Institution: The University of Manchester

Unit of Assessment: 2 (Public Health, Health Services and Primary Care)

Title of case study: Successfully tackling serious fungal diseases to transform global population health

Period when the underpinning research was undertaken: January 2007 – December 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	2005 – present
Malcolm Richardson	Professor of Medical Mycology (Honorary)	2009 – present
Sara Gago	Research Fellow	2010 – present

Period when the claimed impact occurred: August 2013 – December 2020

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

1. Summary of the impact

Over 1,000,000,000 people worldwide are affected by serious fungal disease, resulting in over 1,500,000 deaths annually. University of Manchester (UoM) research led an evidence-based global advocacy programme to address lack of diagnostics and generic antifungals as well as inadequate clinical skills. Denning set up the Global Action Fund for Fungal Infections (GAFFI) in 2013 to mitigate the global impact of fungal diseases. Five antifungal drugs and eight key diagnostics are now flagged by the World Health Organization (WHO) as 'Essential', and GAFFI has produced estimates of fungal diseases for 65 countries. National clinical training programmes in Guatemala and Nigeria for HIV patients with life-threatening fungal infections resulted in improved clinical skills and saved lives.

2. Underpinning research

Our research programme documented the burden of multiple serious fungal diseases and gaps in data and knowledge, as well as a dearth in diagnostics and limited antifungal drug access. Application of UoM-led research in Nigeria and Guatemala has shown how improvements in health systems can transform outcomes.

a. Epidemiology of serious fungal diseases

The first global estimate of any fungal disease incidence was published in 2009 by the Centers for Disease Control and Prevention. Since then, Denning and his international collaborators have reported modelled incidence and prevalence estimates of fungal diseases in >70 published papers. These include global estimates of prevalent cases of chronic pulmonary aspergillosis (CPA) after tuberculosis (TB) [1], complicating sarcoidosis (72,000), allergic aspergillosis in asthma (~4,700,000), and cystic fibrosis (6,675). Also, recurrent vulvovaginal candidiasis (135,000,000), tinea capitis (scalp and hair infection) (>200,000,000) [2], annual incident cases of invasive aspergillosis complicating chronic obstructive pulmonary disease (1,000,000 - 2,700,000), cryptococcal meningitis in AIDS (223,000) [3] and sight-threatening fungal keratitis (1,050,000-1,500,000). GAFFI has published over 65 country-specific incidence and prevalence estimates for serious fungal diseases. Cryptococcal meningitis deaths were estimated at 181,100, 15% of all AIDS deaths [3]. Modelling of the beneficial impact of timely diagnosis and treatment of lethal infections in AIDS [4] showed that many deaths were avoidable: >60,000 deaths had only 60% cryptococcal antigen testing and treatment with Amphotericin B and Flucytosine. All of

these estimates have substantially increased fungal disease awareness, supporting health systems planning.

b. Chronic pulmonary aspergillosis (CPA) misdiagnosed as tuberculosis (TB)

The airborne fungus *Aspergillus* is the most common mould-affecting human lungs, causing invasive life-threatening infection, CPA and 'fungal asthma'. We estimated 1,170,000 prevalent cases of CPA after TB globally [1]. Prospective cohort and cross-sectional studies were launched in Nigeria, Uganda, Brazil and Indonesia. In Nigeria, 19% of people with unconfirmed TB (~45% of the total) without HIV infection had CPA, not TB. In Indonesia, 10 (8%) of 128 patients had CPA at the end of TB therapy. The 5-year mortality of CPA is 82.5%, if left untreated. We co-ordinated the first multicentre trial of a commercial Pneumocystis PCR test (common cause of pneumonia in AIDS), drove development of new *Aspergillus* antibody tests, and, with GAFFI, pioneered a novel health systems approach to rapid diagnostics provision for HIV-infected patients via a Diagnostic Laboratory Hub in Guatemala [5].

c. Enhanced access to antifungal therapy

Most current antifungal drugs are generic and were launched decades ago. Lack of antifungal availability is a critical gap, leading to serious illness and death. We undertook the first global analysis of antifungal drug availability [6]. Amphotericin B (licensed 1959) is not available in 42 of 155 (43.1%) countries; Flucytosine (licensed 1973), required for cyptococccal meningitis in AIDS, is unavailable in 94 of 120 (78.3%) countries (and was not available in a single African nation). Itraconazole (licensed 1991) is essential for histoplasmosis and aspergillosis, but its daily price varied from <USD1 to USD102, and in Nigeria and South Africa it is three-to-four times more costly than in the UK.

