Institution: University of Birmingham

Unit of Assessment: UoA 1, Clinical Medicine

Title of case study: Development of faecal microbiota transplant (FMT) to improve outcomes of patients with recurrent *Clostridioides difficile* infection

Period when the underpinning research was undertaken: 2010–2020

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:
Peter Hawkey	Professor Clinical and Public Health Bacteriology	July 2001–June 2020

Period when the claimed impact occurred: October 2017–December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Professor Hawkey has impacted on the treatment of patients suffering recurrent and refractory (not responding to antibiotic therapy) *Clostridioides difficile* infection (rCDI), the foremost cause of hospital-acquired diarrhoeal disease worldwide. Hawkey's development of faecal microbiota transplants (FMT) as a licenced medicinal clinical product for patients suffering recurrent and refractory *C. difficile* infections resulted in the following impacts:

- **Patient outcomes have improved** through the provision of FMT for treatment of rCDI across 52 NHS trusts.
- **UK guidelines have been adopted by the joint British Society of Gastroenterology (BSG) and Healthcare and Infection Society (HIS)** recommending the use of FMT for recurrent/refractory CDI.
- **The cost of treatment of patients with rCDI infection has been reduced** as FMT provides a significantly cheaper treatment option.

2. Underpinning research

Clostridioides difficile (*C. difficile*) **is a bacterium that infects the bowel** and is the leading cause of hospital-acquired diarrhoeal disease worldwide, causing considerable morbidity and mortality. In 2017/18, there were 13,286 cases of *C. difficile* infection (CDI) reported by NHS Trusts in England (2.24 cases per 1,000 hospital admissions).

CDI usually affects people who have been treated with broad-spectrum antibiotics and is easily spread to other patients in hospital. Antibiotics deplete the normal gut flora, allowing *C. difficile* to proliferate and produce toxins which damage the gut wall.

CDI can cause serious bowel problems and is thus very debilitating, particularly in the elderly. 30% of patients do not respond to usual antibiotic treatment and of these patients only 20–40% respond to secondary treatment with specialised antibiotics (fidaxomycin, vancomycin). This means that approximately 1,650 patients/year will suffer recurrent and refractory *C. difficile* infection (rCDI), a chronic debilitating disease which is unlikely to respond to further antibiotic treatment and for which no viable treatment options remain. It is estimated that 15–20% of these patients will die as result of rCDI.

Professor Hawkey (Professor of Clinical and Public Health Bacteriology, University of Birmingham (UoB)) is an internationally recognised researcher and key opinion leader who has been working on the problem of CDI for more than 20 years, both in the UK (R1–R3) and in China (R4). CDI rapidly increased in the 2000s and became critical in 2006 when 65,000 cases

were reported in the UK with 5,000 deaths. In response to this, a coherent UK control strategy had to be developed quickly.

Hawkey was invited by the Department of Health to chair an expert panel to deliver national guidance for the control of CDI (published 2008, updated in 2013; R5). One potential treatment for CDI is faecal microbiota transplant (FMT), which was identified as a therapeutic option in the 2008 report and further expanded on in the 2013 update. FMT involves the administration of faecal flora from a healthy donor to a patient suffering from rCDI, after which *C. difficile* is supressed or eliminated, thus curing the patient.

Hawkey established a FMT service in 2012, supported by Public Health England (PHE) and Heartlands Hospital Birmingham. Shortly after this service was established, and following a ruling by the European Medicines Agency (2014) that member countries could regulate FMT either as a medicine or a transplant, the Department of Health (England) chose the medicine route which caused the PHE service to cease operations. If FMT was to continue to be used widely, **it was necessary to develop and register it as a medicine with the MHRA**. In a key output, Prof. Hawkey described his research into FMTs for rCDIs and the development of the methodology for successful regulatory licencing (R6) including the following key findings (KF):

- **KF1**: Identification and introduction of the most suitable methods to control faecal homogenisation and microbial containment (centrally provided material and specialised preparation methods);
- **KF2**: The most effective and safe protocol for production and delivery of FMT as a medicine — nasogastric tube delivery combined with PPI inhibitor and gastric propellant;
- **KF3**: Extensive screening of donors to reduce risk factors (e.g. high BMI, absence of microbial pathogens) for donation.

3. References to the research

R1. Coexistence of multiple multilocus variable-number tandem-repeat analysis subtypes of *Clostridium difficile* PCR ribotype 027 strains within fecal specimens. Tanner HE, Hardy KJ, **Hawkey PM**. J Clin Microbiol. 2010 Mar;48(3):985-7. **DOI: 10.1128/JCM.02012-09**.

