diagnosis, LD Bio Aspergillus ICT and western blot show greatly improved sensitivity and ability to detect *Aspergillus*-specific IgG in patient sera. Comparing these two assays, the LD Bio Aspergillus ICT outperforms the western blot, exhibiting increased sensitivity. The Aspergillus ICT appears to be a useful tool in the diagnosis of CPA where routine assays fail to detect *Aspergillus* antibodies and provide a false negative result.

	LD Bio		Bordier	Microgen
	WB	ICT	ELISA	Precipitins
Positive	17	19	8	1
Negative	4	2	9	12
Tested	21	21	17	13
Sensitivity	81.0%	90.5%	47.1%	7.7%
95% CI	62.6 - 95.3%	66.4 - 97.2%	24.5 - 71.1%	0.2 - 32.0%

Posaconazole tablet therapeutic drug monitoring in patients with chronic pulmonary aspergillosis

I. Rodriguez-Goncer, C. Kosmidis, R. Richardson, C.B Moore, M.D Richardson, D.W Denning

Objectives: Posaconazole tablet offers better bioavailability than liquid suspension with a favorable side effect profile. Most data are derived from immunocompromised populations, with little experience in immunocompetent hosts such as those with chronic pulmonary aspergillosis (CPA). Due to variability in absorption, Therapeutic Drug Monitoring (TDM) is recommended for the posaconazole suspension, but less is known about its role for patients on posaconazole tablets. Our aim was to explore pharmacokinetics and side effect profile in a cohort of patients with CPA.
Methods: Patients with CPA started on posaconazole tablet from February 2014 to October 2015 were retrospectively analysed. Recorded data included demographics, levels obtained by TDM, prescribed dose, adverse events (AE) attributed to posaconazole by the clinician, and grade according to the Common Terminology Criteria for Adverse Events. The possible correlation of posaconazole levels with demographics, prescribed dose and frequency and severity of AE was analysed. TDM was performed with bioassay; a random level of >1 mg/L was considered therapeutic.
Results: Seventy-two patients received posaconazole tablets. All patients had previously received other azoles, but no patient was on additional antifungal therapy during posaconazole use. Fifty (69%) were male and mean age was 48.5 (SD 12.0). Sixty-one were started on 300mg daily and 11 were started on 200mg daily. Dose adjustments were made in 31 (43%) of patients. Forty-nine (68%) patients developed side effects from posaconazole: 9 (12%) Grade 1, 22 (30%) Grade 2, 17 (23%) Grade 3 and 1 (<0.1%) Grade 4. Seven (9.7%) patients had liver function test (LFT) abnormalities; 5 (6%) Grade 1 and 2 (2%) Grade 2. Most frequent side effects attributed to posaconazole were fatigue (37%), breathlessness (18%), nausea (12%), headache (8%), peripheral neuropathy (8%), diarrhea (6%), chest pain (6%), dizziness (5%), arthralgia (5%), dry skin (4%), hyponatremia (4%) and hair loss (2%). Side effects were present in 115/196 (58.7%) occasions in patients on 300mg and 45/115 (39.1%) in patients on 200mg a day, (p, <0.01). 58 (80%) patients had TDM performed, whereas in 14 patients (19%) posaconazole was stopped due to side effects before a TDM could be sent. A total of 383 measurements (mean of 5.3 per patient, range 0-15) were recorded. Mean posaconazole level was 1.94, (range 0.1-6.4). For patients on 300mg, mean level was 2.13 (SD 1.13), for patients on 200mg, mean was 1.95 (SD 0.84) and for patients on 100mg, mean level was 1.08 (SD 0.32). The proportion of samples with a subtherapeutic level were 19/189 (10%) for patients on 300mg, 11/114 (10%) for those on 200mg, and 15/43 (34.9%) for those on 100mg. Mean level was 1.81 (SD 0.96) for patients reporting no side effects, and 1.90 (SD 1.11) for those reporting side effects (P, 0.42). The mean levels in patients with LFT elevation were 2.48 (SD 3.9).
Conclusion: A dose of 200mg achieved adequate serum posaconazole levels and was better tolerated than the 300mg daily dose in patients with CPA. Sixty-eight percent of patients developed side effects but they were not significantly associated with higher serum posaconazole levels.

Interferon gamma salvage treatment in chronic pulmonary aspergillosis: impact on infectious exacerbations and hospital admissions

Edward Monk, Chris Kosmidis, Chris Harris, Rainer Doffinger, Gemma Hayes, David Denning

Background: Chronic pulmonary aspergillosis (CPA) is characterised by persistent *Aspergillus* infection, often complicated by recurrent bacterial superinfection. The exact immune deficits in CPA are not characterised but poor production of interferon gamma (IFNγ) is common. The immune response to fungal infection has been shown to employ

IFNγ and thus supplemental subcutaneous replacement may confer therapeutic benefit as salvage therapy in CPA patients with impaired IFNγ production.
Materials/methods: Retrospective analysis of patients prescribed IFNγ as salvage therapy for CPA refractory to antifungals was conducted. The rates of lower respiratory tract infection (LRTI) and hospital admission within the 12 months before and after IFNγ therapy initiation were compared (Wilcoxon matched-pairs signed-rank test).
Results: Forty-one patients received IFNγ; 36 were available for follow-up. Twenty patients received IFNγ for >12 months, eight stopped treatment due to early side effects (<6 months) and eight died within 12 months of initiating treatment. Of the 20 patients receiving IFNγ >12 months, nine were female. The median age was 58.5 years (IQR 53-65 years). Pre-existing comorbid respiratory disease was common (bronchiectasis 30%, COPD 25%, previous pneumothorax 20%, fibrosis secondary to connective tissue disease 20% and previous tuberculosis 15%). Eight of the 20 patients had a significant smoking history and three were active smokers. Fifteen (75%) were on concomitant antifungal therapy and five (25%) were on long-term azithromycin. Of the 19 patients investigated by cytokine assay, 17 (89%) had significantly reduced production of IFNγ. Reduction in IL-17 (58%), IL-12 (32%), TNFα (16%), IL-6 (5%) and IL-10 (5%) were observed less commonly. In those treated for >12 months, the mean number of LRTIs requiring antimicrobials reduced from 3.1 to 1.4 episodes/year (p=0.006). A significant reduction in the mean number of hospital admissions/year was also observed (0.8 to 0.3, p=0.04). No significant changes were seen in individuals treated with IFNγ for <6 months.
Conclusions: In CPA refractory to antifungals alone, 12 months of salvage IFNγ therapy significantly reduced the frequency of LRTI requiring antimicrobial therapy and hospital admission. Almost all patients had impaired IFNγ production. Prospective data are needed to further evaluate the role of IFNγ as adjunctive therapy in CPA.

6 Patient and public engagement

The NAC has administered a patient survey annually each year in Q1. Some questions are retained each year, others vary.

6.1 Patients survey 2019

The survey was run over 4 weeks from Feb to March 2019. All questionnaires were completed in Friday clinic. 86 questionnaires were completed, which is a little more than half the number who completed it in 2018. Up to 2018 we asked a question about waiting times and identified a problem for doctors & pharmacy. We did not ask the question this year so we cannot tell if this problem has eased or not.

Summary of main points

Level of service quality remains excellent, but there are a few pointers to improvements needed

- We did not ask the question about waiting times in clinic this year
- Big fall in contacting patients between visits, 49% in 2017 down to 31% in 2019.
- Big drop in patients visiting the patients website (46% 2017 - 18% 2019) This figure preceded the launch of the new website for patients at https://aspergillosis.org/
- Drop in attendance of those surveyed at the patients' meeting from 10% 2018 to 0% 2019. We need to ask encourage greater attendance.
- Drop in awareness of patient led regional meetings (46% 2018 to 30% 2019)

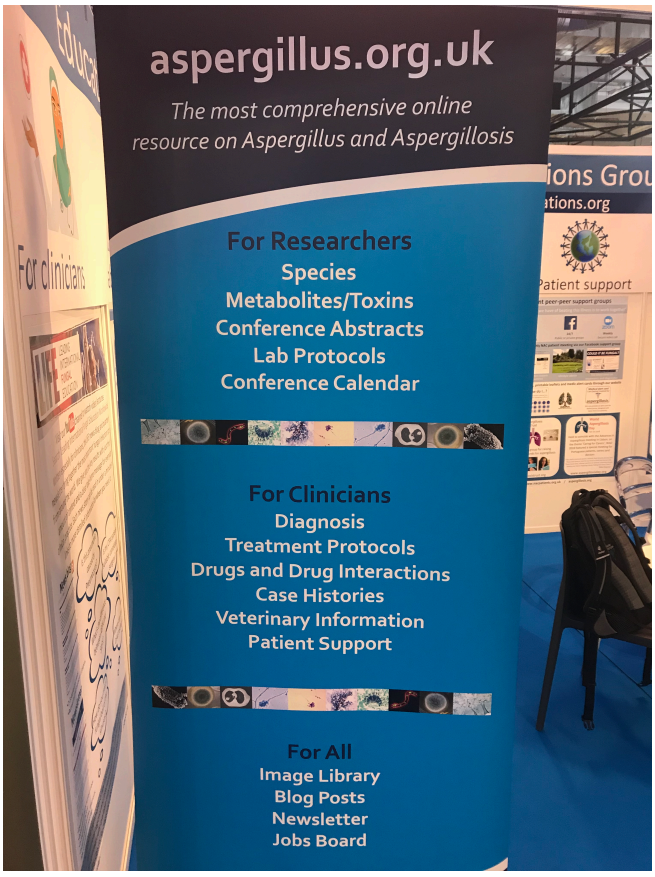
6.2 Community booklet

A community booklet is produced and 1000 per year were distributed to all patients who do not have access to a computer, informally at clinic. This allows readers to know what is happening in the service and with other patients and carers. It includes news items, why and how to use facemasks, coping with stress, medicine advice details and seasonal advice eg. allergies. It also provides contact numbers or website addresses for groups that offer social support.

