Institution: King's College London		
Unit of Assessment: UoA1		
Title of case study: Reducing the burden of hospital associated *Clostridioides difficile* infections across England		
Period when the underpinning research was undertaken: 2011 - 2018		
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:**
Dr Simon Goldenberg	Reader in Clinical Microbiology	2013 – present
Professor Gary French	Professor of Microbiology	May 1990 – November 2011
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

In the mid 2000's, an outbreak of *Clostridioides* (previously known as *Clostridium*) *difficile* infection caused hundreds of infections and deaths in the UK. King's research provided strategies to help combat this disease in Guy's and St Thomas' NHS Foundation Trust (GSTT) by improving active case finding and laboratory diagnosis. King's also evaluated and introduced unique infection control interventions which led to the development and adoption of novel therapeutic approaches referenced in NHS guidance. This has resulted in a significant reduction in all-cause mortality, infection rates and disease recurrence locally at GSTT and nationally across England.

2. Underpinning research

Emergence of Clostridioides difficile Infection (CDI) as a major healthcare associated pathogen. *C difficile* produces toxins that damage the colon lining, causing symptoms ranging from mild, self-limiting diarrhoea to colitis, perforation, sepsis and death. It primarily affects older patients with co-morbidities, particularly those who have been exposed to antibiotics or those who are immunosuppressed. In the mid 2000's CDI grew to become one of the most important healthcare associated infections. In 2006 - 2007 rates of a North American hypervirulent strain were introduced in the UK, with cases increasing to over 55,000 per year and with a case fatality rate of 20-30% (14,000 deaths/year).

King's research shows C. difficile infections are unrecognised and under-reported across the NHS [1]. In 2011, we focused on improving diagnosis / case detection and found that there was significant under-recognition of cases reported nationally, as a result of poorly performing diagnostic assays. Our research identified the diagnostic methods being used, finding that 70% were using insensitive methods leading to under diagnosis. Our research demonstrated the superiority of a multistep algorithmic approach incorporating PCR (Polymerase Chain Reaction) testing. We showed that earlier, more accurate case finding was key to effective infection control interventions.

King's demonstrate that disease prevention measures have been highly effective in reducing hospital infections. In 2015, we evaluated a number of infection control interventions **[2]**. We observed that these interventions (along with improvements in hand hygiene and antimicrobial stewardship) have resulted in significant reductions in the rate of infection over the last decade. Our collaborative research with five other NHS Trusts also demonstrated the effectiveness of the control measures that we have adopted, showing only 7% of cases could plausibly result from in hospital transmission (compared with an average of 20% across all hospitals) **[3]**.

King's show that new treatment approaches using the antibiotic fidaxomicin dramatically improve patient outcomes in CDI. Our work involving seven NHS Trusts and 1168 patients **[4]** has shown how the widespread adoption of a new antibiotic (fidaxomicin) to treat CDI has numerous advantages including significantly reduced recurrence rates (from 16.3 to 3.1%) and lower all-cause mortality (from 17.3 to 6.3%). It demonstrated that the approach of using

fidaxomicin as a first line agent resulted in greater benefit than those Trusts where it was introduced on a more restrictive basis. A further study has also shown that fidaxomicin use is associated with reduced contamination of the hospital environment (reduction of 20.8%) **[2]**.

We participated in a randomized controlled trial of a novel dosing (extended-pulsed) regimen of this drug, which results in improved clinical cure and recurrence rates compared with standard therapies (reduction of 11%) **[5]**. We also looked at the effect of fidaxomicin in special groups where information on the use this drug is lacking, since these patients were excluded from phase 3 trials. This study **[5]** demonstrated the effectiveness of the drug in these poorly studied groups. We have shown the cost effectiveness of this drug in both UK and EU settings using modelling techniques **[7]**. In terms of quality-adjusted life year gain, the higher cost of first line use fidaxomicin compared to vancomycin (another antibiotic used to treat CDI) is offset by lower total hospitalisation costs as a result of lower recurrence rates **[7]**.

Research by King's establishes Faecal Microbiota Transplant as an effective therapy for the treatment of recurrent CDI. Faecal Microbiota Transplant (FMT) is a therapeutic strategy to correct the underlying intestinal dysbiosis that is associated with CDI. This involves transferring a consortium of diverse microorganisms from a healthy donor to the gastrointestinal tract of affected patients. It has a success rate of ~90% in patients with multiply recurrent CDI. King's has shown that this novel treatment is effective therapy for the treatment of CDI **[6]** and in 2016, we opened a Medicines and Healthcare products Regulatory Agency (MHRA) licenced FMT research facility in CIDR laboratory, one of only two in the UK, which provides material for an increasing number of research studies and patients with recurrent CDI. This facility has enabled us to obtain NIHR grants for randomised controlled trials in novel therapeutic areas (cirrhosis and antimicrobial resistance).