3. References to the research

1. **Denning DW**, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to tuberculosis. *Bulletin of WHO* 2011;89:864-72. doi: 10.2471/BLT.11.089441 (169 citations, Web of Science (WoS), 3 November 2020).

2. Bongomin F, **Gago S**, Oladele RO, **Denning DW**. Global and multi-national prevalence of fungal diseases – estimate precision. *Journal of Fungi* 2017;3:E57. doi: 10.3390/jof3040057 (305 citations, WoS, 3 November 2020).

3. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, **Denning DW**, Loyse A, Boulware DR. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet, Infectious Diseases* 2017;17:873-81. doi: 10.1016/S1473-3099(17)30243-8 (534 citations, WoS, 3 November 2020).

4. **Denning DW**. Minimizing fungal disease deaths will allow the UNAIDS target of reducing annual AIDS deaths below 500 000 by 2020 to be realized. *Philosophical Transactions of the Royal Society of London. Series B, Biological sciences* 2016: 371:20150468. doi: 10.1098/rstb.2015.0468 (42 citations, WoS, 3 November 2020).

5. Samayoa B, Bonillo O, Medina N, Lau-Bonilla D, Mercado O, Moller A, Perez JC, Alastruey-Izquierdo A, Arathoon E, **Denning DW**, Rodríguez-Tudela JL. The Diagnostic Laboratory Hub, a new healthcare system reveals the incidence and mortality of tuberculosis, histoplasmosis and cryptococcosis of PLHIV in Guatemala. *Open Forum Infectious Diseases* 2019 7(1):ofz534. doi: 10.1093/ofid/ofz534 (5 citations, WoS, 3 November 2020)

6. Kneale M, Bartholomew JS, Davies E, **Denning DW.** Global access to antifungal therapy and its variable cost. *Journal of Antimicrobial Chemotherapy* 2016;71:3599-606. doi:10.1093/jac/dkw325 (40 citations, WoS, 3 November 2020).

4. Details of the impact

Context

Pre-2013, public health mycology was a non-existent discipline, until dissemination of our research transformed this landscape at the WHO and in the international academic arena. The scale of the problem is huge: nearly 50% of all AIDS deaths are attributable to fungi [2,3,4] and the leading infectious cause of death in leukaemia is aspergillosis. However, funding for fungal disease research represents only 2% of all infection and immunity funding, and the antifungal drugs market spend is also disproportionately low.

Pathways to Impact

For 20 years UoM investigators have led research on and clinical care for aspergillosis. We set up the world's first national service for any infectious disease in 2009 (National Aspergillosis Centre, NAC) in Manchester, providing a global beacon for chronic and allergic pulmonary aspergillosis. Our modelling [1] led to the first comprehensive attempt to estimate the country-specific burden of most serious fungal diseases. In 2013, Denning founded an international foundation - GAFFI - primarily as an evidence-based global advocacy voice for fungal diseases. Multiple UoM-led epidemiological studies have estimated CPA burden and impact. Our research and GAFFI efforts have improved global awareness of the lack of diagnostics and generic antifungal agents [6] and UoM has led global engagement to address these missing elements in healthcare systems.

