Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study: Generating significant commercial impact, improving patient outcomes and reducing healthcare costs through use of antimicrobial catheters worldwide

Period when the underpinning research was undertaken: 2004-2019

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:
Professor Roger Bayston	Professor of Surgical Infection	1995-present
Dr Katie Belfield	Research Fellow	2014-present
Mr Waheed Ashraf	Senior Research Technician	2001-present

Period when the claimed impact occurred: August 2013 to 2020

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

1. Summary of the impact

Innovative research conducted at the University of Nottingham has contributed to the worldwide commercial success of 2 Bactiseal® antimicrobial catheters which have improved the treatment of neurosurgical patients worldwide. Bactiseal®, a neurosurgical catheter, is effective at reducing infection rates by two thirds compared to standard shunt catheters. Reducing infections leads to improved patient outcomes and potential NHS saving of GBP7,000,000 per year. Since 2015, Bactiseal® product sales have grown 50% globally. Bactiseal® products are now sold into 53 countries across all continents, with sales into 39 new countries since 2015. The success of Bactiseal® contributed to the acquisition of Codman by Integra in 2017 for a purchase price of USD1,014,000,000 (10-2017). The research has continued and further products have been developed including a new antimicrobial urinary catheter already being tested in clinical trials.

2. Underpinning research

The problem: catheter infections

Catheters are thin tubes of medical grade materials used for draining a variety of fluids in the body. Once placed in the body, catheters are prone to bacterial colonisation and subsequent patient infections, which are difficult to treat and can lead to poor patient outcomes, including death. The lumen, the inner surface of the catheter, is sealed off from the body's immune system. Bacteria colonise the catheter surface and the protein conditioning film that forms on the lumen as fluids drain, with different bacteria thriving in different catheter types. Bacteria can create a biofilm once attached to the conditioning film on the lumen, which protects the bacteria from antimicrobials, further preventing effective treatment of infections.

Background: Developing and launching Bactiseal® and Bactiseal® EVD

As reported in the previous REF (https://impact.ref.ac.uk/casestudies/CaseStudy.aspx?Id=41008), Professor Bayston developed a technology that enables catheters to be impregnated with antimicrobial molecules after manufacture, allowing the antimicrobials to remain evenly distributed throughout the catheter. This enables the antimicrobials to act on bacteria and developing bacterial biofilm over a long period of time. A patent was filed in 1986 combining this technology with the antimicrobial combination of 0.15% clindamycin and 0.054% rifampicin, used to prevent antimicrobial resistance and target the bacteria that thrive in neurosurgical catheters. This patented technology led to Codman launching Bactiseal®, an internally draining neurosurgical shunt in the 1990's and Bactiseal® EVD (External Ventricular Drain), an externally draining neurosurgical catheter in 2004.The commercialisation of Bactiseal® products (comprising both Bactiseal® and Bactiseal® EVD) formed the basis of the previous REF case study. Bactiseal® products are sold by Codman, and **Professor Bayston has no financial interest in Codman or Bactiseal® products.**

Research facilitating the success and worldwide sales of Bactiseal® products

Professor Bayston developed a novel and highly clinically predictive test, the In Vitro Challenge (IVC) test, which mimics the catheter fluid 'flow conditions' experienced in a patient. This enables catheter testing under the same conditions found in the patient

including patient derived protein conditioning film. In **2004 (1)** Professor Bayston undertook research for the first time using his novel IVC test into how Bactiseal® exerted its effect: by inhibiting bacterial adherence to the lumen or killing adhered bacteria? The research found Bactiseal® didn't prevent bacterial adherence, instead Bactiseal® killed 100% of bacteria once attached to the lumen. This is crucial as attached bacteria are up to 1,000 times less susceptible to antimicrobials. This was the case despite the patient derived protein conditioning film that formed on the lumen from the Cerebrospinal Fluid (CSF) the catheter was draining. This research **(1)** detailing how Bactiseal® worked to prevent infection, alongside training provided by Professor Bayston, has educated Codman employees leading to increasing Bactiseal® sales.

