Institution: Sheffield Hallam University		
Unit of Assessment: UOA05 - Biological Sciences		
Title of case study: Antimicrobial materials: better outcomes for orthopaedic surgery		
Period when the underpinning research was undertaken: 2005-2017		
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:**
Thomas J Smith	Professor of Microbiology	2001 - present
Tim Nichol	Senior Lecturer in Microbiology	2016 - present
Robert Akid	Professor of Materials Science	1999 - 2012
Period when the claimed impact occurred: 01 August 2013 - 31 December 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Increasing problems with antibiotic-resistant organisms require "smarter" use of antibiotics to maximise their effectiveness and minimise resistance problems. This need is particularly acute in orthopaedic surgery, including hip and knee joint replacements, where infection around the prosthesis can be devastating. Our research on elution of antibiotics when added to the bone cement used to secure the prosthesis into the bone has provided impartial information for clinical microbiologists and surgeons to use antibiotics more effectively for local delivery in orthopaedic surgery. This has benefitted surgeons, orthopaedic microbiologists, patients and the NHS between 2013 and 2020 in the UK and Europe.

2. Underpinning research

Infections are a serious complication of 1-2% of joint replacement procedures. Such patients require additional surgery (termed revision) to remove infected tissue and replace the prosthesis. Addition of antibiotics into the cement used to secure the prosthesis can protect against occurrence or recurrence of infection. Such local (rather than oral or intravenous) antibiotics localise where they are needed and minimise resistance problems by reducing exposure of the patient's natural microflora to the antibiotic. Increasing problems with antibiotic resistance and the need to maximise the utility of existing antimicrobials dictate that a wider range of antibiotics must be used within orthopaedic materials.

Working with senior clinicians, researchers at SHU identified an opportunity to use skills of microbiology, analytical chemistry and materials science to address the lack of manufacturer-independent information about the effects of adding antibiotics to orthopaedic material. All experimental work was done at SHU between 2005 and 2017. Different aspects have been led by UOA5 microbiologists Smith T and Nichol and (before leaving SHU in 2012) materials scientist, Akid.

New laboratory methods were developed for quantitative characterisation of antibiotic-loaded biomaterials. The research addressed: (**R1**) kinetics of antibiotic elution (dissolving out) from the material (measured quantitatively via liquid chromatography-mass spectrometry [LC-MS]); (**R2**) whether the eluted antibiotic is still active against pathogens including bacteria that cause prosthesis infections; (**R3**) effects of the antibiotic on the material's physical strength. With funding (£8,000) from orthopaedic manufacturer Biomet (now ZimmerBiomet), the widely used antibiotic gentamicin was investigated in polymethylmethacrylate (PMMA) bone cement in comparison with the front-line anti-MRSA antibiotic daptomycin (**R1**). Funding from the Pfizer AIR foundation (£46,750) allowed investigation of linezolid and tigecycline in the same material (**R2**). The properties of temocillin added to gentamicin-containing bone cement (**R3**) were investigated through a grant (£2,000) from the Society for Applied Microbiology, a gift of antibiotic from

Eumedica and University support. Results indicated that all five antibiotics were compatible with maintaining physical strength of the bone cement and all eluted in an active form to levels sufficient to kill bacterial pathogens in the laboratory model system (**R1**-**R3**). Results under wear, which occurs in certain types of two-stage revision surgery where PMMA cement surfaces temporarily form the load-bearing surfaces of the joint, unexpectedly showed that physical wear decreased antibiotic elution for gentamicin and tigecycline, whereas elution was unaffected or increased with daptomycin or linezolid (**R1**, **R3**).

Giving PMMA bone cement "spacers" (pieces of cement used to fill gaps from bone removed) an uneven "teabag" surface was shown to promote antibiotic elution (**R4**). Addition of vancomycin to one brand of bone cement was shown to be as effective in terms of reliable release kinetics as using a commercial pre-prepared cement, but led to varied but more rapid release (which may be advantageous in some instances) if mixing was done more quickly (**R5**). Trabecular metal (a porous tantalum material used in some prostheses for its good bone-regrowth properties) was shown, in contrast to suggestions in the literature, not to have intrinsic antimicrobial properties (**R6**).