6.3 The Aspergillus Website @ www.aspergillus.org.uk

The Aspergillus Website remains the world's most comprehensive resource for the pathogenic and allergenic fungi Aspergillus and the diseases that they cause. It is completely free to all users. It is supported from the UK National Health Service and unrestricted educational grants from various corporate donors, notably Mayne Pharma, Pfizer, Dynamiker, Gilead and Zambon. The Aspergillus Website provides simple, free access to >74,000 pages all indexed in Google, ready to be searched, over 13,300 scientific articles (including a unique collection of 831 historical articles) and ~15,900 conference abstracts from 1974 onwards. The comprehensive list of drugs and drug interactions with antifungals is continually updated. The drug interaction database (including the antifungal drug interaction app for apple and android phones) is popular and well used. This database is also available as an 'App' via iPhone and Android smartphones to allows ease of access and use, both are updated regularly. Nearly 2,300 potentially harmful interactions are listed. Over 3,300 (Android) and 501 (iOS) APPs have been downloaded. Externally there are over 23,000 active links to www.aspergillus.org.uk and www.aspergillosis.org.

The Aspergillus Website (Figure 5) is listed at number 1, 1, 2 and 3 in Google.co.uk, number 1, 1, 2 and 3 in Google.com, number 1, 1, 4, 3 in Bing and Yahoo! for 'aspergillus', 'ABPA' 'aspergillosis' and 'aspergilloma' respectively. Searching Twitter for 'aspergillus' ranks our twitter page at number 1. Searching Facebook for 'aspergillus' or 'aspergillosis' lists our 40 groups and pages as (by far) the major content on the platform, Our largest group Aspergillosis Support has 1724 members which has grown at the rate of 10 members per week throughout 2019 and activity on that group alone is in excess of 13,000 events in 2019. If 'aspergillus' is

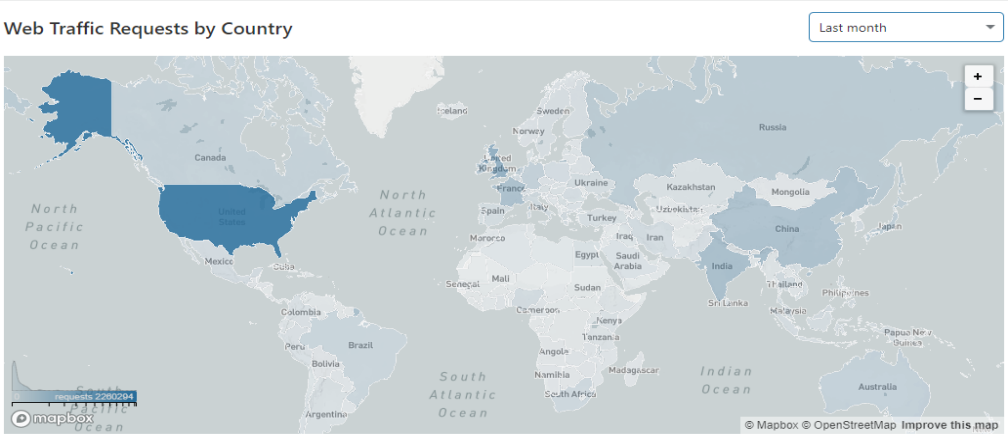


searched in Google, there are 11.5 million results.

Current monthly figures show that 100,000 - 130,000 individual computers accessed The Aspergillus Website and Patients' website alone per month, 5,000 to 8,000 people daily. This equates to 8.5 million 'requests for content'. Smaller devices (smartphones and tablets) continue to rise as a proportion of all devices used to access our websites, patients in particular preferring to use them 65% of the time reflecting changes in how we browse the internet. Overall usage of the Aspergillus Website's seems to have levelled out over the last twelve months, but the Patients Website has been completely refreshed this year and that resulted in a short term drop in viewing figures in early 2019 which may account for some of the lack of increase.

Mapping of www.aspergillus.org.uk (see figure below for 2019 figures, darker shading = more users) shows that The Website reaches people in over 147 countries. USA is the country from which we get most visits with UK and India in the next 2 places, France and China in 4th & 5th place respectively.

Figure 6: Country usage of the Aspergillus Website in early 2019.



Top Traffic Countries / Regions
Last month

Country / Region	Traffic
United States	2,260,294
United Kingdom	610,803
India	329,256
France	294,783
China	284,897

Over 54% of users access the Aspergillus Website using iPhone of iPad, 10% use an Android phone and only 36% use a laptop or personal computer. Twitter posts are put out almost every day (@AspergillusWeb – 1,350 followers), Blogs twice a week, and monthly newsletters from the Aspergillus Website are sent out to over 27,000 (free) subscribers. This figure is driven by newly registered members seeking to access our secure 'articles'.

6.4 Website for patients and carers *(aspergillosis.org)*

The Patients Website has had a complete refresh in 2019 which includes moving it to a new domain name aspergillosis.org. We felt that the old domain name

(nacpatients.org.uk) was rather exclusive as most users were no longer patients of NAC and aspergillosis.org was also more easily found via Google if a patient was to search for more information. Megan Bridgeland, here as a student for a year adopted this website as her project and as part of her studies has converted this website to act as the centre of a community rather than a static information resource. This was important as our communities has expanded enormously since the old website was built in 2012.

Since the changeover the domain name does not register in the top page of Google searches so as yet is not being as intensively used as the old website. The old website had declined in use over the last 5 years as most activity switched to Facebook. Despite these limitations use is gradually increasing and in June 2019 attracted 1800 unique visitors who looked at 4300 pages. The top countries utilising the Patients' Website by origin are: 1. UK, 2. USA, 3. Australia, 4. India, 5. Russia. There are >400 active links to this website.

The provision of live and recorded online events held by the National Aspergillosis Centre, happening on a monthly basis are now hosted within the Facebook communities and generally get >500 viewers each month.

6.5 Patients & carers support meetings

This monthly meeting aims to give support to all who attend the NAC clinics. This allows people who do not have computer access to find informal support from NAC staff and encourages face to face social support between patients & carers. The meeting is attended by 8 – 15 people each month. The meetings are led and organised by Dr Graham Atherton with assistance from Chris Harris and Helen Findon.

The subjects covered are available at https://aspergillosis.org/monthly-patient-carer-support-meeting-recordings/ and include

- MFT Specialist Physio Mairead Hughes on Stress Incontinence and Pelvic Health
- Graham Atherton on Health Hazards caused by Vaping
- Georgia Taylor (MFT) on Air Pollution and Sustainability
- Sara Gago (University of Manchester) on genetics and aspergillosis
- Helen Findon on Rare Disease UK
- Beth Bradshaw on Medical Alert cards
- Megan Bridgeland Launch of new Patients Website

6.6 Community structure

Our online communities have been very popular since 2000 but our patient surveys indicated that up to half of our patients do not have access to a computer which denies them access to our extensive resources online. Our support community is thus a combination of online and offline meetings & resources.

The community is supported in several ways:

Online
Many patients and carers use online support discussion groups and the FIT supports these people in several ways:

- Our (Facebook) worldwide communities are very active with >3,000 participants engaging 5000 times per month (https://www.facebook.com/groups/aspergillussupport/),

- The NHS Choices (Now NHS online) online community is no longer hosted on NHS website but has over 2000 members
- Local online Facebook groups (30 groups, 11 in the UK serving 684 people)
- Facebook group specifically for carers (158 members) (https://www.facebook.com/groups/aspergillosis.carers/)
- The Professional LinkedIn members (Aspergillus and Aspergillosis Group) has over 530 members.

