Institution: The University of Manchester

Unit of Assessment: 1 (Clinical Medicine)

Title of case study: Transforming patient outcome of pulmonary aspergillosis with better and faster diagnosis and therapy

Period when the underpinning research was undertaken: January 2000 – July 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
David Denning	Professor of Infectious Diseases in Global Health Senior Lecturer	2005 – present 2000 – 2005
Rob Niven	Senior Lecturer in Respiratory Medicine	2000 – present
Timothy Felton	Clinical Senior Lecturer Honorary Senior Lecturer Honorary Research Fellow Clinical Research Fellow	2020 – present 2014 – 2020 2013 – 2014 2009 – 2013

Period when the claimed impact occurred: 1 August 2013 – 31 July 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

The airborne fungus *Aspergillus* causes life-threatening invasive aspergillosis and chronic pulmonary aspergillosis ((CPA), five-year mortality >50%) and exacerbates asthma. The University of Manchester (UoM)'s world-leading aspergillosis research has: 1) improved diagnostics, aiding earlier effective treatment; 2) led to new treatments through multiple drug studies; 3) improved patient survival and quality of life. Notably, Voriconazole results in 13% improved survival in invasive aspergillosis and has been used to treat millions of patients (peak annual sales over USD750,000,000). Since August 2013, the National Aspergillosis Centre (NAC), led by Denning, has treated >800 new patients, with >9,900 outpatient follow-up attendees. Manchester publications are embodied in European and US treatment guidelines for invasive aspergillosis and CPA.

2. Underpinning research

Denning was the primary academic in the clinical evaluation of Pfizer's antifungal azole Voriconazole. He wrote the protocol and led the case evaluation process for the landmark study, which demonstrated that Voriconazole was superior to amphotericin B, the only intravenous drug available (and never prospectively studied) [1]. This was the first study to demonstrate an improvement in survival in any invasive fungal disease (13% absolute survival benefit compared to amphotericin). It led to global approval of Voriconazole.

In 2003, Denning published a landmark paper on CPA, integrating complex radiological findings with mycological data and patients' clinical courses to provide a new understanding (and nomenclature) for a disease entity first described in 1848 [2]. This definition of disease has been used across the world for epidemiology and prospective studies, and to evaluate diagnostics. This and a subsequent body of 96 publications from Manchester (2002–2020), described the epidemiology and clinical course of disease and closely related entities (notably *Aspergillus nodule*). These publications also evaluated the performance of several different commercially available serological assays and demonstrated the value of antifungal

therapy (previously only surgery was offered), notably the safe and effective azole antifungal Posaconazole [3]. The high frequency of azole resistance on therapy (15–20%), and several genetic and pathophysiological features of the disease, have also been described. Numerous retrospective analyses documented the impact of antifungal therapy on arresting progression and improved quality of life (the first such descriptions for any fungal disease) using standardised tools.

Fungal asthma, which affects 10–15,000,000 people globally, is a subset of severe asthma that accounts for a significant proportion of treatment costs. In 2009, Denning and colleagues described the link between severe asthma and fungal sensitisation (SAFS) and defined SAFS as a disease entity. They undertook a double-blind randomised controlled trial (RCT) of the oral antifungal Itraconazole for the treatment of SAFS [4] which demonstrated a quality of life benefit, based on the validated Asthma Quality of Life Questionnaire score, and a markedly reduced total blood IgE (allergy marker) with treatment. This was the first blinded RCT evaluating antifungal therapy for a subset of severe adult asthmatics, showing benefits in improved quality of life and allergy markers, rather than lung function which has been historically the key endpoint of most severe asthma prospective studies.

Case observations at UoM led to the clinical description of *Aspergillus* bronchitis, the first series of patients (n=17), and provided criteria for diagnosis [5]. This represents an important new clinical entity in respiratory medicine, particularly affecting those with bronchiectasis.

Denning also published an estimate of the global burden of allergic bronchopulmonary aspergillosis (ABPA) using deterministic modelling [6], a seminal step in the development of epidemiological data to highlight the unmet medical need for ABPA patients worldwide.

3. References to the research

1. Herbrecht R, **Denning DW**, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern W, Marr KA, Ribaud P, Lortholary O,Sylvester R, de Pauw B, Rubin RH, Wingard JR, Stark PS, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF. Voriconazole versus Amphotericin B for primary therapy of invasive aspergillosis. *New England Journal of Medicine* 2002;347:408–15. DOI:10.1056/NEJMoa020191
2. **Denning DW**, Riniotis K, Dobrashian R, Sambatakou H. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: Case series, proposed nomenclature change and review. *Clinical Infectious Diseases* 2003;37 (Suppl 3):S265–80. DOI:10.1086/376526.
3. **Felton TW**, Baxter C, Roberts S, Hope WW, **Denning DW**. Efficacy and safety of Posaconazole for chronic pulmonary aspergillosis. *Clinical Infectious Diseases* 2010;51:1383–91. DOI: 10.1086/657306
4. **Denning DW**, O'Driscoll BR, Powell G, Chew F, Atherton GT, Vyas A, Miles J, Morris J, **Niven RM**. Randomized Controlled Trial of Oral Antifungal Treatment for Severe Asthma with Fungal Sensitization. The Fungal Asthma Sensitization Trial (FAST) Study. *American Journal of Respiratory and Critical Care Medicine*. 2009 Jan 1;179(1):11–8. DOI:10.1164/rccm.200805-737OC.
5. Chrdle A, Mustakim S, Bright-Thomas R, Baxter C, **Felton T, Denning DW**. *Aspergillus* bronchitis without significant immunocompromise. *Annals of the New York Academy of Sciences* 2012; 1272:73–85. DOI: 10.1111/j.1749-6632.2012.06816.x
6. **Denning DW**, Pleuvry A, Cole DC. Global burden of ABPA in adults with asthma and its complication chronic pulmonary aspergillosis. *Medical Mycology* 2013; 51:361–370. DOI:10.3109/13693786.2012.738312