Neurosurgical patients, many of whom are children, can experience poor outcomes following a neurosurgical catheter infection, including reduced mental acuity, multiple operations and death. Professor Bayston, keen to improve outcomes for these patients, undertook research to understand why infection rates remained high in neurosurgical catheters. One available neurosurgical catheter was BioGlide, which had a hydrophilic polymer grafted onto the catheter surface. BioGlide claimed to reduce bacterial adhesion to the lumen by creating a hydrophilic surface the bacteria couldn't adhere to. Using his IVC test, Professor Bayston's research in **2005 (2)** established that the BioGlide catheter was not effective at preventing bacterial colonisation under 'flow conditions'. Professor Bayston's research was also partly driven by having co-authored a paper on silver nanoparticles in medical devices in 2004. Another neurosurgical catheter available was Silverline, an EVD impregnated with silver nanoparticles which claimed to be effective given the use of these silver nanoparticles. Professor Bayston's research in **2010 (3)** using his IVC test looked at the efficacy of Silverline in killing attached bacteria under 'flow conditions'. The research found the EVD's didn't kill 100% of bacteria under flow conditions establishing Silverline catheters to be ineffective. These findings have been confirmed by others in clinical trials, such as the BASICS trial **(e)**. Professor Bayston's research into alternative neurosurgical catheters **(2, 3)** has supported the success of Codman's Bactiseal® EVD range.

Research into effective antimicrobial urinary catheters

To expand use of Professor Bayston's technology for impregnating catheters beyond neurosurgical catheters, a new patent was filed in 2007 by UoN **(4)**. The new patent uses his catheter impregnation technology combined with the use of triclosan and at least one other antimicrobial, to reduce antimicrobial resistance and provide duration of catheter activity of at least 80 days. Patients requiring urinary catheters are often plagued with infections arising from bacteria which thrive in urine (uropathogens) and these infections give rise to catheter blockages, recurrent infections requiring antimicrobial use and subsequent resistance development. There are currently no effective antimicrobial urinary catheters for short term use (less than 28 days), and none for long term use. Professor Bayston undertook research into urinary catheters to improve the outcomes for these patients, having developed a new antimicrobial urinary catheter, based on his new patent **(4)**. The newly developed urinary catheter was reported in the previous REF (https://impact.ref.ac.uk/casestudies/CaseStudy.aspx?Id=41008). In 2015 **(5)**, he published research, conducted using his IVC test between 2013 and 2014, impregnating the catheters with rifampicin, sparfloxacin, and triclosan to target uropathogens and prevent antimicrobial resistance. The research found the catheter was able to prevent bacterial colonisation by common uropathogens for 7 to 12 weeks, the maximum length of time a urinary catheter remains in a patient. Ahead of publication, the data from this research led to an NIHR i4i grant in 2015 **(G1)** to test the safety and tolerability of the new urinary catheter in patients. As part of the research from the i4i grant, in 2019 using his IVC test he found that the combination of rifampicin, sparfloxacin, and triclosan was able to prevent catheter blockages (mineral encrustation) and bacterial colonisation, even by multi-drug resistant strains, for up to 12 weeks **(6)**. The results from i4i grant funded research **(6)** were so potentially significant for this group of patients this led to a major NIHR EME grant in 2020 **(G2)** to test the efficacy in 274 patients in 8 UK centres.