The provision of live and recorded online events held by the National Aspergillosis Centre, happening on a monthly basis are now hosted within the Facebook communities and generally get >500 viewers each month.
Offline

- Monthly meeting at National Aspergillosis Centre (NAC) attended by 10-20 per month. This meeting offers social support and also a series of talks on a wide variety of subjects aimed at helping patients self manage, reducing anxiety, explaining some of the tests we do at NAC and outlining encouraging research progress.
- Weekly meeting via Zoom conferencing software attended by 4 – 10 people
- 120 community booklets, written quarterly are given out per month. This publication contains seasonal advice, informative articles and artwork & recipes contributed by the patient's community. Regular meetings are held to get patient & carers opinions on how we should update the booklets.
- Monthly newsletter issued to every patient attending clinic (250 per month).
- Three information booklets have been produced which are each a collection of leaflets intended for use by either CPA, ABPA and Aspergillus bronchitis patients.
- A series of 13 information leaflets are available and handed out in clinic by clinical staff as required for new and existing patients

6.7 Public awareness

Promoting awareness of aspergillosis and the National Aspergillosis Centre is particularly important as we suspect that many thousands of people remain undiagnosed. This results in people not being appropriately treated and the national statistics for serious fungal disease remain low in the UK and abroad. Consequently government health & research funding is low. Improving awareness helps make far more people in the UK aware of aspergillosis and the National Aspergillosis Centre, improving the chances that more cases of aspergillosis will be looked for and found.

This year we have taken our lead on where our efforts ore most needed from the comments and discussions made by people in our patients groups.

- Patients are incorrectly diagnosed or not diagnosed at all for an average of 5 years. We are attempting to get support to produce elearning for non-specialist clinicians to address this need.
- The British Lung Foundation have asked us to re-write their information on aspergillosis, intended for patients and carers with a wide variety of lung diseases, some of which may be masking a form of aspergillosis.
- Patients are increasingly finding it difficult to manage the demands aspergillosis makes on their health and time, partly because of the lack of awareness in clinical staff worldwide and partly due to having to coordinate the advice of multiple specialists when they have conditions that require them to see multiple doctors (avarege of over 20 for a rare condition) and take a complicated array of medication. We are supporting Rare Disease UK and Genetic Alliance UK in their work to support people

by lobbying for the provision of care coordinators by UK NHS for aspergillosis patients.

We have designed and produced a Medical Alert card for aspergillosis patients which is intended to support a patient or carer who is in crisis and needs help quickly. Patients also seem to appreciate how it helps to validate their illness with people who do not know what aspergillosis is, and helps them with the many complicated drug names when they are being asked to provide information on what medication they are taking.

7 Research and key publication findings

7.1 Papers and book chapters

Amongst the 71 papers and book chapters published in calendar year 2018 (see Appendix 5) (81 were published in 2018), there were several areas of direct relevance to patients with CPA and aspergillosis.
Some key findings include:

- European guidelines for the diagnosis, prophylaxis and management of all forms of chronic and invasive aspergillosis
- Recommendations for the diagnosis of CPA in low and middle income countries
- A major audit of 200 patients with CPA from the NAC and their 12 omonth outcomes
- Summary of posaconazole for CPA, given as a n-of-1 trials as per the NAC service specification
- Human genetic variant (ZNF77) allows *Aspergillus fumigatus* to colonise the airway in high numbers
- Neutrophil defects allowing ABPA to develop and
- Common occurrence of cystic fibrosis carrier status (10%) in ABPA patients.

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3. Overton NLD, Denning DW, Bowyer P. Mutations in EEA1 are associated with allergic bronchopulmonary aspergillosis and affect phagocytosis of *Aspergillus fumigatus* by human macrophages. **PLoS ONE** 2018;13: e0185706.
4. Bongomin F, Harris C, Hayes G, Kosmidis C, Denning DW. Twelve month outcomes of 206 patients with chronic pulmonary aspergillosis. PLoS One 2018;13: e0193732.
5. Page ID, Baxter C, Hennequin C, Richardson MD, van Hoeyveld E, van Toorenenbergen AW, Denning DW. Receiver operating characteristic curve analysis of four Aspergillus-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis. **Diag Microbiol Infect Dis** 2018;91:47-51.
6. Bongomin F, Batac C, Richardson MD, Denning DW. Aspergillus onychomycosis: Mycology and epidemiology. **Mycopathologia** 2018;183:485-93.
7. Bazaz R, Denning DW. Subacute invasive aspergillosis associated with Sorafenib therapy for hepatocellular carcinoma. Clin Infect Dis 2018;67:156-157.
8. Rodriguez-Goncer I, Harris C, Newton PJ, Kosmidis C, Muldoon EG, Denning DW. Assessment of posaconazole salvage therapy in chronic pulmonary aspergillosis by using predefined response criteria. **Int J Antimicrob Ag** 2018;52:258.
9. Gago S, Ben Ghazzi N, Overton NLD, Denning DW, Bowyer P. The human ZNF77 transcription factor controls *Aspergillus fumigatus* load at the bronchial epithelium. **Nat Communications** 2018;9:3835.
10. Gamaletsou MN, Hayes GE, Harris C, Muldoon EG, Brock J, Denning DW. F508del CFTR gene mutation in patients with allergic bronchopulmonary aspergillosis. **J Asthma** 2018;55:837-43.
11. Otu AA, Langridge P, Denning DW. Nebulised N-Acetylcysteine for Unresponsive Bronchial Obstruction in Allergic Brochopulmonary Aspergillosis: A Case Series and Review of The Literature. **J Fungi** 2018 Oct 15;4(4).
12. Richardson MD, Page ID. Role of serological tests in the diagnosis of mold infections. **Curr Fungal Infect Rep** 2018;12:127-136.

7.2 Key book chapters related to CPA:

1. Denning DW. Aspergillosis. Eds Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Harrison's Principles of Internal Medicine. 20th ed. McGraw-Hill, New York, 2018. Chapter 212. pp1532-1537.
2. http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-pulmonary-aspergillosis (2011-)
3. http://www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis (2011-)

7.3 New antifungals

There are 7 new antifungal agents for systemic use and 2 for inhaled use in clinical development (Rezafungin (once weekly echinocandin), SCY078 (oral glucan synthase inhibitor (similar to an echinocandin)), olorofim (an orotomide, oral and IV, novel structure and mode of action), APX001 (novel structure and mode of action, oral and IV), VT-1161 (oral broad spectrum antifungal). Since last year, VL-2397 (novel structure and mode of action, IV and focussed on invasive aspergillosis) has been abandoned and MAT2203 (an oral formulation of amphotericin B) appears to have stalled. PUR1900 (inhaled itraconazole) and PC945 (inhaled broad spectrum antifungal) are in early phase 2. The NAC is being proactive in working with industry to develop studies that could lead to the first approval of an antifungal agent for CPA (as none have been prospectively studied in phase 2 or phase 3 development to date). SCY078, PUR1900 and PC945 are in clinical study at the NAC.

7.4 Global health and CPA

In 2018, the burden of fungal diseases, including CPA, has been estimated and published for the following countries in: Italy, Norway, Romania, Serbia, Kazakhstan, Iran, Jordan, Burkina Faso, Uruguay, Colombia, Argentina, Malawi, Mozambique, Cameroon, and Malaysia. Numerous abstracts were also presented in 2018 documenting the burden of serious fungal diseases in other countries. This takes the mapping and estimation by country of these diseases to >100 countries, of which 62 are published (and 7 more submitted for publication).

8. Public awareness and educational outreach

8.1 Awareness among the public

There appears to be a little more public visibility of fungal diseases, with major press articles on *Candida auris*, azole resistance in *Aspergilllus* and numerous other stories published. The NAC is at the forefront of these attempts in the UK and internationally. Public awareness of aspergillosis is particularly important as we suspect that many thousands of people remain undiagnosed. Such people are not being appropriately treated. The NAC is assisted in public relations with an external agency to assist getting key health and educational messages out.

Our informed patients and carers are important advocates and ambassadors for the diseases and NAC. There is still much to do however.

Appendix 7 shows all Aspergillus blogs and press releases issued by the NAC. Seven press releases and 39 blogs were published in 2018-19, with very frequent regular tweets from the Aspergillus Website, MRCR, Aspergilosis Trust and LIFE.

8.3 Educational resources and outreach

The NAC has lead several important educational initiatives for health professionals (Figure 7) including the Aspergillus Website (section 6.3) (www.aspergillus.org.uk) in its 21st year in 2019; Leading International Fungal

Education (LIFE) (www.LIFE-Worldwide.org) (launched in 2012 in English and Spanish); the global advocacy foundation the Global Action Fund for Fungal Infections (GAFFI) (www.GAFFI.org), founded in 2013; a database and apps for antifungal drug interactions (www.aspergillus.org.uk/content/antifungal-drug-interactions) from 2013. In addition, 51 news items were published on LIFE for healthcare professionals: http://life-worldwide.org/media-centre/news

Working with the charity the Fungal Infection Trust the world's first online Microscopy and Histology course (www.microfungi.net), in 4 Modules has now been translated into French, Spanish and Portuguese. Translations of Module 4 were launched in February 2019. The course is approved by the Royal College of pathologists for Continuing Professional Development (CPD).

In June 2019, there are 1205 registered users in 119 countries on Microfungi.net (up from 756 in 2018), logging in up to 16 times per day and recording over 50,000 activity records per month. Users can refer to the course materials indefinitely, even if they have completed all the modules and received their certificates. 160 learners are registered to use the translated Modules. Certificates are not awarded for the introductory Module 1 but 143 have been awarded for Module 2, 175 for Module 3 and 26 for Module 4 as of June 2019, a total of 344.

