Institution: University of Sheffield		
Unit of Assessment: A-03 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Influencing guidelines and dental practice on antibiotic prophylaxis for infective endocarditis prevention		
Period when the underpinning research was undertaken: 2009–2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Martin Thornhill	**Role(s) (e.g. job title):** Professor in Clinical Research	**Period(s) employed by submitting HEI:** 2005–present
Period when the claimed impact occurred: Aug 2013–Dec 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Oral bacteria are implicated in 35-45% of cases of infective endocarditis (IE), a life-threatening heart infection. Antibiotic prophylaxis (AP) before invasive dental procedures is the only prevention measure recommended for individuals at increased risk of IE, but controversy surrounding its use led NICE to recommend against AP before invasive dental procedures in 2008. Our subsequent systematic review of prescription data and hospital discharge statistics identified a significant increase in IE incidence in England, and we have continued to research the link between oral bacteria and IE and the role of AP in IE prevention to inform guideline committee decisions. Our research has influenced the recommendations of AP guideline committees in the UK, the US, Sweden, and Japan and underpinned changes in advice to UK dentists and patients.

2. Underpinning research (indicative maximum 500 words)

Infective Endocarditis (IE) is a bacterial heart valve infection with a mortality rate of 30% in the first year. Approximately 35-40% of IE cases are caused by bacteria that originate from the mouth. Since the 1950s, international standards of care have dictated that antibiotic prophylaxis (AP) be given to dental patients at moderate or high risk of IE during invasive dental procedures. However, due to concerns about the risk of adverse reactions to AP, the overuse of antibiotics and the lack of randomised-controlled trial evidence for the efficacy of AP, from 2007 International guidelines began to recommend reducing AP use to only those at high risk of IE. In 2008, NICE recommended complete cessation of the use of AP, making the UK the only country in which AP was not recommended for those at high risk of IE.

From 2013, an international, multidisciplinary team led by Thornhill investigated the effect that the NICE guidelines had on AP prescribing and IE incidence in England **[R1].** Using a retrospective secular trend study, analysed as an interrupted time series, the team compared the incidence of infective endocarditis before and after the introduction of the NICE guidelines using prescribing data from January 2004 to March 2013 and hospital discharge episode statistics for patients with a primary diagnosis of IE from January 2000 to March 2013. The Sheffield research found a large decrease in AP prescribing and a highly significant increase in IE incidence, with an increase of 35 cases per month compared to the number of cases before the NICE guideline changed. In 2016, this study was followed with a health economic analysis that established the cost-effectiveness of using AP to prevent IE in individuals at high-risk, with

an estimated NHS savings of £5.5–8.2 million annually and an annual health gain of >2,600 quality of life adjusted years **[R2].**

In 2017, Sheffield collaborated with the Centre for Evidence-Based Medicine in Oxford, to conduct a comprehensive systematic review of AP efficacy. Having identified 178 eligible studies, 36 were included in the review (10 time-trend studies, 5 observational studies and 21 trials). The review concluded that despite the low-quality and limited evidence base, guidelines advising AP for patients at highest risk provide a pragmatic and justified approach **[R3].**

Although our research identified benefits for AP in relation to risk, definitions of what constitutes a high or moderate risk of IE have changed over the years, largely based on expert opinion. To clarify this basis for treatment, Sheffield used English hospital admission data to identify individuals admitted between January 2000 and March 2008 with diagnoses or cardiac procedures that might put them at risk of IE. This data was used to quantify and compare the risk of developing or dying from IE for patients who had predisposing cardiac conditions or various cardiac interventions. The results showed that some conditions that had been considered high risk are actually not, and that conversely, some conditions carry higher risk than had been thought **[R4].**