3. References to the research

R1. Dodds, S., **Smith, T. J., Akid, R**., Stephenson, J., Nichol, T., *Banerjee, R.D., Stockley, I.* and *Townsend, R*. 2012. Contrasting effects of physical wear on elution of two antibiotics from orthopedic cement. *Antimicrob. Ag. Chemoter*. 56, 1471-1475. https://doi.org/10.1128/AAC.01588-10

R2. **Nichol, T., Smith, T. J.**, *Townsend, R., Stockley, I*. and **Akid, R.** 2017. Analysis of linezolid and tigecycline as candidates for local prophylaxis via antibiotic-loaded bone cement. *J. Antimicrob. Chemother*. 72, 410-416. https://doi.org/10.1093/jac/dkw410

R3. Barker, S., Nichol, T., Harrison, P. L., *Stockley, I., Townsend, R.* and **Smith, T. J.** 2015. Temocillin: a new candidate antibiotic for local antimicrobial delivery in orthopaedic surgery? *J. Antimicrob. Chemother*. 70, 780-783. https://doi.org/10.1093/jac/dku425

R4. *Salih, S.,* Paskins, A., **Nichol, T., Smith, T**. and *Hamer, A.* 2015. The cement spacer with multiple indentations: increasing antibiotic elution using a cement spacer 'teabag'. *Bone Joint J*. 97-B, 1519-24. https://doi.org/10.1302/0301-620X.97B11.35618

R5. *Frew, N. M., Cannon, T.,* **Nichol, T., Smith, T. J.** and *Stockley, I.* 2017. Comparison of the elution properties of commercially available gentamicin and bone cement containing vancomycin in comparison with "home-made" preparations. *Bone Joint J*. 99-B, 73-77. https://doi.org/10.1302/0301-620X.99B1.BJJ-2016-0566.R1

R6. Harrison, P. L., *Harrison, T., Stockley, I*. and **Smith, T. J.** 2017. Does tantalum exhibit any intrinsic antimicrobial or antibiofilm properties? *Bone Joint J.* 99B, 1153-1156. https://doi.org/10.1302/0301-620X.99B9.BJJ-2016-1309.R1

Additional indicators of the quality of the underpinning research

Outputs were rigorously peer-reviewed prior to publication in leading journals in the field. References are for research that was carried out by researchers at the university with staff employed by the university at the time of publication marked in bold and collaborators in NHS Trusts marked in italics. R.2 was selected as the "Editor's Choice" by the journal editor.

4. Details of the impact

Increasing the range of antibiotics used in PMMA bone cement and other materials for revision joint operations

Arthroplasty is a common surgical procedure that alters or completely replaces a damaged, worn or diseased joint in the body, such as the hip or knee, with an artificial joint to restore normal motion. In the vast majority of cases, this enables people to live more active lives free of chronic pain. Over time, a joint replacement may fail and can become painful and swollen, requiring a second, or revision operation. This is a more complex procedure that requires specialised implants

and tools to achieve a good outcome for the patient. Infected prostheses are associated with severe pain and the condition of the patient is likely to deteriorate if not treated surgically; patients with substantial joint pain awaiting surgery are likely to report "worse than death" scores in health/wellbeing questionnaires (**E1**).

Between 1 August 2013 and 31 December 2020, 12 hip or knee prosthesis revision operations were undertaken by five orthopaedic surgeons in Sheffield Teaching Hospitals NHS Foundation Trust (STHFT) that were directly informed by our PMMA bone cement work and specific antibiotics research (**R1**, **E2**). The arthroplasty operations had failed due to infection; these specific cases were all instances in which the organisms causing pre-existing infections required additional antibiotics beyond the standard gentamicin antibiotic included in bone cement. The revision operations were enabled because the antibiotics that the clinical microbiology indicated (temocillin for Gram-negatives and daptomycin for Gram-positives) had been shown suitable for application in bone cement in our independent in vitro work. Revision operations, where such bespoke local antibiotic therapy is needed, constitute in the region of 1% of all arthroplasty operations.