Collectively these online resources provide a substantial proportion of the world's high quality educational and advocacy materials for the world in fungal diseases.

European Respirarory Society, Paris September 2018

The first ever symposium on chronic pulmonary aspergillosis was held at the world's largest respirarory meeting (European Respiratory Society) in September 2018: www.ers-education.org/events/international-congress/paris-2018.aspx?idParent=211365 This was attended by >2000 doctors. The ERS has an attendance of >20,000 overall.

THE NAC communications and patient engagement team ((Figure 8: Dr Akan Otu, Dr Graham Atherton, Mrs Chris Harris, Dr Beth Bradshaw, Ms Deborah Kennedy and Prof David Denning) took the opportunity to run a stand at the ERS, being visited by doctors from around the world. Leaflets on the NAC, drug interactions, LIFE educational resources, the Aspergillus Website, fungal microscopy amd histopathology courses, MRCM and patient support were distributed.

The topic was highlighted in an article in Le Monde by Paul Benkimoun in September 17th 2018.
https://www.lemonde.fr/sciences/article/2018/09/17/l-aspergillose-une-maladie-respiratoire-meconnue_5356323_1650684.html

British Thoracic Society, London, December 2018

Staff from the National Aspergillosis Centre (Chris Harris and Fiona Lynch) attended the British Thoracic Society Winter Meeting in London (Figure 9) to guage awareness of the NAC, the number of patients they care for with aspergillosis (all forms) and familiarity with antifungal prescribing. 102 doctors from Belfast, Scotland, Wales, South of England and North of England completed a short questionnaire. The questions were based around the service available in Manchester, drugs available, cost implications and drug monitoring.

Responses indicate that 76 (75%) did not know that high cost drugs such as voriconazole, posaconazole, isavuconazole, IV courses of amphotericin B and micafungin were all paid for if the patients were referred to the NAC. Some did not know the NAC existed. Those that did prescribe these high cost drugs had never been challenged about the cost of antifungals. Some doctors preferred to manage their own patients with this disease even though they were aware of our centre. Most doctors treated patients with ABPA and those that treated CPA only treated 1- 2 patients.

66 doctors were aware of the importance of therapeutic drug monitoring but 36 were completely unaware of any drug monitoring and had certainly not come across resistance in their cases. A total of 75 reported that they had no experience of drug resistance.

Some doctors reported that they would feel more comfortable sending patients with this type of complex disease to our service as they were not experts in this field and only saw 1-2 patients with this type of disease. Therefore managing the patients with confidence was often difficult for them but they suggested shared

care would be extremely valuable as it would allow them to learn about the disease without being solely responsible for the management of the patient in this setting.

British Thoracic Society (BTS) Winter Meeting 2018

WINTER MEETING 2018

British Thoracic Society

9 Statutory reports

9.1 MRSA

No cases of MRSA were reported.

9.2 *C. difficile* and CPE infections

No cases of *C. difficile* infection were reported.
One reported case of CPE (carbapenamase producer)

9.3 Serious Untoward Incidents (SUIs)

No SUI's were reported.

9.4 Complaints

No complaints were made in 2018-19.

9.5 Hospital Incident Reporting System (HIRS) alerts

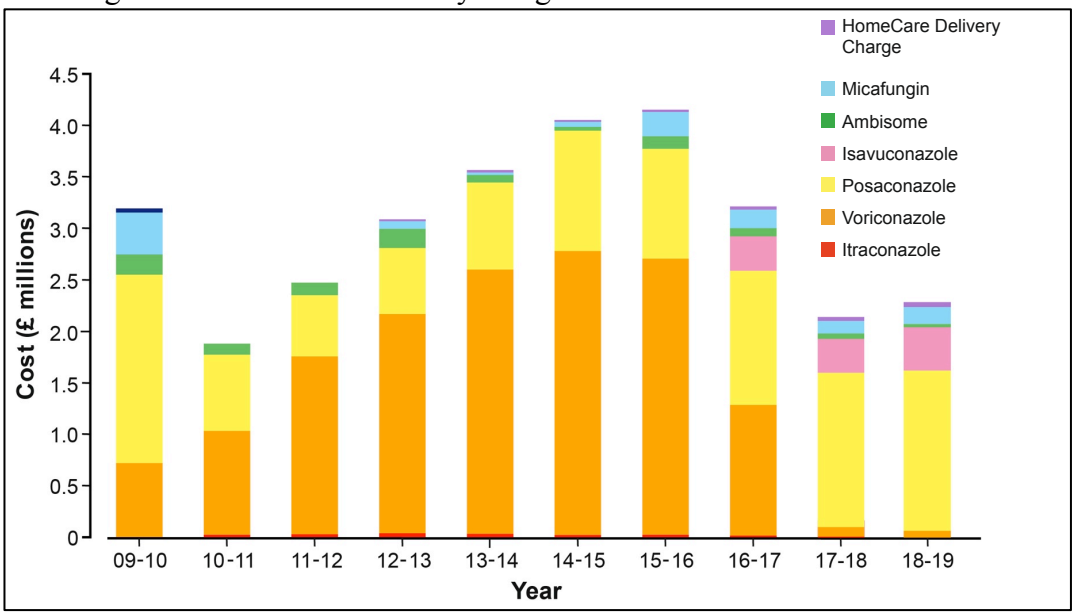
1 HIRS was submitted relating to appointment times in clinic

10 Antifungal expenditure

Antifungal expenditure was similar in 2018/19 compared with 2017/18, a total of £2,295,256. Both itraconazole (£7,884) and voriconazole (£65,928) are generic. A

substantial number of patients on itraconazole get their prescription from their GP, or local consultant, which is not true for any of the other antifungals. There has been a slight rise in expenditure on posaoconaole (£1,556,442), and isavuconazole (£419,655), commensuarate with a growth in the total number of patients cared for. Micafungin (£165,129) has increased at the expense of Ambisome (£32,399). Home care delivery charges amounted to £47,788.

Figure 10. Antifungal expenditure by financial year for the NAC set out by drug, including costs of homecare delivery and gamma interferon



11 Future developments and direction

11.1 The developments planned for 2018/19 are:

- Implementation of year 2 of the NIHR BRC research plan in infection, including mycobiome assessment of CPA patients, and publication of CPA genetic results. In progress, with genetic results in final stages of preparation for publication. A very small number of mutations (3-5) in different genes allow diagnosis of CPA with >95% certainty. Additional discovery of highly specific mutations in *Aspergillus fumigatus* in aspergilloma isolates to be submitted in parallel. Microbiome work in *Aspergillus* bronchitis in progress.
- Re-introduction of Skype clinics for some consultation for distance patients. Not achieved.
- Increased clinic capacity required – including evening clinics. Space is a challenge. Clinic capacity has been slightly increased (extra clinic room), without resorting to evening clinics.
- Recruitment of 2 additional nurses, 1 NHS consultant, 50% of a senior physiotherapist and another administrator for the non-CPA patients with aspergillosis. All achieved.
- Increased audit efforts to better understand how to more quickly assess progression of CPA, associations with the development of resistance and radiological interpretation and scoring approaches. In progress. Radiological scoring has failed. Major audit of factors predicting an early death in analysis (800 CPA subjects).
- Initiate a focussed program on assessment of therapeutic response that will satisfy regulatory authorities. Not achieved.

- Introduce an Aspergillus IgG serology test into the MCRM portfolio to replace Aspergillus precipitins assay, and assist in diagnosing 'sero-negative' cases. Validation work complete and published, internal application process for acceptance ongoing.

11.2 The developments planned for 2019/20 are:

- Re-introduction of Skype clinics for some consultation for distance patients.
- Better understanding of the lung response to aspergillomas to related to the immune background of the lesions.
- Publish data on the value of measuring and treating with gamma interferon
- In collaboration with the Commissioning team change to a new model of proving servies to a greater number of patients who find it difficult to attend the NAC in Manchester.
- Add azole resistance in Aspergillus to NAC reporting metrics.
- In collaboration with geneticists, work through the logistics and model of undertaking routine of focussed genetic analysis of patients as a component off the clinical service.

Appendix 1

Categorisation of complexity (Banding)

Stage 1

- Ambulant and independent
- No evidence of antifungal resistance
- No treatment or treatment with itraconazole capsules

Stage 2

- Significant impairment of respiratory function, sufficient to impair activities of daily living, but ambulant
  and/or
- Concurrent anti-mycobacterial treatment
  and/or
- Failed or developed toxicity to itraconazole capsules
  and
- No evidence of azole antifungal resistance

Stage 3

- Antifungal azole resistance documented
  and/or
- Long term nebulised or IV antibiotic treatment required (bronchiectasis, Pseudomonas colonisation)
  and/or
- Wheelchair bound
  and/or
- HIV infected
  and/or
- Severe hepatic or renal disease

Appendix 2

Referral to appointment time audit - April 2018 – March 2019

* The month seen is not always the month they are determined to have CPA, because of missing diagnostic data. Transition refers to new CPA diagnosis in a patient already under our care.