To investigate whether stopping AP for those at moderate risk of IE might increase IE incidence, we then performed the largest study ever on the impact of the 2007 AHA guideline change. High-risk, moderate-risk, and unknown/low-risk individuals with linked prescription and Medicare or commercial health care data were identified in the Truven Health MarketScan databases from May 2003 through August 2015 (198,522,665 enrollee-years of data). AP prescribing and IE incidence were evaluated by Poisson model analysis. The results confirmed the efficacy of AP for preventing IE in individuals at high risk of IE and demonstrated a much smaller, but still significant, effect in those at moderate risk **[R5].**

3. References to the research (indicative maximum of six references)

R1. Dayer, M. J., Jones, S., Prendergast, B., Baddour, L. M., Lockhart, P. B., & **Thornhill, M. H.** (2015). Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. *The Lancet, 385*(9974), 1219–1228. https://doi.org/10.1016/s0140-6736(14)62007-9

R2. Franklin, M., Wailoo, A., Dayer, M. J., Jones, S., Prendergast, B., Baddour, L. M., Lockhart, P. B., & **Thornhill, M. H.** (2016). The Cost-Effectiveness of Antibiotic Prophylaxis for Patients at Risk of Infective Endocarditis. *Circulation, 134*(20), 1568–1578. https://doi.org/10.1161/circulationaha.116.022047

R3. Cahill, T. J., Harrison, J. L., Jewell, P., Onakpoya, I., Chambers, J. B., Dayer, M., Lockhart, P., Roberts, N., Shanson, D., **Thornhill, M.,** Heneghan, C. J., & Prendergast, B. D. (2017). Antibiotic prophylaxis for infective endocarditis: a systematic review and meta-analysis. *Heart, 103*(12), 937–944. https://doi.org/10.1136/heartjnl-2015-309102

R4. **Thornhill, M. H.**, Jones, S., Prendergast, B., Baddour, L. M., Chambers, J. B., Lockhart, P. B., & Dayer, M. J. (2018). Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. *European Heart Journal, 39*(7), 586–595. https://doi.org/10.1093/eurheartj/ehx655

R5. **Thornhill, M. H.**, Gibson, T. B., Cutler, E., Dayer, M. J., Chu, V. H., Lockhart, P. B., O'Gara, P. T., & Baddour, L. M. (2018). Antibiotic Prophylaxis and Incidence of

Endocarditis Before and After the 2007 AHA Recommendations. *Journal of the American College of Cardiology, 72*(20), 2443–2454. https://doi.org/10.1016/j.jacc.2018.08.2178

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

Impact on national and international policy and public debate

In 2015, NICE announced an immediate review of its guidelines stating that the publication **[R1]** "triggered an exceptional update" **[S1].** While NICE concluded it would not re-introduce AP for those at high risk because the study was not a randomised controlled trial, the 2015 European Society for Cardiology (ESC) in depth review, citing **[R1]** concluded that "*the weight of evidence and opinion is now in favour of the efficacy and usefulness of AP in preventing IE in those at high-risk*" **[S2, S3].**

Other national guideline committees also reviewed their guidelines based on our research. The Swedish guideline committee, who had previously followed NICE guidance, switched to follow ESC guidance **[S3].** The Japanese guideline committee changed their recommendations to include providing AP for invasive dental procedures to those at moderate or high risk of IE **[S3].** The American Heart Association concluded their review in 2020 stating for dental procedures "*that antibiotic prophylaxis is reasonable for the subset of patients at highest risk of developing IE and at high risk of experiencing adverse outcomes from IE*" **[S3].**

NICE's decision not to recommend AP for high-risk patients despite the findings **[R1]** attracted considerable scrutiny from the dental and medical press and national and international media **[S4].** In addition, our research **[R2]** supported further scrutiny of and changes to the NICE guidelines. The MP for South Croydon helped a constituent whose husband died from IE following an invasive dental procedure to raise the issue directly with the CEO of NICE, using our research **[R1]** as evidence to support a change in the guidelines **[S5].** Their efforts successfully influenced NICE to change the guideline wording in June 2016 **[S6, S7].** The previous wording was changed to include the word "routinely", as follows: "*Antibiotic prophylaxis against infective endocarditis is not recommended routinely for people undergoing dental procedures.*" The NICE CEO said, "*This amendment should now make clear that in individual cases antibiotic prophylaxis may be appropriate*" **[S2, S6, S7].**