King's research demonstrates the cost effectiveness of treating CDI for the NHS [8]. Our research has also examined the financial cost and overall healthcare burden of both initial CDI and recurrent disease to the local healthcare economy. This used micro-costing methods to estimate fine detail parameters which are often not considered during health economics studies. In partnership with Public Health England and London School of Hygiene and Tropical Medicine, we used multi-state modelling to determine the excess length of stay of patients with severe and non-severe CDI, as well as those with recurrent disease.

3. References to the research

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3. Eyre DW, Fawley WN, Rajgopal A, Settle C, Mortimer K, **Goldenberg SD**, Dawson S, Crook DW, Peto TEA, Walker AS, Wilcox MH. Comparison of Control of *Clostridium difficile* Infection in Six English Hospitals Using Whole-Genome Sequencing. *Clin Infect Dis*. 2017 Aug 1;65(3):433-441. DOI: 10.1093/cid/cix338

4. Goldenberg SD, Brown S, Edwards L, Gnanarajah D, Howard P, Jenkins D, Nayar D, Pasztor M, Oliver S, Planche T, Sandoe JA, Wade P, Whitney L. The impact of the introduction of fidaxomicin on the management of *Clostridium difficile* infection in seven NHS secondary care hospitals in England: a series of local service evaluations. *Eur J Clin Microbiol Infect Dis*. 2016 Feb;35(2):251-9. DOI: 10.1007/s10096-015-2538-z. *Winner of the 2016 UK Prix Galien award for research (Real World Evidence category).*

5. Guery B, Menichetti F, Anttila VJ, Adomakoh N, Aguado JM, Bisnauthsing K, Georgopali A, **Goldenberg SD**, Karas A, Kazeem G, Longshaw C, Palacios-Fabrega JA, Cornely OA, Vehreschild MJGT; EXTEND Clinical Study Group. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a

randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis*. 2018 Mar;18(3):296-307. DOI: 10.1016/S1473-3099(17)30751-X

6. Goldenberg SD, Batra R, Beales I, Digby-Bell JL, Irving PM, Kellingray L,Narbad A, Franslem-Elumogo N. Comparison of Different Strategies for Providing Fecal Microbiota Transplantation to Treat Patients with Recurrent *Clostridium difficile* Infection in Two English Hospitals: A Review. *Infect Dis Ther*. 2018 Mar;7(1):71-86. doi: 10.1007/s40121-018-0189-y.

7. Cornely OA, Watt M, McCrea C, **Goldenberg SD**, De Nigris E. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients aged ≥60 years (EXTEND): analysis of cost-effectiveness. *J Antimicrob Chemother*. 2018 Sep 1;73(9):2529-2539. DOI: 10.1093/jac/dky184

8. van Kleef E, Green N, **Goldenberg SD**, Robotham JV, Cookson B, Jit M, Edmunds WJ, Deeny SR. Excess length of stay and mortality due to *Clostridium difficile* infection: a multi-state modelling approach. *J Hosp Infect*. 2014 Dec;88(4):213-7. doi: 10.1016/j.jhin.2014.08.008.

4. Details of the impact

The improvements that were made in the clinical management of suspected or confirmed cases of CDI in Guy's and St Thomas' NHS Trust (GSTT) resulted from research conducted by King's academics. This work has been adopted by GSTT and cited in national CDI guidance. This has led to a dramatic and sustained improvement in care for patients with CDI on a local and national level.

King's algorithm led to improvement in diagnosis and detection of cases locally and nationally. Accurate and timely laboratory diagnosis is critical to allowing any infection control interventions to be implemented. In 2010, GSTT introduced a new testing algorithm developed by King's **[1]** that was able to more accurately (increased sensitivity and specificity) identify cases **[A.1]**. The Trust also implemented better infection control interventions based on King's research **[2, 3]** including rapid isolation, adherence to personal protective equipment and improving hand hygiene; enhanced methods of environmental decontamination (including novel technologies such as sporicidal cleaning agents and automated cleaning technologies using vaporised hydrogen peroxide and UV light) **[A]**. This led to dramatic reduction in cases, hospital spread, rate of infection, in-hospital transmission and environmental contamination of the hospital environment. The Site General Manager at GSTT confirmed that the system has steadily helped to reduce the spread of infections, particularly CDI at GSTT **[A.2]**.