See separate data file

Appendix 3

Heat maps showing the geographical distribution of new and existing CPA patients March 2019

Figure 11. New CPA patient referrals 2018-19 (n= 131)

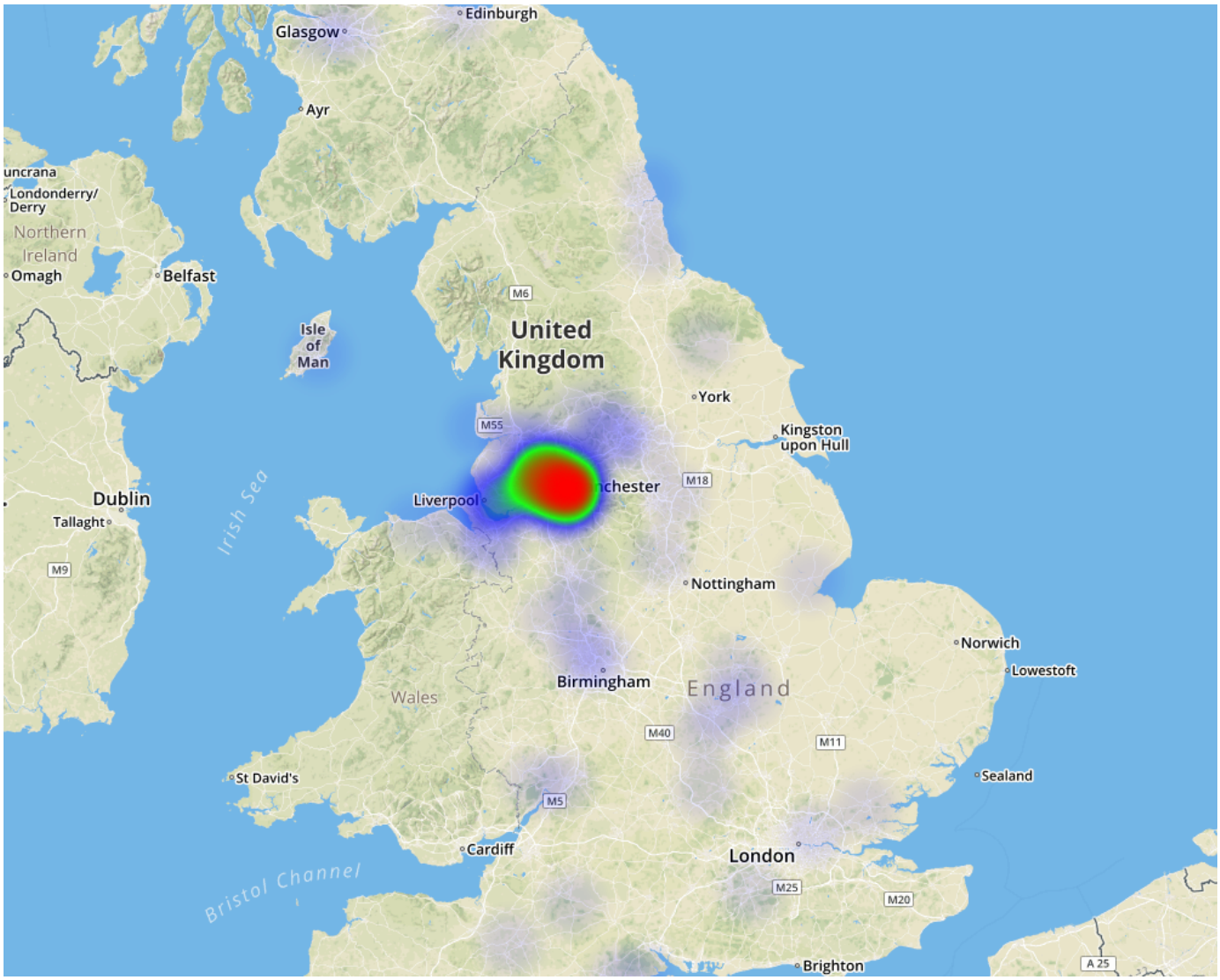
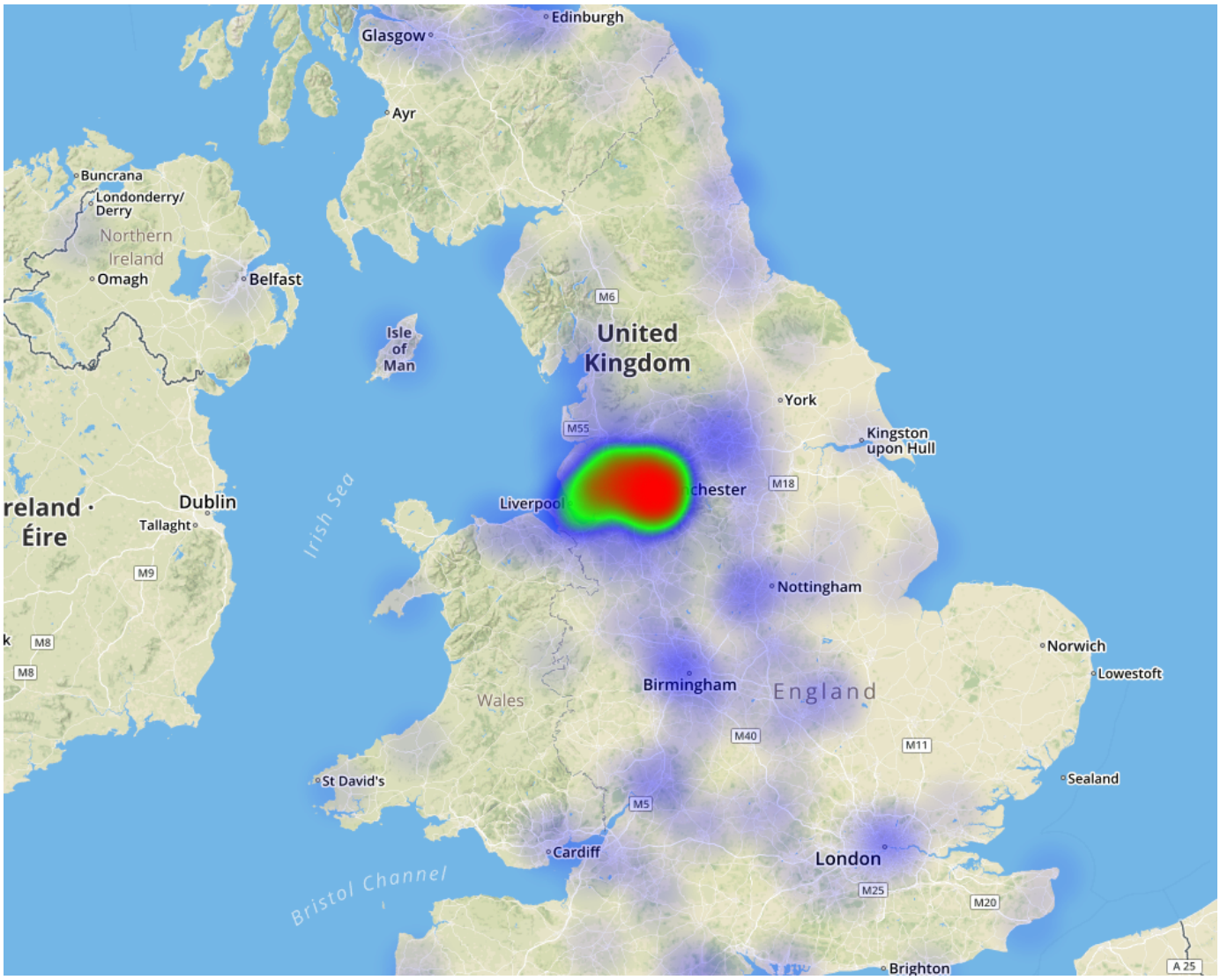


Figure 12 CPA review patients 2018-19 (n= 535)



Appendix 4

Quality of life (SGRQ), weights and MRC dyspnoea scores for new referrals 2018/19

See separate data file

Appendix 5

Publications from the NAC, MFIG, and MCRM, published in 2018

1. Bongomin F, Moore CB, Masania R, Rowbotham E, Alastruey-Izquierdo A,Novak-Frazer L, Richardson MD. Sequence analysis of isolates of *Aspergillus* from patients with chronic and allergic aspergillosis reveals a spectrum of cryptic species. **Future Microbiol** 2018;13: 1557-1563.

2. Rautemaa-Richardson R, Rautemaa V, Al-Wathiqi F, Moore CB, Craig L, Felton TW, Muldoon EG. Impact of a diagnostics-driven antifungal stewardship programme in a UK tertiary referral teaching hospital. **J Antimicrob Chemother**. 2018; 73:3488-3495.

3. Rodriguez-Goncer I, Bongomin F, Doran HM, Novak-Frazer L, Masania R, Moore CB, Richardson MD. A case of pulmonary cryptococcoma due to *Cryptococcus gattii* in the United Kingdom. **Med Mycol Case Rep**. 2018; 21:23-25.

4. Bongomin F, Oladele RO, Gago S, Moore CB, Richardson MD. A systematic review of fluconazole resistance in clinical isolates of Cryptococcus species. **Mycoses**. 2018; 61(5): 290-297.