Impact on UK dental professionals and patients

Although the change in the wording of the NICE guidelines removed the barrier preventing dentists from providing AP, the NICE guidelines provided no advice about who should be considered for AP, which invasive dental procedures should be covered, or which AP regimen should be used, causing considerable confusion among dentists, cardiologists, GPs and patients. Our research informed our advice for dentists in the BDJ **[S8]** to help them navigate conflicting guidance. The Scottish Dental Clinical Effectiveness Program (SDCEP), which provides advice and guidance for dentists in Scotland, provided official advice *Antibiotic Prophylaxis Against Infective Endocarditis* **[S9]** in 2018 for the implementation of the NICE guideline 64 using our research findings **[R1]** and advice **[S2, S8].** It adopted our advice **[S8]** that all patients at risk of IE should be advised of warning signs and symptoms after undergoing an invasive dental procedure, regardless of whether they receive AP, which is essential for early diagnosis, improved survival and better outcomes **[S2].** The SDCEP advice was endorsed by NICE and the British Cardiac Society and the Chief Dental Officers for England, Wales, and Northern Ireland in 2018, making the advice applicable UK-wide **[S9].**

In 2019, we worked with the British Cardiac Society and British Heart Valve Society and helped them design a card that patients can carry to inform their dentists about any decision they have made with their cardiologist or cardiothoracic surgeon about their wish for AP when undergoing invasive dental procedures. It also provides information on AP and on the warning signs and symptoms of IE following any dental treatment or other invasive procedure based on the SDCEP advice **[S10].**

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. NICE Clinical Guideline 64.1 (Sept 2015) p9. The NICE 2015 review of its AP guidelines (CG64); the influence of R1 is detailed in paragraphs 1-3 on page 9.

S2. Editorial in the British Dental Journal describes the important role played by our research in the changes that have occurred both in the NICE guidance and the development of the SDCEP Implementation Advice (https://www.nature.com/articles/sj.bdj.2018.761).

S3. Combined: confirmation of use of our Sheffield research in various international guidelines. An email from the Chair of the Japanese AP guideline committee confirming the important role played by our research in the decision of the guideline committee (https://www.jstage.jst.go.jp/article/circj/83/8/83_CJ-19-0549/_pdf/-char/en). Evidence pertaining to the role our research played in determining the guidance of the ESC Guideline for the management of infective endocarditis (https://doi.org/10.1093/eurheartj/ehv319). The AHA guideline 2020 (https://www.ahajournals.org/doi/10.1161/CIR.0000000000000923).

S4. Media articles (print and online).

S5. Confirmation of Sheffield research use by the wife of a patient who died from dentally related IE to campaign for NICE to change its guidance and confirmation from the MP for South Croydon the importance of our research in the campaign for NICE to change its AP guidance.

S6. Correspondence between MP for South Croydon and CEO of NICE confirming use of Sheffield research in direct lobbying from the MP and response from the NICE confirming that the word 'routinely' would be added to NICE CG64.

S7. NICE CG64 with July 2016 update inserting the word 'routinely' on p 5.

S8. Sheffield articles providing advice to practitioners on AP in IE in British Dental Journal (https://doi.org/10.1038/sj.bdj.2016.49 and https://doi.org/10.1038/sj.bdj.2016.554).

S9. Letter from the SDCEP Steering Group Chair confirming the important role played by our research in the development of the SDCEP advice and its adoption, not just in Scotland, but across all four devolved nations of the UK.

S10. AP information card for patients. A BDJ article announcing the launch of the patient card that we developed with the British Cardiovascular Society and British Heart Valve Society to dentists along with a copy of the card (July 2019).