3. References to the research

Underpinning research

1. Bayston R, Ashraf W, Bhundia C. 2004. Mode of action of an antimicrobial biomaterial for use in hydrocephalus shunts. *The Journal of Antimicrobial Chemotherapy* 53, 778-782. DOI: 10.1093/jac/dkh183
2. Bayston R, Bhundia C, **Ashraf W**. 2005. Hydromer-coated catheters to prevent shunt infection? *J Neurosurg (Pediatrics 2)* 102, 207–212. DOI: 10.3171/jns.2005.102.2.0207
3. Bayston R, Vera L, Mills A, **Ashraf W**, Stevenson O, Howdle SM. 2010. In vitro antimicrobial activity of silver-processed catheters for neurosurgery. *J Antimicrob Chemother* 65, 258–265. DOI: 10.1093/jac/dkp420
4. Bayston R. 2007. Medical devices and methods of making medical devices. EP1804845 (W02006032904) Europe
5. Fisher LA, Hook AL, **Ashraf W**, Yousef A, Barrett DA, Scurr DJ, Chen X, Smith EF, Fay M, Parmenter CDJ, Parkinson R, **Bayston R.** 2015. Biomaterial modification of urinary catheters with antimicrobials to give long-term broadspectrum antibiofilm activity. *Journal of Controlled Release* 202, 57-64. DOI: 10.1016/j.jconrel.2015.01.037
6. Belfield K, Chen X, Smith EF, **Ashraf W**, **Bayston R**. 2019. An antimicrobial impregnated urinary catheter that reduces mineral encrustation and prevents colonisation by multi-drug resistant organisms for up to 12 weeks. *Acta Biomaterialia* 90, 157-168. DOI: 10.1016/j.actbio.2019.03.042

Grants

G1 2015 Lead applicant: Professor Roger Bayston. Characterisation, commercialisation and clinical studies of a long-term antimicrobial urinary catheter. Sponsor: NIHR. 2015 – 2018, GBP336,548.
G2 2020 Chief Investigator: Professor Roger Bayston. Catheter Against Urinary Tract Infection Trial: a randomised trial of antimicrobial-impregnated urinary catheters for long-term indwelling urinary catheter users (CAUTI Trial). Sponsor: NIHR. 2020 – 2023, GBP1,591,419.55

Patents

UK, no. 1 804 845 (E), Germany, no. 1 804 845 (E), France, no. 1 804 845 (E), Japan, no. JP 5393030 B2, Malaysia, no. MY-157750-A, Canada, no. 2 580 894

4. Details of the impact

Catheters are prone to bacterial colonisation, allowing infection to take hold, proving difficult to treat and leading to poor patient outcomes. Research conducted by the University of Nottingham has contributed to the success of Bactiseal® products (Bactiseal® and Bactiseal® EVD's) worldwide, with Bactiseal® products contributing to the acquisition of Codman by Integra from Johnson & Johnson in 2017. As uptake of Bactiseal® products has increased worldwide, patient outcomes have improved and healthcare costs have reduced, associated with the reduced infection rates compared to other catheters. New research into urinary catheters has resulted in improved patient outcomes from using a new antimicrobial urinary catheter.

Commercial impact

The initial commercialisation of Bactiseal® products (Bactiseal® and Bactiseal® EVD's), manufactured and sold by Codman, was reported in a previous Impact Case Study: https://impact.ref.ac.uk/casestudies/CaseStudy.aspx?Id=41008**. Since then, the acquisition of Codman by Integra from Johnson & Johnson in 2017 for a purchase price of USD1,014,000,000 (10-2017) represents new commercial impact (a(a), p. 2, b, p. 40).** Professor Bayston's research has contributed to the effective marketing, promotion and increased sales of Bactiseal® products **(1, a(a, b))** and the success of the Bactiseal® EVD range **(2, 3, a(a), p. 1)**. The Sales Director UK, IRE & BENELUX at Integra confirmed the importance of Bactiseal® products to the Integra Acquisition of Codman from Johnson & Johnson in 2017 **(a(a), p. 2**). The purchase completed on 2nd October 2017 for a purchase price of USD1,014,000,000 (10-2017), confirmed by the Integra 2018 Annual Report **(b, p. 40)**. Since 2005, Professor Bayston has provided consultancy expertise to Codman and training to Codman employees **(a(a), p. 1)**. The Sales Director described the role of Professor Bayston's research and training in the success of Bactiseal® product sales: "*Prof Bayston has helped educate Codman employees about causes and prevention of CSF catheter infections* **(a(a), p. 1)***...The training, including… the mode of action of Bactiseal®* ***[1]****…how to handle objections… has prepared us to promote the use of Bactiseal® to non*