5. Kean, R., Delaney, C., Sherry, L., Borman, A., Johnson, E., Richardson, M., Rautemaa-Richardson, R., Williams, C. & Ramage, G. Transcriptome assembly and profiling of *Candida auris* reveals novel insights into biofilm mediated resistance. **mSphere**. 2018 Jul 11; 3(4)

6. Oladele, R., Ogunsola, F. T., Toriello, C., Ayanlowo, O., Foden, P., Fayemiwo, A., Osaigbovo, I., Iwuafor, A., Shettima, S., Ekundayo, H., Richardson, M. & Denning, D. Prior subclinical histoplasmosis revealed in Nigeria using histoplasmin skin testing. **PLoS ONE**. 2018; 13(5)

7. Ashrafi, M. H., Novak Frazer, L., Bates, M., Baguneid, M., Alonso-Rasgado, M. T., Xia, G., Rautemaa-Richardson, R. & Bayat, A. Validation of biofilm formation on human skin wound models and demonstration of clinically translatable bacteria-specific volatile signatures. **Scientific Reports**. 2018; 8(1): 9431

8. Page, I., Richardson, M. & Denning, D. Siemens Immulite Aspergillus-specific IgG assay for chronic pulmonary aspergillosis diagnosis: Immulite Aspergillus-specific IgG cut offs. **Medical Mycology**. 2019; 57(3): 300-307.

9. Bongomin, F., Moore, C., Masania, R., Rowbotham, E., Alastruey-izquierdo, A., Novak Frazer, L. & Richardson, MD. Sequence analysis of isolates of *Aspergillus* in chronic and allergic aspergillosis reveal a spectrum of cryptic species. **Future Microbiol,** 2018, 13: 1557-1563

10. Rodriguez-Goncer, I., Thomas, S., Foden, P., Richardson, M., Ashworth, A., Barker, J., Geraghty, G., Muldoon, E. & Felton, T. Invasive pulmonary aspergillosis is associated with adverse clinical outcomes in critically ill patients receiving veno-venous extracorporeal membrane oxygenation. **Eur J Clin Microbiol Infect Dis**, 2018;37(7):1251-1257

11. Richardson, M. & Page, I. Role of Serological Tests in the Diagnosis of Mould Infections. **Curr Fungal Infect Rep** 2018;123:127-136.

12. Richardson, M. & Cole, D. Fungal burden in different countries. **J Fungi**. 2018;4, 3.

13. Richardson, R., Mellinghoff, S., Hoenigl, M., Koehler, P., Clarke, R., Kumar, A., Lagrou, K., Lass-Flörl, C., Meis, J., Menon, V. & Cornely, O. EQUAL Candida Score: An ECMM score derived from current guidelines to measure QUAlity of Clinical Candidaemia Management. **Mycoses** 2018. 61, 5.

14. Bassetti M, Carnelutti A, Peghin M, Aversa F, Barchiesi F, Girmenia C, Pagano L, Sanguinetti M, Tortorano AM, Montagna MT, Viale P, Viscoli C, Denning DW. Estimated burden of fungal infections in Italy. **J Infect** 2018; 76:103–106.

15. Oladele R, Ayanlowo OO, Richardson MD, Denning DW. Histoplasmosis in Africa: An emerging or a neglected disease? **PLoS Negl Trop Dis** 2018; 12: e0006046.

16. Bertuzzi M, Hayes GE, Icheoku UJ, van Rhijn N, Denning DW, Osherov N, Bignell EM. Anti-*Aspergillus* activities of the respiratory epithelium in health and disease. **J Fungi** 2018; 4:8.

17. Wadi J, Denning DW. Burden of serious fungal infections in Jordan. **J Fungi** 2018; 4:15.

18. Nordøy I, Liv Hesstvedt L, Andersen CT, Mylvaganam H, Kols NI, Falch BM, Tofteland S, Müller F, Denning DW. An estimate of the burden of fungal disease in Norway. **J Fungi** 2018; 4:29.

19. Mares M, Moroti-Constantinescu VR, Denning DW. The burden of fungal diseases in Romania. **J Fungi** 2018; 4:31.

20. Kemaykin VM, Tabinbaev NB, Khudaibergenova MS, Olifirovich AA, Abdrakhmanova LM, Denning DW, Klimko N. Severe and chronic fungal diseases in the Republic of Kazakhstan. **J Fungi** 2018; 4: 34.

21. Bamba S, Zida A, Sangaré I, Cissé M, Denning DW, Hennequin C. Burden of severe fungal infections in Burkina Faso. **J Fungi** 2018; 4:35.

22. Macedo-Viñas M, Denning DW. Estimating the burden of serious fungal infections in Uruguay. **J Fungi** 2018; 4:37.

23. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, Lass-Flörl C, Lewis RE, Munoz P, Verweij PE, Warris A, Ader F, Akova M, Arendrup MC, Barnes RA, Beigelman-Aubry C, Blot S, Bouza E, Brüggemann RJM, Buchheidt D, Cadranel J, Castagnola E, Chakrabarti A, Cuenca-Estrella M, Dimopoulos G, Fortun J, Gangneux JP, Garbino J, Heinz WJ, Herbrecht R, Heussel CP, Kibbler CC, Klimko N, Kullberg BJ, Lange C, Lehrnbecher T, Löffler J, Lortholary O, Maertens J, Marchetti O, Meis JF, Pagano L, Ribaud P, Richardson M, Roilides E, Ruhnke M, Sanguinetti M, Sheppard DC, Sinkó J, Skiada A, Vehreschild MJGT, Viscoli C, Cornely OA. Diagnosis and management of Aspergillus diseases: executive summary of

the 2017 ESCMID-ECMM-ERS guideline. **Clin Microbiol Infect**. 2018; 24 (Suppl 1):e1-e38.

24. Oladele R, Otu AA, Richardson MD, Denning DW. Pneumocystis pneumonia in resource-poor settings. **J Health Care Poor Underserved** 2018; 29:107-158.

25. Velayuthan RD, Samudi C, Kaur H, Ng KP, Denning DW, Shankar EM. Estimation of burden of serious human fungal infections in Malaysia. **J Fungi** 2018; 4:38.

26. Alvarez-Moreno CA, Cortes CA, Denning DW. Burden of fungal infections in Colombia. **J Fungi** 2018; 4:41.

27. Overton NLD, Denning DW, Bowyer P. Mutations in EEA1 are associated with allergic bronchopulmonary aspergillosis and affect phagocytosis of *Aspergillus fumigatus* by human macrophages. **PLoS ONE** 2018; 13: e0185706.

28. Bongomin F, Harris C, Hayes G, Kosmidis C, Denning DW. Twelve month outcomes of 206 patients with chronic pulmonary aspergillosis. **PLoS One** 2018; 13: e0193732.

29. Mandengue C, Denning DW. The burden of serious fungal infections in Cameroon. **J Fungi** 2018; 4:E44.

30. Riera FO, Caeiro JP, Denning DW. Burden of serious fungal Infections in Argentina. **J Fungi** 2018; 4:51.

31. Page ID, Baxter C, Hennequin C, Richardson MD, van Hoeyveld E, van Toorenenbergen AW, Denning DW. Receiver operating characteristic curve analysis of four Aspergillus-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis. **Diag Microbiol Infect Dis** 2018; 91:47-51.

32. Oladele R, Toriello C, Ogunsola FT, Ayanlowo OO, Foden P, Fayemiwo AS, Osaigbovo II, Iwuafor AA, Shettima S, Ekundayo HA, Richardson MD, Denning DW. Prior subclinical histoplasmosis revealed in Nigeria using histoplasmin skin testing. **PLoS One** 2018; 13: e0196224.

33. Bongomin F, Batac C, Richardson MD, Denning DW. Aspergillus onychomycosis: Mycology and epidemiology. **Mycopathologia** 2018; 183: 485-93.

34. Kalua K, Zimba B, Denning DW. Estimated burden of serious fungal diseases in Malawi. **J Fungi** 2018; 4: 61.

35. Bazaz R, Denning DW. Subacute invasive aspergillosis associated with Sorafenib therapy for hepatocellular carcinoma. Clin Infect Dis 2018; 67: 156-157.

36. Sacarlal J, Denning DW. Estimated burden of serious fungal diseases in Mozambique. **J Fungi** 2018; 4: 75.

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41. Gago S, Ben Ghazzi N, Overton NLD, Denning DW, Bowyer P. The human ZNF77 transcription factor controls *Aspergillus fumigatus* load at the bronchial epithelium. **Nat Communications** 2018; 9: 3835.

42. Gamaletsou MN, Hayes GE, Harris C, Muldoon EG, Brock J, Denning DW. F508del CFTR gene mutation in patients with allergic bronchopulmonary aspergillosis. **J Asthma** 2018; 55: 837-43.

43. Fraczek MG, Chishimba L, Niven RM, Simpson A, Smyth L, Denning DW, Bowyer P. Corticosteroid treatment is associated with increased filamentous fungal burden in airways. **J Allergy Clin Immunol** 2018; 142: 407-414.