Reach and Significance of the Impact

a. Combatting aspergillosis:

In the UK, 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 [A]. Our modelling evidence has provided the impetus, clinical need arguments and commercial opportunities for the world's first prospective clinical antifungal developments in CPA (liposomal caspofungin (Fujifilm)) and allergic aspergillosis (inhaled azoles (Pulmatrix, Pulmocide, TFF Pharmaceuticals and Zambon)), recently acknowledged at a US Food and Drug Administration public workshop [B]. Pulmatrix stated "*the progress of our efforts to treat pulmonary fungal infections continue to be substantially aided by the world-renowned expertise… available at the University of Manchester*" [Ci] and confirmed they have "*raised over $60 million* [USD60,000,000] *through partnership and financing efforts to support R&D efforts…These efforts have been heavily influenced by the work of Dr Denning and his colleagues at the University of Manchester*" [Ci]. UK company Pulmocide stated UoM's research "*has enabled Pulmocide to focus on indications of highest unmet clinical need"* and had resulted in "*increasing awareness by public health and regulatory authorities as to the importance of new therapies"* [Cii]. Our extensive experience in diagnosis and therapy has also been incorporated into European [Di], United States [Dii] and low and middle income country [Diii] guidelines for diagnosis and management of CPA.

b. WHO adoption of fungal diseases, antifungal drugs and diagnostics:

Multiple proactive public health interventions have been adopted by WHO after dialogue with and applications from GAFFI based on UoM research, including:

- Adoption of 5 antifungal drugs on the WHO's Essential Medicines List (EML) (Amphotericin B and Flucytosine in 2013; Itraconazole, Voriconazole and Topical Natamycin in 2017 [Ei]; Echinocandins application submitted for 2021). For context, from 1977 the WHO EML includes 460 medicines and is adopted by >140 countries.
- Several diagnostics were included on the WHO's first List of Essential In Vitro Diagnostics, including microscopy, fungal culture, blood culture, histopathology and cryptococcal antigen and in 2019, *Histoplasma* antigen [Eii]. *Aspergillus* antigen and antibody, and *Pneumocystis* PCR have been accepted for the 2021 list as a direct consequence of UoM-led research.

- WHO adoption in 2017 of chromoblastomycosis and other deep mycoses as Neglected Tropical Diseases (NTDs), under the broad label of 'Skin NTDs' [F].
- Ensuring resistance surveillance in *Candida* spp. was incorporated into the WHO global antimicrobial resistance surveillance (GLASS) programme in 2018, the first time that fungi have been included as part of any global antimicrobial resistance surveillance [G].

c. Global health systems improvements:

In Guatemala, a national diagnostic and clinical training programme for opportunistic infections in AIDS was initiated during 2015 [6]. Developed by UoM, in collaboration with GAFFI, diagnostics and training were provided by Asociacion de Salud Integral (ASI). Guatemala has the worst record in Latin America of late stage, first presentations of HIV infection (over 45%). The programme has rapidly tested >2,500 patients annually (with 18% life-threatening infection risk), allowing immediate administration of correct antifungal, anti-TB, and/or anti-HIV therapy. Greatly improved clinical management led to a fall in histoplasmosis 6-month mortality risk to 29% (previously >55%). The overall programme mortality fell by 8% from 2017 to 2018.

The Chairman of the Board of El Mecanismo de Coordinación de Guatemala heralded "*… the importance and success of this program, which has shown … how to avoid unnecessary deaths from advanced HIV…*" [Hi] (translated). The President of Infectious Diseases Society of Guatemala stated, "*The University of Manchester and GAFFI deserve a great deal of credit for designing and implementing a world first program of this scale*" [Hii]. The UNAIDS Country Director, Guatemala, stated, "*We congratulate GAFFI, the University of Manchester and ASI on this achievement... Undoubtedly, initiatives like this provide the framework for countries to institutionalize integrated approaches to meet the global goal of ending AIDS as a public health threat by 2030"* [Hiii]. Our work in Guatemala demonstrated how to achieve better clinical outcomes. As a result of this and GAFFI's advocacy, the Pan American Health Organization published the first international guidelines for disseminated histoplasmosis in AIDS [I], a mycology reference laboratory is being set up in Paraguay, and replication of the Guatemalan programme is planned in other countries, including Panama and Costa Rica.