users… also to handle questions and concerns from users...The result has been a more confident and more expert sales organization, able to present strong clinical and cost avoidance arguments and to change the behavior of clinicians leading them to use Bactiseal more extensively as part of protocols to reduce CSF catheter infections" **(a(b)).** In October 2020 the Sales Director confirmed that **since 2015** (previous sales data unavailable following the 2017 acquisition)**, sales of Bactiseal® products have commenced in 39 new countries worldwide,** with Bactiseal® products now being **sold into 53 countries around the world and across all continents (a(a), p. 2)**. The increase from 14 to 53 countries since 2015 represents an increase of 279% of countries sold into**. Since 2015 there has been an increase of 50% in volume of Bactiseal® catheters sold worldwide (a(a), p. 2)**. The Sales Director confirmed the success of the Bactiseal® EVD range had been supported by "*the published research demonstrating the lack of efficacy of a surface coating **[2, 2005]** or silver ion treated catheter **[3, 2010]** when challenged with an in vitro bacterial infusion test"* **(a(a), p. 1)**.

Bactiseal® Efficacy: Clinical Benefits

Bactiseal® is highly clinically effective at preventing infections, with infection rates of just 2%, compared to other catheters at 6%. The BASICS trial **(c)** is a NIHR funded randomised control trial and economic evaluation conducted in the UK across 1,605 patients in all age categories between June 2013 and October 2017. Professor Bayston declined to be involved in the BASICS trial to avoid bias but gave advice on diagnostic criteria and microbiological investigations. The BASICS trial found the infection rate in patients with Bactiseal® to be just 2% compared to standard shunts (6%) and silver coated shunts (6%). This effect was found across all age categories, with the risk of infection being highest in children, reducing in adults and particularly low in the elderly **(c, p. 1536).** The paper identified that "*antibiotic shunts have good clinical and cost-effectiveness and will inform neurosurgery practice and shunt choice for the benefit of patients"* **(c, p. 1536).** A NIHR Health Technology Assessment of the BASICS trial has highlighted that **for every 100 new paediatric Bactiseal® shunts inserted, this should avoid 6 or 7 infections (d, p. 59)**.

Bactiseal® Efficacy: Patient Benefits

As Bactiseal® sales have increased worldwide, patient outcomes have improved worldwide through the reduced infection rates associated with Bactiseal® compared to other neurosurgical catheters. Once a catheter-associated infection has occurred this can lead to poor patient outcomes; by avoiding these infections, these poor outcomes are avoided. The NIHR Health Technology Assessment of the BASICS trial identified that for patients, many of which are children and the group at highest risk of infection **(d, p. 59) each avoided infection avoids the potentially catastrophic and life changing health sequalae associated with such infection (d, p. 60)**. Shine, the UK's leading hydrocephalus charity highlighted these poor outcomes in their Bactiseal® petition, "*Make BACTISEAL standard practice for shunt surgery"*. This petition was launched during Hydrocephalus Awareness Week February 2020 and explains that infections are "*a serious problem, requiring long hospital stays, lengthy treatment with antibiotics, further surgery, and the possibility of meningitis and even irreversible brain damage"* **(e)**. The Shine petition is targeted at the NHS to ensure Bactiseal® is used "*First time, every time*" in all new shunt surgery in England, Wales and Northern Ireland. As the petition explains "*By reducing the risk of shunt infections, we can avoid unnecessary stress for patients and their families, and improve the overall outlook post-surgery*" **(e)**. In August 2019 the CEO of Shine stated Shine "*are particularly proud of Professor Bayston's professional achievements in the development of the Bactiseal® shunt, which has had such an enormous positive impact of the treatment of hydrocephalus world-wide, and on the lives of so many individuals we work with"* **(f)**. With Bactiseal® products being sold into 39 new countries worldwide since 2015 **(a(a), p. 2)**, outcomes of the patients in these 39 new countries have improved through the reduced infection rates associated with Bactiseal® products.