R2. Extended multilocus variable-number tandem-repeat analysis of *Clostridium difficile* correlates exactly with ribotyping and enables identification of hospital transmission. Manzoor SE, Tanner HE, Marriott CL, Brazier JS, Hardy KJ, Platt S, **Hawkey PM.** J Clin Microbiol. 2011 Oct;49(10):3523-30. **DOI: 10.1128/JCM.00546-11**.

R3. Investigation of community carriage rates of *Clostridium difficile* and *Hungatella hathewayi* in healthy volunteers from four regions of England. Manzoor SE, McNulty CAM, Nakiboneka-Ssenabulya D, Lecky DM, Hardy KJ, **Hawkey PM.** J Hosp Infect. 2017 Oct;97(2):153-155. **DOI: 10.1016/j.jhin.2017.05.014**

R4. Molecular Epidemiology of *Clostridium difficile* Infection in a Major Chinese Hospital: an Underrecognized Problem in Asia? **Peter M. Hawkey**, Clare Marriott, Wen En Liu, Zi Juan Jian, Qian Gao, Thomas Kin Wah Ling, Viola Chow, Erica So, Raphael Chan, Katie Hardy, Li Xu, Susan Manzoor. J Clin Microbiol. 2013 Oct; 51(10): 3308–3313. **DOI: 10.1128/JCM.00587-13**.

R5. Updated guidance on the management and treatment of *Clostridium difficile* infection, Public Health England, 2013 [PHE gateway number: 2013043]; link to guidance document].

R6. Results from the first English stool bank using faecal microbiota transplant as a medicinal product for the treatment of *Clostridioides difficile* infection. McCune VL, Quraishi MN, Manzoor S, Moran CE, Banavathi K, Steed H, Massey DCO, Trafford GR, Iqbal TH, **Hawkey PM**. EClinicalMedicine. 2020 Mar 16;20:100301. **DOI: 10.1016/j.eclinm.2020.100301.**

4. Details of the impact (indicative maximum 750 words)

Hawkey's work has impacted on the treatment of patients suffering from recurrent and refractory *C. difficile* infection (rCDI). Specifically, it has improved patient outcomes through provision of FMT for rCDI, reduced the costs of treatment, influenced healthcare guidelines and facilitated the introduction of FMT in new clinical indications.

Patient outcomes have improved through the provision of FMT for treatment of rCDI

Patient outcomes have improved as a direct result of the development and implementation of a **new clinical intervention** for FMT delivery for rCDI treatment (KF1-3). In 2017, Hawkey developed the **first licenced FMT product** (October 2017; S1) for patients with rCDI in England. Since then, the number of UK trusts using FMT has risen from 19 in 2018 to 54 in 2020 (S2). In addition, Hawkey contributed to the implementation of FMT within UK hospitals through establishment of **UoB's Microbiome Treatment Centre** (September 2018; S1), which worked in partnership with NHS England, to ensure that FMT is the standard of care for all patients with rCDI. The FMT service was awarded the **NHS England's Innovation Tariff**, which guaranteed free supply of FMT to all English trusts (2018–2020) thereby overcoming financial and procurement barriers to the introduction of FMT into clinical practice. Since its establishment in 2017, the **Microbiome Treatment Centre has supplied/treated 215 patients across the UK**.

FMT treatment is highly effective when compared to previous treatments. For example, an in-depth analysis of the first 124 treated patients showed that a clinical response was seen at day 7 in 84% of patients, and a clinical cure after 90 days in 78% (R6). This compares with studies using antibiotic therapy for the treatment of rCDI that report clinical cure rates of ≤40%.

For the 1,650 patients/year who suffer rCDI, and who do not respond to antibiotic therapy, there remains an unmet clinical need and approximately 15% (245) of infections will prove fatal. As a result of the high response rates, FMT treatment would be expected to cure up to 1,290 patients with rCDI per year (78% of 1,650) and reduce the number of deaths down to 55 (15% of the 22% of patients who do not respond) (R6). Adverse events were shown to be rare and unrelated to FMT. Of the first 124 patients treated, only 2 patients died within 7 days of receiving an FMT: 1 due to uncontrolled CDI and another from underlying bowel cancer (R6). Minor adverse events, including constipation, abdominal pain and bloating, were reported in ≤4 patients, demonstrating that the protocol developed by Hawkey is safe and minimises patient discomfort.

Improved patient outcomes were further evidenced by a reduction in bowel movements in FMT-treated patients. Recurrent CDI (rCDI) significantly impacts on daily life with patients being ill for 3–6 months and passing up to 20 bowel movements a day. Treatment with FMT through the UoB licenced service **significantly improved symptoms**. In recurrent CDI, clinical response to FMT was seen in 91% of patients (64/70) at day 7 with a reduction to <3 bowel movements per day, and a consequent improved quality of life (R6). A BBC interview with one of Hawkey's patients who received FMT treatment through the service illustrates the beneficial effects that FMT treatment has on a patient's daily life: "after 48 hours, it was like a miracle. At the time, I didn't like the idea at all, but I can only thank the person who donated for giving me back my life" (S3).