We have also initiated implementation in Africa. In Nigeria, we supported the launch of a UoM-developed training programme in diagnosis and treatment of cryptococcal meningitis in AIDS for >700 healthcare professionals across 13 sites. This programme led to significantly improved understanding of screening, diagnosis and best management practices [J], thereby providing a platform for implementing further capacity building interventions in HIV care.

5. Sources to corroborate the impact

A. The National Aspergillosis Centre: Annual reports 2013/14 to 2019/20 - *showing growth in patient numbers, impact and outputs*: www.aspergillosis.org/nac-reports/

B. US Food and Drug Administration Virtual Public Workshop. Addressing Challenges in Inhaled Antifungal Drug Development September 25, 2020. *Talks given by representatives from Pulmatrix, Pulmocide, TFF Pharmaceuticals and Zambon in a session co-chaired by Denning who also presented*. www.fda.gov/drugs/news-events-human-drugs/addressing-challenges-inhaled-antifungal-drug-development-09252020-09252020.

C. Testimonial letters from industry *confirming the importance of UoM research and publications in the field*.

   i. Pulmatix (Chief Executive Officer) 7 June 2020

   ii. Pulmocide (Chief Scientific Officer) 5 June 2020

D. European, United States and low and middle income country guidelines for chronic pulmonary aspergillosis - *UoM research group's extensive experience in diagnosis and therapy has been incorporated into guidelines for diagnosis and management of CPA*:

i. European: Denning DW et al. (2016) Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J; 47(1):45-68

ii. United States: Patterson TF et al. (2016). Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis; 63(4):e1-e60

iii. Low and middle income countries: Denning DW et al. 2018. Case definition of chronic pulmonary aspergillosis in resource-constrained settings. Emerg Infect Dis; 24(8):e171313

E. WHO Model Lists - *updated after applications based on UoM research*

i. Model List of Essential Medicines (June 2019) – *antifungals include Amphotericin B, Flucytosine,Itraconazole, Voriconazole and Natamycin eye drops - adopted after applications based on UoM research.*

ii. Second WHO Model List of Essential in Vitro Diagnostics (May 2019) – *includes fungal culture, direct microscopy, cryptococcal antigen (2018), Histoplasma antigen (2019) - adopted after applications based on UoM research.*

F. WHO Neglected Tropical Diseases- Inclusion of chromoblastomycosis and other deep mycoses in 2017 - *after application based on UoM research*.

G. WHO's Global Antimicrobial Resistance Surveillance System (GLASS):

i. 'Early implementation protocol for inclusion of *Candida* spp.' August 2019 *uses European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for Antifungal Susceptibility Testing breaking points and methods which Denning contributed to in early stages.*

ii. *EUCAST technical note on Fluconazole.* Clin Microbiol Infect. 2008 Feb;14(2):193-5. Erratum in: Clin Microbiol Infect. 2009 Jan;15(1):103 – *example of Denning's contribution to EUCAST in early stages.*

H. Letters of testimonial from Guatemala - *confirming the value of diagnostic and clinical training programmes designed by UoM in collaboration with GAFFI and ASI and its adoption*:

i. Letter from Presidente Junta Directiva (Chairman of the Board of Directors) Mecanismo de Coordinacion de Pais, Republica de Guatemala 29 June 2020 (letter written in Spanish)

ii. Letter from President of Asociación Guatemalteca de Enfermedades Infecciosas (Infectious Diseases Society of Guatemala) 1st July 2020

iii. Letter from UNAIDS Country director, Guatemala 2nd July 2020

I. Pan American Health Organization Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV. April 2020- *first international guidelines/recommendation developed following Guatemala program.*

J. Tackling cryptococcal meningitis in Nigeria, one-step at a time; the impact of training. Oladele RO, Jordan A, Akande P, et al. *PLoS One*. 2020;15(7):e0235577. Published 2020 Jul 6. DOI:10.1371/journal.pone.0235577 – *training programme developed by UoM led to improved understanding of Nigerian policy on screening, diagnosis and best management practices.*