Since 2007, PHE has carried out mandatory enhanced surveillance of CDI for NHS acute trusts, which includes GSTT. When the annual report was first introduced, GSTT had a hospital-onset CDI rate of 40.5 cases/100,000 Occupied Bed Days (OBDs). By the beginning of the impact assessment period this had already decreased to 13.5/100,000 OBDs and in 2019/2020 the rate decreased even further to 7.0 **[B.1]**.

2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20
13.5	15.8	15.4	11.2	7.8	6.3	7.0

Source [B.1]

This has resulted in GSTT achieving the lowest CDI rate in the Shelford Group (of 10 leading academic NHS organisations), a position which it has held for the past three financial years. This rate is almost half that of the next best performing Shelford Group Trust (Sheffield Teaching Hospitals NHS Trust, with a rate of 15.2 cases/100,000 OBDs) **[B.1]**. This is further confirmed by GSTT's Joint Director of Infection Prevention and Control **[A.1]**: "*King's research has significantly influenced hospital policy on control of this infection in the Trust. The introduction of many of the strategies outlined in King's research has enabled rates of infection to be reduced to one of the lowest of any comparable NHS Trust.*"

In March 2012, the Department of Health published updated guidance on the diagnosis and reporting of CDI **[B.2]** referencing King's research **[1]**. When this national guidance was published, the hospital-onset CDI rate in England was 17.3/100,000 OBDs, by 2019/20 this had reduced to 13.6 **[B.1]**. The current protocol for testing and diagnosing remains unchanged and it's based on the peer-reviewed, published research which includes King's work **[1]** as outlined on an NHS Improvement 2019/20 document on CDI objectives for NHS organisations **[B.3]**.

King's research on fidaxomicin contributed to the growing evidence that it reduces recurrence rates and lowers mortality and provides cost savings for the treatment of potentially fatal CDI. Fidaxomicin **(FDX)** was approved for use in the UK in 2012. It is one of the only four drugs approved for CDI treatment. That same year, GSTT became one of the first hospitals in the country to routinely use this new drug for the treatment of adults. King's research **[4]** showed that within the 1168 patients treated, there was a significant reduction in recurrence rates (from 16.3 to 3.1%) and lower all-cause mortality (from 17.3 to 6.3%). This was the first and only real-world evaluation of available antibiotics for CDI in the UK, that confirmed that first-line use of fidaxomicin could improve clinical outcomes in the treatment and management of CDI and its associated recurrences, resulting in an overall cost saving **[4]**.

This work was awarded the Prix Galien award for Real World Evidence in 2016 **[C]**. Worldwide, the Prix Galien is regarded as the equivalent of the Nobel Prize in biopharmaceutical and medical technology research. Sir Michael Rawlins, chair of the UK Prix Galien judging panel, said: "*A unique series of local service evaluations were conducted in 2013-2014 to evaluate the impact of Dificlir [trade name for fidaxomicin] introduction on the NHS. The evaluation, studied in real-world settings, included investigating its effects on service delivery, the management of CDI and its costs, primarily to inform local decision-making. Results indicated the very significant contribution that Dificlir's use can make to tackling the major public health problems of antimicrobial resistance through targeted antibiotic therapy and infection control* **[C.2]**."

Additionally, our work demonstrating the clinical benefits of using FDX **[4]** as well as its cost effectiveness **[5,7,8]**, has enabled its inclusion in the list of NHS England high-cost drugs **[D]**. Drugs on this list are centrally funded by NHS England, which means it doesn't come as a cost to individual NHS Trusts, thus making it more accessible for them to use.

Methods to combat CDI were further validated by King's research. After GSTT introduced King's algorithm and FDX, an analysis **[3]** was conducted to verify the effectiveness of these measures in comparison with other NHS Trusts (Leeds Teaching Hospitals, Calderdale and Huddersfield, City Hospitals Sunderland, St. Helens and Knowsley Teaching Hospitals and Great Western Hospitals). The data ranging from June 2013 to August 2014, revealed a low rate of in-hospital transmission at GSTT; only 7% of isolates could be potentially linked to a previous case at GSTT, compared with an average of 20% at the other NHS hospitals (range 7-24%) **[3]**.