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45. Nacher M, Blanchet D, Bongomin F, Chakrabarti A, Couppié P, Demar M, Denning D, Djossou F, Epelboin L, Govender N, Leitão T, Mac Donald S, Mandengue C, Marques da Silva SH, Oladele R, Panizo MM, Pasqualotto A, Ramos R, Swaminathan S, Rodriguez-Tudela JL, Vreden S, Zancopé-Oliveira R, Adenis A. Histoplasma capsulatum antigen detection tests as an essential diagnostic tool for patients with advanced HIV disease in low and middle income countries: A systematic review of diagnostic accuracy studies. **PLoS Negl Trop Dis**. 2018 Oct 19;12(10):e0006802.

46. Loyse A, Burry J, Cohn J, Ford N, Chiller T, Ribeiro I, Koulla-Shiro S, Mghamba J, Ramadhani A, Nyirenda R, Aliyu SH, Wilson D, Le T, Oladele R, Lesikari S, Muzoora C, Kalata N, Temfack E, Mapoure Y, Sini V, Chanda D, Shimwela M, Lakhi S, Ngoma J, Gondwe-Chunda L, Perfect C, Shroufi A, Andrieux-Meyer I, Chan A, Schutz C, Hosseinipour M, Van der Horst C, Klausner JD, Boulware DR, Heyderman R, Lalloo D, Day J, Jarvis JN, Rodrigues M, Jaffar S, Denning D, Migone C, Doherty M, Lortholary O, Dromer F, Stack M, Molloy SF, Bicanic T, van Oosterhout J, Mwaba P, Kanyama C, Kouanfack C, Mfinanga S, Govender N, Harrison TS. Leave no one behind: response to new evidence and guidelines for the management of

cryptococcal meningitis in low-income and middle-income countries. **Lancet Infect Dis** 2018 Oct 18. pii: S1473-3099(18)30493-6.

47. Otu A, Bongomin F, Kosmidis C, Denning DW. Acute kidney injury: an unusual complication of posaconazole use. **J Chemother** 2018; 30: 380-383.

48. Hedayati MT, Armaki MT, Jamshid, Charati Y, Hedayati N, Seyedmousavi S, Denning DW. Burden of fungal infections in Iran. **J Infect Dis Dev Ctries** 2018; 12:910-18.

49. Oladele RO, Osaigbovo II, Ayanlowo OO, Otu AO, Hoenigl M, Cornely OA, Chakrabarti A, Denning DW. The role of medical mycology societies in combating invasive fungal infections in low and middle income countries: a Nigerian model. **Mycoses** 2018; 62:16-21.

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Appendix 6

Patient survey Q1 2019

Questions and summary ansewers with NAC comments in blue. See report section 6.1 for summary

Q1. Is this your first visit to the National Aspergillosis Centre?
5% Yes

Q2 How satisfied are you with the courtesy shown to you by:
Receptionist 98%, Clinic Nurses 98%, Aspergillus specialist nurse 99%, Doctor 98% and Physio 97%.
All figures are for satisfied or better.
A point of concern is that one or two individuals expressed that they were very unsatisfied. In both cases they gave predominantly negative answers throughout the questionnaire. In both cases they rated the hospital as excellent!

Q3. How satisfied are you with the quality of care you received from:
Receptionist 98%, Clinic Nurses 98%, Aspergillus specialist nurse 99%, Doctor 98% and Physio 97%.
A point of concern is that one individual expressed that they were very unsatisfied. They gave predominantly negative answers throughout the questionnaire. They rated the hospital as excellent!

Q4. Have you been contacted by a member of the NAC team, after or in between clinic visits?
31% Yes. 75% of these contacts were from a nurse, 12.5% from a doctor and 12.5% admin.
100% satisfied or better.
NOTE this figure was 49% in 2017 and 35% in 2018 – there is a continuing trend towards less contact.

Q5. Have you had a consultation with a specialist nurse (aspergillosis nurse) today?
6% had consulted with a nurse - all were 100% satisfied or better with their knowledge and communication.

Q6. Have you received care from the specialist physiotherapists (Phil or Mairead)?
15% had received care from Physio , all were 100% satisfied or better.
NOTE 30% received care from physio in 2018, so quite a big drop in numbers seen, but could reflect carryover of the word today from the previous question.

Q7. Have you received any written information about your condition?
67% (48) had received information. There were 6 comments which were neutral or positive, one praised a letter by Prof Denning in particular. One was a concern "I never have any feedback after appointments like my other clinic visits at different hospitals "
NOTE this figure was 63% in 2018, so slight improvement noted.

Q8. How satisfied are you with this information you received about your condition?
95% were satisfied or better.

Q9. Did someone tell you about potential symptoms regarding your illness or medication to watch out for at home?
74% (55) Yes, so some room for improvement here.

Q10. When you had important questions to ask a doctor did you get answers that you could understand?
100% yes, though one comment stated "The lack of continuity is an issue. One feels that one is starting from the beginning again with each new face that one sees. It would be helpful if patients, where possible, could be scheduled in with the same clinic doctor on each appointment" This is a common comment in the patients meeting.

Q11. We would like to offer best supportive care/end of life care to our patients. We understand that this can be a sensitive subject.
Is this something you have thought about?
My conclusion: 78% have not thought about this, so perhaps most do not want to think about end of life (this is reinforced by answers to Q12), but it might be worth handing out a leaflet?
Comments are revealing:
Hopefully it won't apply to my specific condition, I don't think about it, Assume that it's not relevant to me - but I could be wrong!, Would like quality of life, Not looking forward to the future. Hope to be looked after at Wythenshawe.
My conclusion: It might be that some are not aware, or don't want to be aware of the seriousness of their condition?

Q12. Would you like the opportunity to discuss end of life care with the NAC team?

Around 90% did not want to discuss, with slight difference in preference about who the conversation should be with (doctor rather than nurse).

Q13. Have you ever had an in-patient stay here at Wythenshawe hospital?

32% yes, of which 96% felt that they had been treated with respect and dignity. One individual answered no.

Comment: They are very good

Q14. Would you recommend Wythenshawe Hospital to friends and family?

99% Yes
My conclusion: There are lots of comments (25) all of which are positive with one exception. Of these the following are noteworthy: Excellent service and care, Great support in intensive care. OPAT is sensational. BUT the 4-bay wards are horrendous. The Asp clinic could be better controlled re. timeliness, Welcoming and friendly

doctors and staff, Excellent care, respect and dignity, The care received is outstanding.

Q15. We provide a postal service for drug levels and sputum samples. If you have used this service, have you any comments or ideas how this can be improved?

- I was a little confused about how to assemble the packaging to return it. It's not the easiest thing to do. Also had to ask on Facebook support group about storage = fridge or not, as collected on a Sunday.
- Very good
- Local nurses always seem unsure. Instructions could be clearer
- Very good
- Yes - more info - at the clinic I'm probably not properly focussed on what I'm being told
- good service
- only problem are sputum samples, can't get the pot in the post box
- sometimes difficult to place jars in plastic transit packs
- Good
- Happy as is
- My local hospital says most likely can't do blood samples any more. Help! Need authorisation for Macclesfield hosp and Congleton
- yes, good service
- Patients have difficulty getting local phlebotomists to take bloods. Perhaps more detailed information to pass to phlebotomists.
- No, found it easy to use with no problems

My conclusion: Overall it looks like there are quite a few small improvements to be made to the postal service around three things – information on what to do, using the packaging and difficulty getting a few local blood services to cooperate.

16) We have commissioned a company to deliver antifungal drugs to patients' homes. If you have had this service, do you have any comments?

- The delivery is very satisfactory and they are nice
- Brilliant service
- Good service
- very good
- OK
- Service very good
- Works really well
- yes they are very good and the drugs arrive when they say they will
- very good
- The service was excellent
- very satisfied
- generally good. However they often ask "how many tablets do you have left?" when they should know if they are supplying 1 or two more. Often they call when I am away from home so I have no idea.
- Good service

My conclusion: Drug delivery works pretty flawlessly.

Q17. Have you visited the new Aspergillosis patient website? (http://www.aspergillosis.org/)

Only 19% **(35% in 2018)** yes despite information leaflets available in clinic. This website has been available since Easter 2019. Room for improvement in raising awareness.

Of those that had visited, 100% were satisfied or better.

If you have not visited, is there a reason why?

Out of 21 comments, 7 (33%) stated that they had no access to the internet and 10 (48%) were not aware that the website existed. It isn't clear how many of the latter group would visit the website if they knew about it, but there is room for improvement in raising awareness.

NOTE this figure was 35% in 2018 – big drop for the second year running. There is now a new website in place.

Q18. We have developed several patient information leaflets. How useful did you find them?
76% thought our leaflets were useful. Of the remaining people 23% had not received a leaflet. Only one person (1%) had received a leaflet and rated it as not useful. There is room for improvement in handing out leaflets.

Is there any other information that you feel would be useful?

Comments: perhaps - what's the expected progression (different with every patient?). When medication will make a difference? When do you STOP expecting an improvement?, Paticipate on the Facebook group to learn more how to manage this condition.