Healthcare guidelines have been developed for the use of FMT for recurrent CDI

UK guidelines on the use of FMT for recurrent/refractory CDI have been adopted by the joint British Society of Gastroenterology (BSG) and Healthcare and Infection Society (HIS) (S4i–ii). Hawkey acted as a key panel member in shaping these guidelines, contributing academic expertise and knowledge in key areas including: "preparation of FMT as a medicinal product" and "distributing to 3rd party hospitals across the UK" (S5). Key to these guidelines was the incorporation of key findings (KF1–KF3) identified whilst the medicinal product was being developed.

The cost of treatment of patients with rCDI infection has been reduced

As the leading cause of hospital-acquired diarrhoeal disease worldwide, rCDI contributes a substantial economic burden with mean total costs for recurrent infection estimated to be £31,121 per patient/per episode (2014–2017) (S6). This includes hospital costs from prolonged stays, antibiotic therapy and chronic health incapacity. **FMT treatment of rCDI represents a significantly cheaper treatment option and affords opportunities for costs savings** (S7).

- Full cost of treatment for FMT using the nastrogastric route developed by Hawkey is £8,880/patient, which is substantially less than the standard treatment using the antibiotics fidaxomicin (£14,399) or vancomycin (£17,279).
- The cure rate in patients treated with FMTs (78%) versus antibiotic therapy (30–40%) indicates that FMT treatment leads to earlier hospital discharge and reduces the need for long-term treatment with antibiotics, thus minimising the risk of the development of antibiotic resistance.

The results of full economic evaluation illustrate that FMT is highly cost-effective. The methodology developed by Hawkey (administration via nasogastric tube, use of proton pump inhibitor and gastric propellant) **meet the NICE cut-off of £20,000 per QALY** (quality adjusted life year), the maximum allowed cost for a treatment to add 1 year of perfect health (S7).

In addition, Hawkey's work on FMT is offering insights into the management of other diseases. As the UoB Microbiome Treatment Centre was the first clinical service aimed at restoration of the gut microbiome through FMT, it supported the use of this intervention in other diseases in which disruption of the microbial ecosystem of the human gut are a contributing factor. For example, a multicentre national trial supported by NIHR into the **therapeutic benefits of FMT in ulcerative colitis** (STOP COLITIS) led by Prof Tariq Iqbal (UoB) (S8).

5. Sources to corroborate the impact

S1. Evidence of service provided by University of Birmingham (Microbiome treatment centre), confirming first licenced product and free supply of FMT medicinal product to all English trusts through awarded innovation tariff.
S2. Report related to numbers of trusts regularly using service pre/post licencing.
S3. BBC News article illustrating patient benefit
S4. (i). The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare and Infection Society (HIS) guidelines. **DOI: 10.1016/j.jhin.2018.07.037**. **(ii).** The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. Gut. 2018 Nov;67(11):1920-1941. **DOI: 10.1136/gutjnl-2018-316818**.
S5. Testimonial confirming contribution of Prof. Hawkey and University of Birmingham research to Guideline development (01/12/2020).
S6. Evidence of substantial economic burden of recurrent CDI infection. Healthcare resource use and attributable cost of Clostridium difficile infection: a micro-costing analysis comparing first and recurrent episodes R Tresman & SD Goldenberg. J Antimicrob Chemother 2018; 73: 2851–2855. **DOI:10.1093/jac/dky250**.
S7. Abdali ZI, Roberts TE, Barton P, Hawkey PM. Economic evaluation of Faecal microbiota transplantation compared to antibiotics for the treatment of recurrent *Clostridioides difficile* infection; EClinicalMedicine. 2020 Jun 27;24:100420. **DOI: 10.1016/j.eclinm.2020.100420**
S8. STOP-Colitis pilot trial protocol: a prospective, open-label, randomised pilot study to assess two possible routes of faecal microbiota transplant delivery in patients with ulcerative colitis. Quraishi MNN, Yalchin M, Blackwell C, Segal J, Sharma N, Hawkey P, McCune V, Hart AL, Gaya D, Ives NJ, Magill L, Loi S, Hewitt C, Gerasimidis K, Loman NJ, Hansen R, McMullan C, Mathers J, Quince C, Crees N, Iqbal T. BMJ Open. 2019 Nov 11;9(11):e030659. **DOI: 10.1136/bmjopen-2019-030659**