Economic Impact: Clinical Cost Benefit

As Bactiseal® sales have increased worldwide, healthcare costs have been reduced worldwide through the reduced infection rates associated with Bactiseal® compared to other neurosurgical catheters. Once a catheter-associated infection has occurred this

can lead to increased healthcare costs; by avoiding these infections, these additional healthcare costs are avoided. The BASICS trial included an economic evaluation that found **Bactiseal® shunts provide a saving of GBP135,753 per infection avoided (c, p. 1537)** through reduced additional surgery and prolonged hospital care. **If Bactiseal® was used in all new patients it would provide the NHS with a saving of approximately GBP7,000,000 per year (g)**. A NIHR Health Technology Assessment also highlighted that for every 100 new paediatric Bactiseal® shunts inserted, this should avoid 6 or 7 infections translating to a potential cost saving of GBP814,000 to GBP950,000 **(d, p. 59)**. With Bactiseal® products being sold into 39 new countries worldwide since 2015 **(a(a), p. 2)**, healthcare costs for the patients in these 39 new countries have reduced through the reduced infection rates associated with Bactiseal® products.

Consultancy and training Impact

Professor Bayston has delivered lectures for healthcare professionals since 2002 as part of his involvement with Codman. The Sales Director explains "*The combination of publications and lectures derived from your research have impacted healthcare professionals' understanding of CSF catheter infections and the treatment of patients worldwide.* ***The quality of the research has positioned you, in our opinion, as a world leading subject matter expert who has influenced the current generation of neurosurgeon*****"* (a(a), p. 1)**. Since 2002, Professor Bayston has delivered annual lectures and been actively involved in the European Hydrocephalus Symposium, organised by Codman **(h(a))**. Since 2009 there have been 2 annual lectures **(h(a))** each attended by approximately 25 people (consultant surgeon and neurologist delegates) **(h(a)).** Events have been held in 6 countries in Europe and delegates have attended from 15 countries across 3 continents (Africa, Asia and Europe) **(h(a))**. Professor Bayston has also been highly involved as a Faculty member in other Codman events, such as the 2015 and 2016 Advanced Hydrocephalus Management & Technology Learning Centre lectures for healthcare professionals **(h(b))**.

New antimicrobial urinary catheter: patient benefits

Urinary catheter patients have found the new antimicrobial urinary catheter to be better than their usual urinary catheter and give rise to less pain than usual. In a tolerability and patient acceptability pilot study undertaken with 30 patients between 2016 and 2018, 42% of patients found the new catheter to be better than their usual catheter. 32% of patients also reported less pain than usual from the new catheter **(i(a), p. 343)**. Patients took part in telephone interviews responding to the question "*How would you rate this catheter compared to your usual?*". In the first interview, just 24 hours after the catheter was fitted, 3 patients (10%) reported improved sensation **(i(a), p. 339, i(b), p. 2)**. In the last interview, after the catheter was removed, 6 patients (20%) reported improved comfort, 3 patients (10%) expressed a desire to keep the catheter and 2 patients (6.67%) expressed a desire to have a second catheter. Without being prompted to think about infections, 3 patients (10%) also reported infection reduction in their last interview **(i(b), p. 2).**

5. Sources to corroborate the impact

(a(a)) Integra Letter of Support, **(a(b))** Integra supplementary email
(b) Integra 2018 Annual Report (weblink, last accessed 7th January 2021),
(c) Antibiotic or silver versus standard ventriculoperitoneal shunts (BASICS): a multicentre, single-blinded, randomized trial and economic evaluation (2019), DOI: 10.1016/S0140-6736(19)31603-4
(d) NIHR Health Technology Assessment of BASICS trial (2020), DOI: 10.3310/hta24170
(e) Shine Bactiseal petition (weblink, last accessed 8th January 2021)
(f) Shine Letter of Support
(g) University of Liverpool article: Innovative treatment to prevent common brain infection could save NHS £7 million per year (weblink, last accessed 8th January 2021)
(h(a)) Integra email confirming training impact **(h(b))** Codman training event posters
(i(a)) A tolerability and patient acceptability pilot study of a novel antimicrobial urinary catheter for long-term use, 2018, DOI: 10.1002/nau.23858, **(i(b))** Supporting information