Q19. We have regular monthly patient meetings here in Manchester
Have you attended a patient meeting?
100% No **(90% in 2018)**
Most of these 36 (45%) had not been to a meeting because it was inconvenient or they are happy the way they are. 5% do not need the extra support. 37 (50%) did not answer any subsidiary question.
My conclusion: Given that we make attending the meeting as convenient as possible by holding it close to the clinic it is difficult to see what we can do to convince 45% of the people who answered this question to attend. Of the remainder 5% do not feel that they need the support.
There is little sign apparent from these figures that we could do better at getting people to attend these meetings here other than one person who stated that they might attend if they knew more about them, however 37 (50%) people did not answer any of the subsidiary questions so we do not know anything about why they had not attended a meeting. There was no question asking directly what we could do to get them to attend, something I feel we might add in in 2020.

Two comments provide a clue. One stated "I find mixing with people sets my asthma off" so avoids meetings for fear of health worsening. I have heard similar comments from people who are concerned about catching an infection at the meeting.
Another wrote "parking from mid morning is impossible some days" and finally one person commented "When I know more, I am likely to attend ".
Consequently in order to maximise attendence we should explain what the meeting is about more clearly to our patients, and mention that we provide free car parking.

20) There have been several patient led support groups set up around the UK.
a) are you aware of these groups?
Only 30% Yes **(46% in 2018)**, so relatively few are aware. Details are in all of the booklets we provide for clinic so perhaps this reflects how many read that information. Not sure what we can do to change this – refresh the newsletters?

b) if yes, have you made contact with a group?
Of those who replied only 1 (3%) had made contact **(4% in 2018)**

c) If no, why have you not made contact?
12 replies (60%) not interested/inconvenient
6 replies (30%) did not know and presumably might like to join but it heavily depends on ta group being in their area. There are only a few groups throughout UK so there is only ever going to be a small number of people who can actually attend a group meeting. Despite the intention that these groups provide a meeting point for people who have no access to the internet, these are mostly run via internet with some having informal phonecalls between friends rather than leader/group member calls.
We could probably greatly clarify what these groups are and what they are for in our information given out at clinic, but unless we ran hundreds there is never going to be one close to most people in a clinic.

d) Would you like information about setting one up in your area? (if yes, please let a member of staff know)
4 replies, 3 no. One person wants to set up a group.

21) Over the last year, the presentations from the patient meetings have been recorded and put on the aspergillosis patient website. Have you viewed any of the presentations?
96% of people have not viewed any presentations. We don't make it very clear that these are available in our clinic information, this could be improved.

22) It has been possible for patients and carers, if they were not able to attend a meeting, to view the meetings live over the internet using Facebook. Have you ever watched a meeting live over the internet?
94% replied no. We don't make it very clear that this is possible in our clinic information, this could be improved.

23) Do you travel to clinic by hospital transport?
10% Yes, 80% of those were satisfied or better with the service. One person was unsatisfied so some room for improvement.
Could you please provide us with the first part of your postcode? Eg. M23

DE24 (Derby 78 miles), L30 (Liverpool 41miles), M32 (Wythenshawe), WA13 (Lymm 12miles)

24) Are you generally happy to participate in clinical research?
79% Yes, of these 100% happy with procedures and consent process.

25) There is a weekly online meeting for patients and carers on Thursday at 11:00am, currently using Zoom software. Have you ever participated?
3% yes. We could do more to publicise this in clinic but a computer is required. It is possible to phone in but it isn't very simple to do this.

26) Have you ever attended it? Would you like to know more?
14% yes – there does seem to be a demand for this so more work needed to publicise it.

27) We publish a quarterly booklet for the Aspergillosis community that you can pick up in the clinic waiting room. Have you ever read it?
64% yes.

General comments

- Prof D and his team are fabulous. It's just sad that I had to find him via google and ask my GP to refer. A local hospital had no idea what to do with me! More GP education is required.
- Aspergillus or toxic mould disease is a very large area and the system for treating the condition is not explained in detail. Where can I find out about this in more detail and work to improve my situation?
- I don't have aspergillus so most answers are no ??
- I think my clinic appointments have been so rushed I've not made use of the various resources available. Perhaps patients need to have their attention drawn to these?
- Not sure about some of the answers due to not being able to answer them because of MS. Not mobile.

Graham Atherton 2019

Appendix 7

PR work – Raising awareness and supporting NAC and aspergillosis generally

Public relations are handled by the PR company Goodwork, in co-ordination with the University of Manchester communications team. The Aspergillus blog highlights one or two stories per week (titles listed below), featuring a mixture of relevant world news, new diagnostics and antifungals, and the latest research.

Mar 2019	• Is patient to patient transmission of Aspergillus fumigatus possible? • Posaconazole has better therapeutic efficacy in comparison with itraconazole and voriconazole in ABPA amongst CF patients • TB discovery could save thousands of lives • Children receiving voriconazole should receive ECG monitoring and electrolyte imbalance correction ➢ Press release: 1 in 15 TB sufferers go on to develop chronic pulmonary aspergillosis, treatment could save 1000s of lives
Feb 2019	• Pulmonary Rehabilitation - Is it worth it? ➢ Press release: Ghana's CPA awareness seminar on World Aspergillosis Day
Jan 2019	• MMSA - Sponsored award nominations now open! • New tools to diagnose Allergic Fungal Sinusitis (AFS) have the potential to reduce the need for surgery • New study reports Amphotericin B-resistance in some Aspergillus isolates
Nov 2018	• Pulmatrix Announces Positive Final Results From the Phase 1/1b Clinical Trial of Pulmazole – an Inhaled Dry-Powder iSPERSE™ Formulation of Itraconazole • World Antibiotic Awareness Week • Low rates of antifungal prophylaxis in patients high risk for fungal infections
Oct 2018	• Carriers of cystic fibrosis may be at greater risk for allergic bronchopulmonary aspergillosis • Multi-centre cohort study suggests immune stimulating therapies may be useful in the treatment of acute invasive fungal sinusitis (AIFS) • Mechanism for pH-dependence of flucytosine against Aspergillus revealed • Cohort study of IPA among influenza patients in ICU reports an overall incidence of 19% and overall mortality of 51% ➢ Press release: Director-General of WHO calls for more mycetoma research during visit to Mycetoma Research Centre in Khartoum (Sudan)
Sep 2018	• Lung colonisation by Aspergillus fumigatus is controlled by ZNF77 gene variant ➢ Press release: Test could detect patients at risk from lethal fungal spores
Aug 2018	• Citizen Science: Help Us Test for Antifungal Resistance in the Air at Home & Work • Science Funding, looking to the past and changing the future • Mitochondrial fragmentation in Aspergillus hyphae: a new technique to visualise Granulocyte killing activity • 138 million suffer from recurrent vulvovaginal candidiasis, Lancet review reveals • Case Definition of Chronic Pulmonary Aspergillosis in Resource-Constrained Settings ➢ Press release: New figures show 138 million women suffer from recurrent thrush
July 2018	• Early diagnosis protocol for invasive FRS reduces mortality rate from 43% to 17% in immunosuppressed patients • Pre-emptive vs empirical antifungal treatment in high-risk paediatric cancer

	patients • Higher rate of genetic recombination and antifungal resistance found among A. fumigatus isolates from Eloundem region of Cameroon • GAFFI: Report on Global Fungal Infection Forum III • Effectiveness of antifungals decreased by oncology drugs • Chronic Pulmonary Aspergillosis Network (CPAnet) ➢ Press release: Doctors and scientists meeting in Uganda sets new standards for essential diagnostics in AIDS
June 2018	• National plan needed for lung disease • Two point-of-care tests for invasive aspergillosis launched • Future of asthma research and benefits to patient health • Two vacancies for Clinical Fellow vacancies in Infectious Diseases at Wythenshawe Hospital
May 2018	• Science magazine special issue highlights antifungal resistance • Randomised controlled trial tests azithromycin efficacy for asthma exacerbation • Corticosteroid Use Decreases Voriconazole Concentration • World Asthma Day: Itraconazole is Effective Against Acute-Stage ABPA • World Asthma Day: UK Asthma Deaths Rise 20%
Apr 2018	• The Fogarty International Centre turns 50 • MedLec, a C-type lectin receptor, has crucial role in response to systemic A. fumigatus infection • Patients with non-tuberculous mycobacterium lung disease (NTM-LD) are at greater risk for CPA • Amphotericin B resistance in Aspergillus isolates • Review of CNS fungal infections published in The Lancet Neurology

Social media
Twitter is the main social media platform for promoting NAC activity, with separate accounts for LIFE Worldwide, Aspergillus&Aspergillosis and GAFFI. These are kept active with several tweets and retweets each week.

	Twitter handle	**Followers** (change from last year)	**Tweets**
LIFE Worldwide	@LIFEworldwide	728 (+334)	570
Aspergillus & Aspergillosis	@AspergillusWeb	1639 (+288)	7430
GAFFI	@gaffi_org	1479 (+147)	416
Aspergillosis Trust	@aspertrust	356 (+315)	1391
MRCM	@MycologyRefManc	599 (+503)	347
As of 27th Aug 2019			