4. Details of the impact

Context

Aspergillus fumigatus is the most common species to cause human aspergillosis infections. It causes multiple disease entities, which are diagnosed and managed differently. UoM researchers have transformed disease concepts and management of pulmonary aspergillosis.

Reach and significance of the impact

Global health impact of Voriconazole

Denning's seminal research with Voriconazole [1] led to licensure in 2002 and continued worldwide use as first-line therapy for invasive aspergillosis. Voriconazole remains the globally recommended treatment for invasive aspergillosis [A] and its extensive use in other forms of aspergillosis evidences its effectiveness in ABPA, 'fungal asthma' CPA and *Aspergillus* bronchitis [3].

Pfizer's annual reports show total Voriconazole sales between 2013–2017 of over USD3,000,000,000 [B]. In 2014/15, prior to introduction of generic products, UK National Aspergillosis Centre (NAC) expenditure on Voriconazole was GBP2,800,000, 67% of its total antifungal spend, demonstrating the importance of the drug in treatment [C].

Following a 2017 application citing several UoM papers and supported by Global Action Fund for Fungal Infections (GAFFI), UoM and others, Voriconazole was granted World Health Organization (WHO) 'Essential Medicine' status [D]. This status is given only to the most effective and safe medicines needed in healthcare systems and is used by countries as a basis for their essential medicine lists.

Voriconazole is now available in >115 countries globally and generic versions registered in >35 countries [E].

Clinical guidelines for CPA

Denning, working with the European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society, published the first clinical guidelines specifically for CPA (2016). These recommended treatment with Voriconazole [1]; Posaconazole [3] was recommended as a potential alternative [F]. Denning co-authored Infectious Diseases Society of America guidance recommending Itraconazole and Voriconazole as preferred oral antifungals with Posaconazole a "*useful third-line agent for those with adverse events or clinical failure*" [Ai].

Enabling effective treatment via accurate diagnosis

UoM researchers have described new clinical entities caused by *Aspergillus* in addition to SAFS, namely cancer-mimicking *Aspergillus* lung nodules, and renamed/defined diagnostic criteria for *Aspergillus* bronchitis in non-immunocompromised patients and cystic fibrosis. The June 2018 revision of WHO's International Classification of Diseases (ICD11) includes CPA (and sub-types) and *Aspergillus* bronchitis for the first time [G]. This code is used in health systems worldwide for documenting disease. As a cornerstone of good medicine, accurate diagnostic labelling means these diseases can be treated appropriately.

Guidelines for diagnosing ABPA

Guidelines for diagnosing ABPA resulted from Denning's collaboration with the International Society for Human and Animal Mycology [H]. They are routinely used by clinicians and in prospective clinical studies. The Chief Executive Officer of Pulmatrix, a US company developing an inhaled antifungal medicine, stated: "*Dr Denning's collaboration with a global group of experts was central to the development of clear guidelines for the diagnosis of ABPA… clear and consistent diagnostic criteria are fundamental for the development of a clinical program of treatment and form the foundation of our ongoing clinical program to develop such a treatment*" [Iii].

Increased serological testing

Increased recognition of CPA as a clinical entity led to a resurgence of interest in *Aspergillus* serological testing and radiological interpretation. For example, in 2018, the first point-of-care assay for *Aspergillus* IgG antibody was launched by LDBio, a French diagnostic company. LDBio's Research and Development Director stated, "*the important work done by Manchester on aspergillosis, with its global perspective, was one of the key factors that led us into attempting to produce our LDBio Aspergillus assay*" [Ii]. LDBio have product distributors in 17 countries and their assay is shipped worldwide [Ii].

Pulling antifungal drug development into new areas of need

UoM's SAFS research [4] opened new fields of clinical study and drug development. Amongst four companies developing the first inhaled antifungal therapies are Pulmatrix and Pulmocide, both attracting significant financing for their work.

Pulmatrix's inhaled antifungal is in phase II study in asthmatic patients, initiated in 2019. Their CEO stated, "*Pulmatrix has raised over $60 million* [USD60,000,000] *through partnership and financing efforts to support all R & D efforts. These efforts have been heavily influenced by the work of Dr Denning and his colleagues at the University of Manchester*" [Iii].