King's research enabled expansion of FMT services with a regulated and licensed manufacturing facility. Although the initial treatment with anti-*C. difficile* antibiotics is generally effective, a significant proportion of patients (20-30%) suffer recurrent infection, which is associated with a disrupted/less diverse gut microbiota. Newer methods of manipulating the gut microbiota such **Faecal Microbiota Transplant (FMT)** are key to improving clinical outcomes. King's research provided the evidence base **[6] [E]** for FMT to be introduced at GSTT in 2014.

In 2016, the success of FMT led to the creation of an MHRA licensed stool bank which has been used to treat over 250 patients from Guys and St Thomas. Owing to the current complexity of establishing an MHRA-accredited service for FMT, GSTT has become a centre of referral for other NHS providers in South East England with CDI and Ulcerative Colitis. This is one of only two licensed facilities in England and has facilitated two successful NIHR grant applications for randomised controlled trials of FMT in cirrhosis **[F.1]** and antibiotic resistant organisms **[F.2]**. Clinical success rates for patients treated with FMT have been over 95% and have improved quality of life as outlined in a patient's testimonial **[F.3]**: "*I have a Primary Immunodeficiency and*

get virtually continuous urinary infections and frequent chest infections, all requiring a large number of antibiotics. Several times I have ended up with CDI, a difficult and dangerous gut infection as a side effect of the antibiotics. These have been treated with vancomycin and metronidazole sadly without effect on both occasions. I was left wondering if I was going to die of this. I spent a considerable effort trying to locate someone doing faecal transplants and fortunately eventually found Dr Goldenberg at Guys and St Thomas' NHS trust in 2018. He was a real lifesaver and arranged transplants promptly and on both occasions the CDI was cleared within a few days and my symptoms resolved. I remain eternally grateful to him and hope I don't need to do this again but if I do, I know where great treatment can be found."

King's provide expert advice on treatment of CDI and guidelines for FMT. As a result of this research the case study author has been invited to participate on a number of national working groups/advisory committees. Goldenberg was invited to the Joint British Society of Gastroenterology/Healthcare Infection Society working group on the on the use of FMT to treat CDI. In 2018, the group published a set of UK guidelines for which Goldenberg was joint Chair and joint senior author **[E.1]**. The guidelines are used by both charities' members which combined amounts to over 4,000 professionals in the UK **[E.2]**.

In 2020, he joined the United European Gastroenterology (UEG) working group on FMT Banks and contributed to their European guidelines for processes involved with stool banking, such as handling of donor material, storage and donor screening and reviewed all of the evidence that the guidelines were based on **[G.1]**. UEG is a professional non-profit organisation recognised as the leading authority for digestive health.

5. Sources to corroborate the impact

[A] Sources that corroborate King's research leading to local improvement in diagnosis and detection of cases (GSTT): A.1 Testimonial from Joint Director of Infection Prevention and Control at GSTT [PDF]; **A.2** Testimonial from Site General Manager at GSTT [PDF]

[B] Sources that corroborate King's research leading to national improvement in diagnosis and detection of cases (NHS): B.1 Public Health England National Statistics on *Clostridioides difficile* infection: annual data (2007-2020); **B.2** Updated guidance on the diagnosis and reporting of Clostridium Difficile, NHS, 2012 (page 24, reference 1) [PDF]; **B.3** Clostridium difficile infection objectives for NHS organisations in 2019/20 and guidance on the intention to review financial sanctions and sampling rates from 2020/21(page 3, last paragraph) [PDF]

[C] Sources that corroborate claim of King's research (funded by Astellas) winning Prix Galien award for Real World Evidence in 2016: C.1 Open Health Group news article; **C.2** The Pharmaceutical Journal news article

[D] NHS High Cost Drug List: 2019/20 National Tariff Payment System: national prices and prices for emergency care services (Tab 13b, line 200) [EXCEL]

[E] Sources that corroborate Goldenberg's contribution to Joint British Society of Gastroenterology/Healthcare Infection Society working group: E.1 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. 2018; [PDF] **E.2** BSG Website and HIS Website

[F] Sources that corroborate Goldenberg's work on FMT: F.1 PROFIT Clinical Trial Data; **F.2** FERARO Clinical Trial Data; **F.3** Patient that underwent FMT in 2018 testimonial [PDF]

[G] Sources that corroborate Goldenberg's contribution to UEG Guidelines: G.1 A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group (2020); [PDF] **G.2** UEG Website

[H] The British Society of Gastroenterology website page on Expert Advisory Group on Gut Microbiota and Health