Our research has been influential in clinical decision making beyond the combinations of materials and antibiotics that were tested in the laboratory. Decisions about which antibiotics to use often have to be made quickly (sometimes when the patient is in theatre) and the options for which antibiotic to use may be severely limited. In such instances our research has directly influenced decision making by orthopaedic surgeons by providing them with the confidence to use a broader range of antibiotics based on the known behaviour of a particular class of antibiotics through our research. For example, the decision to use the antibiotic meropenem (a beta lactam) in bone cement was taken because it is known through our research that temocillin (also a beta lactam) is well behaved in bone cement (**R3**). As a result, our research influenced decisions on the use of specific antibiotics in bone cement and Stimulan™ (a resorbable calcium sulfate-based material) in an additional 51 revision prosthesis and other orthopaedic operations in STHFT between 1 August 2013 and 31 December 2020 (**E2**). One specific case, in 2018 in which a spinal infection was treated with antibiotic-loaded material, was considered to be life-saving (**E2**).

The use of local antibiotics in orthopaedic cases, rather than prolonged systemic treatment with intravenous antibiotics which is the alternative, allowed exercising of accepted good practice in terms of minimising exposure of patients' natural microflora to prolonged antibiotics (which may select for resistant pathogens). Use of intravenous antibiotics that would otherwise be needed requires a stay in hospital for the duration of the treatment, resulting in stress for patients and additional cost to the NHS (each patient day on a regular orthopaedic ward costs in the region of £240; £1,380 if an intensive care bed is needed).

Informing the way orthopaedic materials are prepared and used

Specialist cements containing rarer antibiotics and mixtures (such as vancomycin and gentamicin) are typically around £160 per 40 g pack, compared with £45 for standard gentamicin-containing bone cement. Our research shows there is no improvement in the properties of "theatre-mixed" antibiotic-containing cement compared with commercial preparations (**R5**). This has enabled surgeons make informed decisions on preparation of cement. The publication reporting this work was Tweeted 254 times from 140 users across 5 continents over 3 years after publication (**E4**). This has allowed clinical decisions to be made in the knowledge that a cost saving in not using an expensive pre-prepared antibiotic loaded cement will not compromise the properties of the material (**R2**) and thus patient outcomes. One of our research collaborators, Consultant Clinical Microbiologist at STHFT confirms that "*the work on commercial vs. theatre-mixed antibiotic-containing cement saves a lot of money. We've now stopped using the expensive mixed antibiotic containing cements in Sheffield and many other centres have done the same*." (**E2**)

The "teabag" procedure to increase antibiotic elution by increasing the surface area of bone cement (**R4**) is now routinely used in procedures using antibiotic-loaded cement within STHFT; it is a tertiary referral centre for this approach due to its success (**E1**). The method has been brought to wider attention when the Editors of *Bone Joint J* described our work on the "teabag" elution method in the "Research Roundup" Feb 2016 number as "*A simple and elegant technique that could improve the effectiveness of cement spacers with minimal effort and no cost*" (**E5**). Further dissemination by the Consultant Orthopaedic Surgeons at STHFT has generated interest from ENDO Klinik, a specialized clinic in Germany with a worldwide reputation for bone, joint and spinal surgery (**E1**).

It is not anticipated that the work on the absence of intrinsic antimicrobial activity of tantalum (**R6**) will reduce the use of tantalum in orthopaedics, because its use does reduce the risk of infection, presumably by its stimulatory effect on bone growth or some other effect on the surrounding tissue. Nonetheless, it puts clinical decisions and discussions around tantalum on a more factual footing.