UK company, Pulmocide, are developing PC945, a novel triazole inhaled antifungal. Their Chief Scientific Officer (CSO) stated Denning's research "*has enabled Pulmocide to focus on indications of highest unmet clinical need…Publications from the Manchester group have clarified the diagnostic criteria for infections caused by Aspergillus*" [Iiii].

PC945 is currently in phase II trials, including patient recruitment at NAC. It has been used on a "special needs" basis in nine patients, unresponsive to multiple antifungal therapies. Pulmocide reported in July 2020, of nine patients treated, eight showed positive clinical results [J].

On commercial impact, Pulmocide's CSO stated, "*Manchester publications on disease prevalence have clarified indications of maximal future commercial potential. This has been supportive of the Pulmocide ability to attract venture capital investment for the company*" [Iiii]. Pulmocide are supported by top-tier investors including SV Health Investors, Johnson & Johnson Innovation and SR One, GlaxoSmithKline's corporate venture capital arm [Iiii].

Nationally commissioned infectious disease service

Founded and directed by UoM's Denning (2009-2020), Manchester's NAC was the UK's first nationally commissioned infectious disease service, and the world's first national clinical centre for a fungal disease. National commissioning was based on Denning's clinical research expertise [2, 3], clinical care complexity, need for specialised investigations, and antifungal drug cost. NAC and Mycology Reference Centre were awarded European Confederation of Medical Mycology's Diamond Centre of Excellence status in January 2017, the only such UK centre. From August 2013 to March 2020, >2,500 patients were referred to NAC, >800 were diagnosed with CPA and >9,900 outpatient follow up appointments were attended [C].

5. Sources to corroborate the impact

A. Global guidances on invasive aspergillosis - ***citing UoM research and recommending Voriconazole to treat invasive aspergillosis***:

   i. **America**: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America, Patterson TF, Thompson GR 3rd, Denning DW, et al. *Clin Infect Dis*. 2016;63(4):e1-e60- ***cites UoM references 1, and 5 and >30 other Denning papers, cites UoM reference 3 and also recommends Posaconazole***

   ii. **Middle East**: Clinical practice guidelines for the treatment of invasive *Aspergillus* infections in adults in the Middle East region. Al-Abdely HM, Alothman AF,

Salman JA, et al .*J Infect Public Health*. 2014;7(1):20-31 – ***cites UoM reference 1 and seven other Denning papers***

iii. **Australasia:** Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, Blyth CC, Gilroy NM, Guy SD, et al. 2014. *Intern Med J*. 2014;44(12b):1333-1349 – ***cites UoM reference 1 and three other Denning papers***

iv. **Europe:** Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. *Clin Microbiol Infect*. 2018;24 Suppl 1:e1-e38 – ***cites UoM references 1 and 3 and >20 other Denning papers***

B. Pfizer Financial reports- ***showing Voriconazole (Vfend) sales figures***

i. 2015 Financial report- ***includes sales figures for 2013-2015***

ii. 2017 Financial report- ***includes sales figures for 2015-2017***

C. The National Aspergillosis Centre: Annual reports 2013/14 to 2019/20 - ***showing growth in patient numbers, impact and outputs***: www.aspergillosis.org/nac-reports/ 2014/15 NAC antifungal expenditure reported in 18/19 report page 31.

D. Voriconazole WHO Essential Medicine application & listing: application submitted by GAFFI, ***EML application cites UoM reference 1 and other Denning papers, 2017 Voriconazole received EML status***

E. Voriconazole: shown on GAFFI drugs map - ***showing worldwide availability*** https://antifungalsavailability.org/maps/map/voriconazole

F. Chronic pulmonary aspergillosis – Rationale and clinical guidelines for diagnosis and management. (European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and European Respiratory Society (ERS)). Denning DW, Cadranel J, Beigelman-Aubry C, et al. Eur Resp J 2016; 47:45-68. DOI: 10.1183/13993003.00583–2015 - ***first clinical guidelines specifically for CPA***

G. World Health Organisation's International Classification of Diseases: Chronic pulmonary aspergillosis (with sub-categorisation) & *Aspergillus* bronchitis https://bit.ly/3kClPmr - ***creation of new disease entities in International Classification of Diseases: CPA 1F20.12, Aspergillus bronchitis 1F20.14***

H. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Agarwal R, Chakrabarti A, Shah A, et al. Clinical & Experimental Allergy 2013; 43:850–873 DOI: 10.1111/cea.12141- ***guidelines for the diagnosis of ABPA citing UoM references 4 and 6***

I. ***Letters of support from industry for UoM work:***

i. LDBio (R& D Director) 6 July 2020 and list of LDBio distributors.

ii. Pulmatrix (Chief Executive Officer) 7 June 2020.

iii. Pulmocide (Chief Scientific Officer) 5 June 2020 and list of Pulmocide investors.

J. ***Details of patients treated with PC945 on 'special needs' basis*** as of July 2020. http://pulmocide.com/product/pc945/