Knowledge transfer to inform clinical practice

The Sheffield NHS hospitals have been a tertiary referral centre for orthopaedic infections since 1976 and have established Sheffield as a centre of excellence for managing orthopaedic infections. Within Sheffield, the Cavendish Hip Foundation (March 1994 – August 2020) has funded 28 orthopaedic surgeons in training; four of these clinicians have undertaken collaborative research with the University as part of this training programme to contribute to the discipline through publication (**R1**, **R5**, **R6**). Three of these fellows are now consultant surgeons and one is in general practice. The research training has informed clinical practice as evidenced by the 10th Cavendish Hip Fellow (2008 – 2009), now a Consultant Orthopaedic Surgeon based at the Robert Jones & Agnes Hunt Orthopaedic Hospital (RJAH), who confirms "*we perform between 50 and 60 infected 2 stage revision surgeries per year at RJAH and I still use the results from that original experiment in my clinical practice. It has been the foundation of my infected revision surgical practice and passed on to the 20 plus trainee surgeons who have worked with me*." (**E6**). A further Cavendish Hip Fellow, now a Consultant Orthopaedic Surgeon at the BMI Alexandra Hospital in Cheadle, Manchester and the Spire Manchester confirms "*The ground-breaking research particularly with respect to the use of antibiotic loaded bone cement beads, coupled with extensive debridement……has guided me throughout my career as a Consultant Orthopaedic Surgeon specialising in hip and knee replacement surgery*." (**E7**)

Collaborative research between the University and Sheffield-based NHS collaborators (**R1** - **R6**) has enabled access to clinical user expertise ensuring an applied focus to our research and facilitated a direct route to clinical practice; Stockley (consultant orthopaedic surgeon; Beyond Compliance Advisory Panel Member 2013-16); Townsend (consultant clinical microbiologist); Hamer (consultant orthopaedic surgeon; president elect of the British Hip Society 2020-21). Townsend has been called upon to give advice on operations in which our work has informed and enabled his decisions in the UK, Italy, Romania, Ireland and Spain (**E2**). Most recently in a case in Glasgow (December, 2020) he advised on local antibiotic delivery in a patient with a pre-existing infection resistant to gentamicin, the most commonly used local antibiotic (**E2**, **E3**).

From 2008-2013 Stockley and Townsend organised UK-wide annual Orthopaedic Microbiology meeting in Sheffield on a non-profit basis with support from Biomet (now Zimmer Biomet) to disseminate good practice among the orthopaedic surgery and clinical microbiology community to prevent and manage orthopaedic infections. The SHU team presented their work on antibiotics in bone cement at the meetings in 2013 (Nichol and Smith T) to ~80 attendees, mostly practising clinical microbiologists (~60%) and orthopaedic surgeons (~40%) and received overwhelmingly positively positive feedback from evaluation questionnaires, providing a valuable route to transferring the knowledge to the relevant professionals. Many centres set up their own

Multidisciplinary Team (MDT) meetings on the back of this, leading to more positive outcomes for patients (**E2**). Such MDTs are now encouraged through the GIRFT ("getting it right first time") Initiative, supported nationally by NHS England.

Eumedica, the suppliers of temocillin, have informed us that they direct enquirers about the use of temocillin in bone cement to our publication (**R3**, **E8**).

5. Sources to corroborate the impact

E1. Testimonial from Consultant Orthopaedic Surgeons, Sheffield Teaching Hospitals NHS Foundation Trust

E2. Testimonial from Consultant Clinical Microbiologist, Sheffield Teaching Hospitals NHS Foundation Trust including documentary evidence of number of clinical decisions based on research by Sheffield Hallam University

E3. Correspondence between Consultant Clinical Microbiologist, Sheffield Teaching Hospitals NHS Foundation Trust and an orthopaedic department in Glasgow, December 2020

E4. 254 Tweets mentioning **R5** from 140 Users over a period of 3 years following publication on 11 January 2017. Source: Altmetric.

E5. Editor's commentary about underpinning research work (**R4**) published in *Bone and Joint Journal*

E6. Testimonial from Consultant Orthopaedic Surgeon, Orthopaedic Hospital, Oswestry.

E7. Testimonial from Consultant Orthopaedic Surgeon, BMI Alexandra Hospital in Cheadle, Manchester and the Spire Manchester

E8. Correspondence with Eumedica SA.